2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

VIRTUAL COURSE

Course Syllabus

August 6-8, 2020

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

Thursday, August 6, 2020

7:30 am		**REGISTRATION AND CONTINENTAL BREAKFAST**
I. EPILEPSY CLASSIFICATION		
8:00 am	**1**	**CLASSIFICATION OF SEIZURES AND EPILEPSY** Mohamad Koubeissi, MD
8:50 am	**2**	**ELECTRO-CLINICAL SYNDROMES AND OTHER EPILEPSIES** Samata Singhi, MD
9:35 am	**3**	**LESS AGE-SPECIFIC RELATIONSHIP** Samata Singhi, MD
10:15 am		**BREAK**
10:45 am	**4**	**EPILEPSIES ATTRIBUTED TO AND ORGANIZED BY STRUCTURAL-METABOLIC CAUSES** Amar B. Bhatt, MD
11:15 am	**5**	**NON-EPILEPTIC PAROXYSMAL DISORDERS IN PEDIATRIC AGE GROUP** Dewi Depositario-Cabacar, MD
11:45 am	**6**	**NON-EPILEPTIC SEIZURES IN ADULTS** Amar B. Bhatt, MD
12:15 pm	**7**	**EPIDEMIOLOGY OF EPILEPSY** Dewi Depositario-Cabacar, MD
12:45 pm		**LUNCH**
II. ROUTINE EEG		
1:45 pm	**8**	**NORMAL EEG** Amar B. Bhatt, MD
2:20 pm	**9**	**INTERICTAL EPILEPTIFORM PATTERNS** Mohamad Koubeissi, MD
2:55 pm	**10**	**ICTAL PATTERNS** Mohamad Koubeissi, MD
3:30 pm		**BREAK**
4:00 pm	**11**	**ENCEPHALOPATHIC PATTERNS AND ICU EEG** Hai Chen, MD
4:40 pm	**12**	**STATUS EPILEPTICUS AND HYPSARRHYTHMIA** Archana Pasupuleti, MD
5:30 pm		**ADJOURN**

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

Friday, August 7, 2020

7:30 am		**CONTINENTAL BREAKFAST**
III. DIAGNOSTIC WORKSHOP		
8:00 am	**13**	**HISTORY, EXAMINATION, AND SEMIOLOGY/CHEMICAL AND METABOLIC SCREENING** Amar B. Bhatt, MD
8:35 am	**14**	**AMBULATORY AND VIDEO-EEG** Amar B. Bhatt, MD
9:15 am	**15**	**IMAGING** Taha Gholipour, MD
10:00 am	**16**	**FUNCTIONAL NEUROIMAGING (PET, SPECT, FMRI)** William D. Gaillard, MD
10:50 am		**BREAK**
11:20 am	**17**	**MEG AND SOURCE LOCALIZATION** Taha Gholipour, MD
12:00 pm	**18**	**NEUROPSYCHOLOGICAL TESTING** Antonio Puente, PhD
12:30 pm		**LUNCH**
IV. AEDs		
1:30 pm	**19**	**AEDS I: THE SODIUM CHANNEL** Bassel W. Abou-Khalil, MD
2:20 pm	**20**	**AEDS II: THE GABA SYSTEM** Bassel W. Abou-Khalil, MD
3:00 pm	**21**	**AEDS III: AEDS WITH CARBONIC ANHYDRASE INHIBITION** Bassel W. Abou-Khalil, MD
3:45 pm		**BREAK**
4:00 pm	**22**	**AEDS IV: MISCELLANEOUS** Bassel W. Abou-Khalil, MD
4:40 pm		**ADJOURN**

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

Saturday, August 8, 2020

7:30 am		**CONTINENTAL BREAKFAST**
IV. MANAGEMENT (CONTINUED)		
8:00 am	**23**	**PRINCIPLES OF MANAGEMENT I** Pavel Klein, MD
9:00 am	**24**	**PRINCIPLES OF MANAGEMENT II** Pavel Klein, MD
9:45 am		**BREAK**
9:55 am	**25**	**STATUS EPILEPTICUS** Pavel Klein, MD
10:30 am	**26**	**EPILEPSY SURGERY** Gholam Motamedi, MD
11:25 am	**27**	**NEUROMODULATION IN EPILEPSY (VNS, RNS, DBS)** Gholam Motamedi, MD
12:30 pm		**LUNCH**
1:30 pm	**28**	**GENETIC ANALYSIS IN EPILEPSY** John M. Schreiber, MD
2:15 pm	**29**	**DIET THERAPIES, HORMONAL THERAPIES, AND IMMUNOGLOBULIN** Nabil Azar, MD
3:30 pm		**BREAK**
4:00 pm	**30**	**PSYCHOSOCIAL MANAGEMENT AND SYSTEMS-BASED PRACTICE ISSUES** Shubhi Agrawal, MD
4:50 pm	**31**	**DRIVING IN EPILEPSY** Jay Foreman, MD
6:00 pm		**ADJOURN**

General Information

Welcome

Welcome to the 2020 Epilepsy Board Review and Best Practices Course. We hope this review course helps in your preparation for the Boards. Below we have provided you with information to serve as a guide while you participate in this educational activity.

About the Course

This course in best practices and standards of care is designed for the fellow in training, the practitioner of neurology who wishes to review established standards of care and recent basic and clinical advances in epilepsy, or the physician planning to take the epilepsy certifying examination.

Course Facilitators

The George Washington University
Office of Continuing Education in the Health Professions
2600 Virginia Ave, NW, Suite 300
Washington, DC 20037
202.994.4285
cehp@gwu.edu
www.epilepsyboardreview.com

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

If you have any questions relating to the accreditation of this activity, please contact the office of CEHP, 202-994-4285, or via email at cehp@gwu.edu.

Electronic Course Materials

1. Please create your account at https://cme.smhs.gwu.edu
Next page: Instructions to create an account

2. Once you have an account and are logged in, click the My Courses tab in the "My Account" drop-down menu.

3. Under the Pending Activities tab, you will see the "Epilepsy Board Review Course"

Instructions to Create an EthosCE User Account

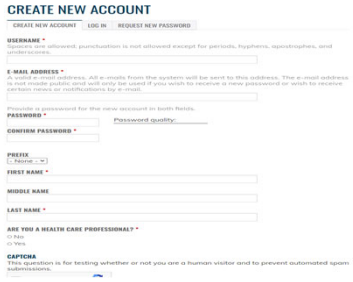
EthosCE

EthosCE User Account

Create New Account

1. Go to: **cme.smhs.gwu.edu**
2. In the upper right, click **Register**
3. Enter required information
   - Username – can be your email address
   - E-mail Address
   - Password/Confirm Password
   - Name
   - Health Care Professional
   - CAPTCHA

EthosCE User Account



Accreditation & Credit Claim

Accreditation

The George Washington University School of Medicine and Health Sciences is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physician CME Credit

The George Washington University School of Medicine and Health Sciences designates this activity for a maximum of **25.5** *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistants

The National Commission on Certification of Physician Assistants (NCCPA) states that the *AMA PRA Category 1 Credit(s)* ™ are acceptable for continuing medical education requirements for recertification.

Other Health Care Professionals

A record of attendance (certificate) will be provided to all other health care professionals for requesting credits in accordance with state boards, specialty societies, or other professional associations.

Program Evaluation and Claiming Credit

Participants will receive a daily e-mail with the link to the evaluation.

At the close of the meeting, participants will be e-mailed an overall course evaluation to claim CME credits.

Course Director

Mohamad Z. Koubeissi, MD
Professor of Neurology
The George Washington University
School of Medicine and Health Sciences
Director, Epilepsy Center
GW Medical Faculty Associates

Faculty

Bassel W. Abou-Khalil, MD
Professor of Neurology
Director of the Epilepsy Center
Vanderbilt University Medical Center

Shubhi Agrawal, MD
Neurologist
Sandra and Malcolm Berman Brain & Spine Institute
LifeBridge Health

Nabil Azar, MD
Medical Director
RealTime Tele-Epilepsy Consultants

Amar Bhatt, MD
Assistant Professor of Neurology
Program Director, Neurology Residency
Rush University Medical Center

Hai Chen, MD
Assistant Professor of Neurology
The George Washington University

Dewi Depositario-Cabacar, MD
Epilepsy, Neurophysiology, and Critical Care Neurology
Children's National Health System

P. Jay Foreman, MD, PhD
Director, Epilepsy Center and Neurodiagnostics Laboratory
Sandra and Malcolm Berman Brain & Spine Institute
LifeBridge Health

William D. Gaillard, MD
Director, Comprehensive Pediatric Epilepsy Program Associate Director, Center for Neuroscience Research
Children's Research Institute
Children's National Medical Center

Taha Gholipour, MD
Assistant Professor of Neurology
The George Washington University

Pavel Klein, MD
Director, Mid-Atlantic Epilepsy and Sleep Center
Adjunct Associate Professor, Neurology
The George Washington University
School of Medicine and Health Sciences

Gholam Motamedi, MD
Professor, Department of Neurology Principal Investigator, Epilepsy Research Georgetown University

Archana Pasupuleti, MD
Neurophysiologist
Children's National Medical Center
The George Washington School of Medicine

Antonio Puente, PhD
The George Washington University
School of Medicine and Health Science

John Schreiber, MD
Neurologist
Children's National Medical Center

Samata Singhi, MD
Director, Epilepsy Monitoring Unit
Kennedy Krieger Institute
Assistant Professor, Neurology and Pediatrics
Johns Hopkins University

Disclosure Information

In accordance with the Accreditation Council for Continuing Medical Education's (ACCME) Standards for Commercial Support, The George Washington University Office of Continuing Education in the Health Professions (CEHP) requires that all individuals involved in the development and presentation of CME activity content disclose any relevant financial relationships with commercial interest(s). CEHP identifies and resolves all conflicts of interest prior to an individual's participation in an educational activity.

The following faculty, planners, and staff report they have no relevant financial relationships with commercial interest(s):

- **Mohamad Koubeissi, MD (Course Director)**
- **Bassel Abou-Khalil, MD**
- **Shubhi Agrawal, MD**
- **Nabil Azar, MD**
- **Amar Bhatt, MD**
- **Hai Chen, MD**
- **Dewi Depositario-Cabacar, MD**
- **P. Jay Foreman, MD, PhD**
- **Taha Gholipour, MD**
- **Gholam Motamedi, MD**
- **Archana Pasupuleti, MD**
- **Antonio Puente, PhD**
- **John Schreiber, MD**
- **Samata Singhi, MD**
- **Radwa Aly (Staff)**
- **Leticia Hall (Staff)**
- **Naomi Loughlin (Staff)**

The following faculty and planners report the following relevant financial relationships with commercial interest(s):

Faculty Member	Disclosure
Pavel Klein, MD	• Speaker's Bureau: Alliance • Speaker Fee: Aquestive, Eisai, Sunovion, UCB Pharma • Consulting Fee: Alliance, UCB Pharma
William D. Gaillard, MD	• Supported by Federal Grants R01 NS44280 NINDS, RO1 MH65395 NIMH, P30HD40677 NICHD, U54 MH066417 & Clinical Epilepsy Section NINDS, NIH • Co-Investigator (Not PI, no salary support): Several Pharmaceutical Industry supported AED clinical trials: Rectal Diazepam, Oxcarbazine, Lamotrigine, Zonisimide, Vigabatrin, Tiagabine, Gabapentin, Clobazam, Rufinimide. • Advisory Board - GE and laundered funds Ovation and Questor

Classification of Seizures and Epilepsy

Mohamad Z. Koubeissi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

CLASSIFICATION OF SEIZURES AND EPILEPSY

Mohamad Z. Koubeissi, MD
Professor of Neurology
Director, Epilepsy Center
The George Washington University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Definitions

Conceptual Definition of Seizure and Epilepsy – 2005 Report

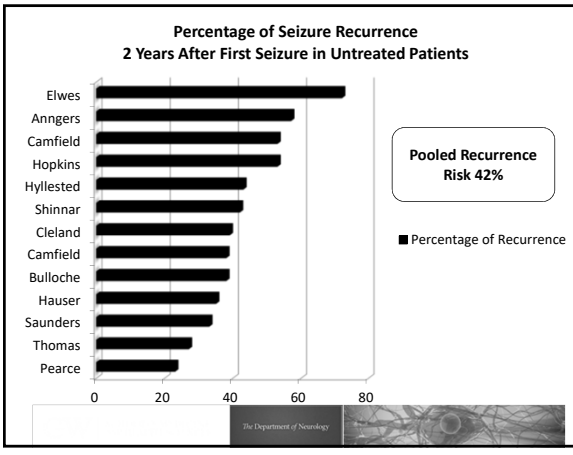
- Seizure = a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain
- Epilepsy = a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition.

Fisher et al (2013). Epilepsia

Operational Definition of Epilepsy

- Epilepsy = the occurrence of two unprovoked seizures occurring at least 24 hours apart (1).
- After two unprovoked non-febrile seizures, the chance of having another is 73% (1) at four years (95% CI is 59%-87%), versus 40-52% after a single unprovoked seizure (2).

1. Hauser WA et al (1998). N Engl J Med 338:429-434. (2) Berg AT, Shinnar S. (1991). Neurology 41:965-972.



Problems with that definition

- A patient with a single seizure and a structural brain lesion has a risk of a second unprovoked seizure that is comparable to the risk for further seizures after two unprovoked seizures (1)
- A patient with a single unprovoked seizure, but with an epilepsy syndrome with a high risk of seizure recurrence
- A patient with a single unprovoked seizure who has reflex (e.g. photosensitive) epilepsy

1. Hesdorffer DC et al (2009). Epilepsia 50:1102-1108.

2015 AAN/AES Evidence-based guideline

- Provoked seizures:
  Defined as seizures due to an acute symptomatic condition (e.g., a metabolic or toxic disturbance, cerebral trauma, stroke) and differ in prognosis from unprovoked seizures.
- Unprovoked seizures:
  (1) A seizure of unknown etiology, or
  (2) A seizure in relation to a demonstrated preexisting brain lesion or progressive CNS disorder (so-called "remote symptomatic" seizure).
- Adults with an unprovoked first seizure have a seizure recurrence risk that is greatest early within the first 2 years (21%–45%) (Level A)

Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S.

MCQ 1

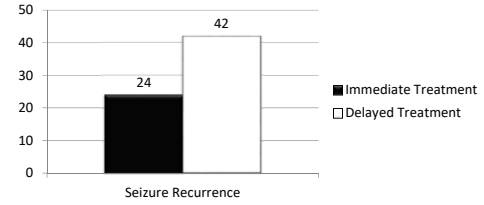
- Which of the following is an unprovoked seizure?
  - A. Alcohol withdrawal seizure
  - B. Seizure in the setting of high dose wellbutrin
  - C. Seizure in the setting of hyponatremia due to beer potomania
  - D. Seizure in the setting of flickering lights
  - E. Convulsive movements following fainting due to dehydration

MCQ 1

- Which of the following is an unprovoked seizure?
  - A. Alcohol withdrawal seizure
  - B. Seizure in the setting of high dose wellbutrin
  - C. Seizure in the setting of hyponatremia due to beer potomania
  - **D. Seizure in the setting of flickering lights**
  - E. Convulsive movements following fainting due to dehydration

FIRST Trial

- Multicenter, randomized, open trial
- First GTC seizure - randomized to immediate treatment or to treatment only after another seizure.



FIRST trial: (*Neurology. 1997 Oct;49(4):991-8. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). Musicco M, Beghi E, Solari A, Viani F.)*

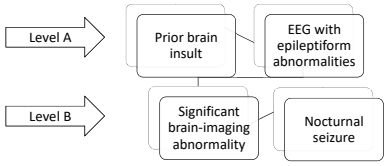
FIRST Trial - Conclusions

- Both groups had the same time-dependent probability of achieving 1 and 2 seizure-free years
- None of the prognostic predictors of relapse was significantly associated with the probability of having 1 or 2 years of seizure control
- ASMs in patients presenting a first GTC seizure reduce the risk of relapse
- Half of the untreated patients will never experience a second seizure
- The probability of long-term remission is not influenced by treatment of the first seizure

FIRST trial: (*Neurology. 1997 Oct;49(4):991-8. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). Musicco M, Beghi E, Solari A, Viani F.)*

2015 AAN/AES Evidence-based guideline

- Clinical variables associated with increased risk may include:

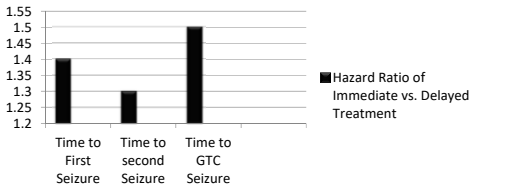


- Immediate medical therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first 2 years (Level B) but may not improve quality of life (Level C)

Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S.

MESS Study

- Unmasked, multicenter, randomized study of immediate (n=722) and deferred (n=721) ASM treatment in individuals with single seizures and early epilepsy

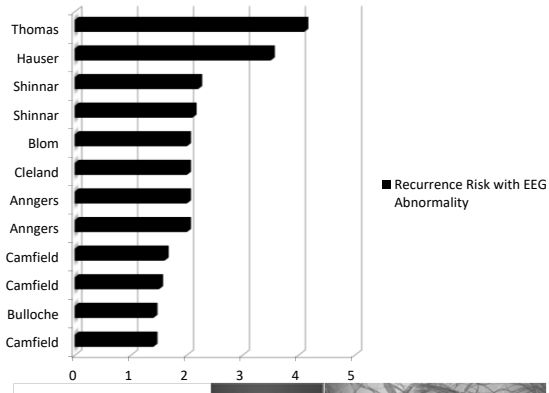


MESS study (Lancet. 2005 Jun 11-17;365(9476):2007-13. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D; Medical Research Council MESS Study Group.)

MESS Study

- Immediate treatment reduced the time to achieve 2-year remission of seizures (p=0.023)
- The two groups did not differ with respect to quality of life outcomes or serious complications
- Immediate ASM treatment reduces the occurrence of seizures in the next 1-2 years, but does not affect long-term remission in individuals with single or infrequent seizures

MESS study (Lancet. 2005 Jun 11-17;365(9476):2007-13. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D; Medical Research Council MESS Study Group.)



2015 AAN/AES Evidence-based guideline

- In the long term, immediate treatment is unlikely to improve prognosis as measured by sustained seizure remission (Level B).
- Patients should be advised that risk of ASM adverse events (AEs) may range from 7% to 31% (Level B) and that these AEs are likely predominantly mild and reversible

Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S.

Broadened Definition by the ILAE Task Force: 2013

- Epilepsy is defined by any of the following conditions:
  - 1. At least two unprovoked seizures more than 24 hrs apart
  - 2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (approximately 75% or more)
  - 3. At least two seizures in a setting of reflex epilepsy
- Epilepsy is considered to be no longer present for
  - individuals who had an age-dependent epilepsy syndrome but are now past the applicable age
  - If seizure-free for at least 10 years off anti-seizure medicines, provided that there are no known risk factors associated with a high probability (>75%) of future seizures

Fisher, R. et al. 2013. Epilepsia

Not Epilepsy

- Febrile seizures in children age 0.5 – 6 years old
- Alcohol-withdrawal seizures
- Metabolic seizures (sodium, calcium, magnesium, glucose, oxygen)
- Toxic seizures (drug reactions or withdrawal, renal failure)
- Convulsive syncope
- Acute concussive convulsion
- Seizures within first week after brain trauma, infection or stroke

Examples

Case	Old Definition	New Definition
A 30 year-old man with two unprovoked seizures one year apart	☐	☐
A 70 year-old man with first unprovoked seizure one year after L MCA stroke	☐	☐
A 6 year-old boy has had 2 seizures 2 days apart while playing a videogame with flashing lights. EEG shows an abnormal photoparoxysmal response.	☐	☐
A 25 year-old man had seizures with face twitching when falling asleep at age 9-11; none since. Past EEG showed centro-temporal spikes.	☐	☐
A 40 year-old man had a left focal motor seizure with secondary generalization. MRI shows right frontal periventricular heterotopia and EEG shows right frontal spikes.	☐	☐

Classifications

Background/History

- Purpose of classification: to provide a framework for diagnosis, management, and prognosis.
- 1964: Henri Gastaut: first endeavor to systematically classify seizures and epilepsies
- 1969: Gastaut published classification on behalf of the International League against Epilepsy (ILAE)
  - Focused on distinguishing between partial onset from generalized onset
  - Multidimensional classification: ictal semiology and EEG, interictal EEG, age of onset, neuropsychiatric phenomena, treatment responses, cause, and the known or hypothesized pathophysiology

Background/History

- 1981: The ILAE modified the seizure classification
  - Partial seizures were subdivided into complex partial, simple partial, and secondarily generalized
- 1985: ILAE proposed a classification of epilepsies and epileptic syndromes
  - The seizure semiology in some epilepsies was described; many of the well defined syndromes were included

Background/History

- 1989: The concept of an epilepsy syndrome was refined and has been essential for diagnosis of epilepsy to this day
  - Epilepsy syndrome: defined by a cluster of coexisting signs and symptoms, including specific seizure type(s), EEG features, age of onset, and often a shared cause and prognosis
  - Causes were divided into idiopathic, symptomatic or cryptogenic ('presumed symptomatic')

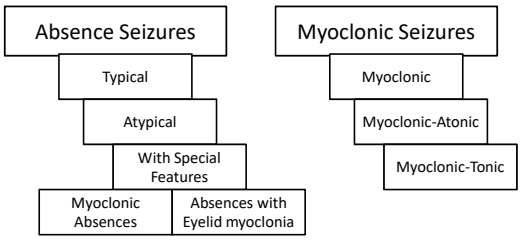
The 2010 ILAE Classification

- Generalized seizures do not involve the entire cortex as shown by imaging and neurophysiological studies
- 'complex partial' and 'simple partial' terminologies are not endorsed
- Focal versus generalized dichotomy is not applied – may coexist
- Retained versus altered awareness during seizures in infants?
- The terms idiopathic, symptomatic, and cryptogenic can be misleading.

The 2010 ILAE Classification: Generalized Seizures

- Definition: Seizures originating at some point within, and rapidly engaging, bilaterally distributed networks. These networks can include cortical and subcortical structures, but do not necessarily involve the entire cortex
- Generalized seizures can be asymmetric

The 2010 ILAE Classification: Generalized Seizures



The 2010 ILAE Classification: Generalized Seizures

- Absence seizures
- Myoclonic seizures
- Tonic–clonic seizures (in any combination)
- Tonic
- Atonic
- Clonic

The 2010 ILAE Classification: Focal Seizures

Definition: Seizures originating within networks limited to one hemisphere, discretely localized or more widely distributed. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere

"Complex Partial" →	Focal dyscognitive /with impaired awareness
"Simple Partial" →	Focal without impairment of consciousness or awareness

Table 1. Classification of seizures[a]

- Generalized seizures
  - Tonic–clonic (in any combination)
  - Absence
    - Typical
    - Atypical
    - Absence with special features
      - Myoclonic absence
      - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic atonic
    - Myoclonic tonic
  - Clonic
  - Tonic
  - Atonic
- Focal seizures
- Unknown
  - Epileptic spasms

[a]Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.

Berg, A. et al. 2010. Epilepsia

Table 2. Descriptors of focal seizures according to degree of impairment during seizure[a]

Without impairment of consciousness or awareness
With observable motor or autonomic components. This roughly corresponds to the concept of "simple partial seizure. "Focal motor" and "autonomic" are terms that may adequately convey this concept depending on the seizure manifestations).
Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary.
With impairment of consciousness or awareness. This roughly corresponds to the concept of complex partial seizure. "Dyscognitive" is a term that has been proposed for this concept (Blume et al., 2001).
Evolving to a bilateral, convulsive[b] seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term "secondarily generalized seizure."

[a]For more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001.
[b]The term "convulsive" was considered a lay term in the Glossary; however, we note that it is used throughout medicine in various forms and translates well across many languages. Its use is, therefore, endorsed.

Berg, A. et al. 2010. Epilepsia

The 2010 ILAE Classification: Notable changes

- Neonatal seizures are no longer a separate entity
- "idiopathic, symptomatic, and cryptogenic" → genetic, structural, metabolic, and unknown. These categories are not mutually exclusive.
- Diagnosis of electroclinical syndromes remains unchanged.
- 'Constellations' define clinically distinctive entities with specific associations, such as hypothalamic hamartoma and gelastic seizures, or mesial temporal lobe epilepsy and hippocampal sclerosis

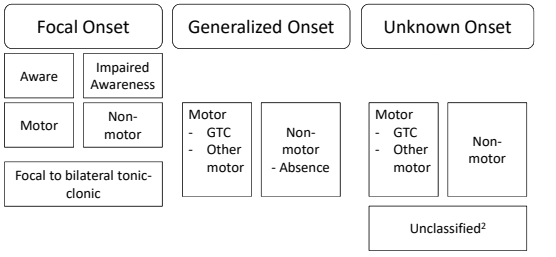
The 2010 ILAE Classification: Notable changes

- Removal of the emotionally laden words 'catastrophic' and 'benign' to describe different epilepsies
- Epileptic encephalopathies have been redefined as diseases in which 'the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and that these can worsen over time

2017 Classification

- 2010 Classification engendered debate within the epilepsy community
- 7 years of an iterative process with worldwide public engagement
- The 2017 classification changed as a result

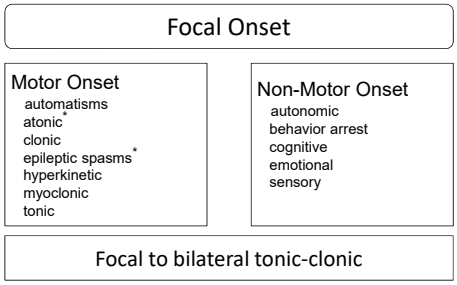
ILAE 2017 Classification[1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms
[2] Due to inadequate information or inability to place in other categories

From Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671

ILAE 2017 Classification - Expanded



From Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671

ILAE 2017 Classification - Expanded

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic*
- epileptic spasms*

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

From Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671

ILAE 2017 Classification - Expanded

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified

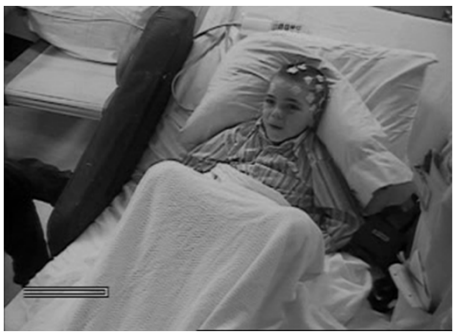
From Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671

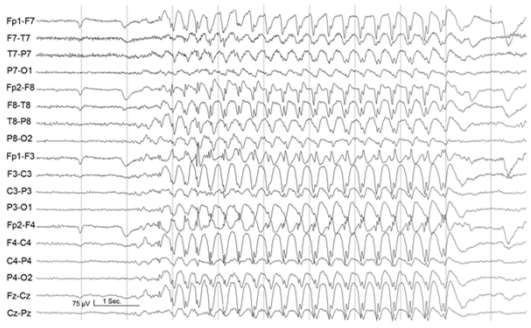
2017 ILAE Classification

- First diagnose the seizure type
- Then diagnose epilepsy type
  - focal, generalized, combined generalized/focal, and unknown
- Then diagnose the epilepsy syndrome
- Etiology is incorporated along each stage
  - 6 subgroups, selected because of potential therapeutic consequences: structural, genetic, infectious, metabolic, immune, and unknown
- New terminology: developmental and epileptic encephalopathy
- The term benign is replaced by the terms self-limited and pharmacoresponsive

Absence Seizures

- Childhood or teenage onset
- Sudden onset, without aura, prompt offset
- Momentary loss of consciousness
- Eyelid flutter/minor automatisms
- 3-15 seconds duration
- Family History
- EEG: 3 Hz Spike-Wave / HV sensitive





Tonic Seizures

- Sudden stiffening
- Extension maximal in arms
- A few seconds in duration
- Associated with falls and injury
- Extra-temporal origin
- Refractory to therapy
- EEG: Flattening/high frequency discharge

Atonic Seizures

- Abrupt onset
- Sudden loss in tone
- Head drop/falls/injuries
- A second or two in duration
- Poor response to AEDs
- Poor overall prognosis
- EEG: Slow spike-wave/flattening

Myoclonic Seizures

- Sudden jerks
- Usually bilateral, maximal in arms
- One second in duration
- Often multiple
- May be photic or sensory triggered
- Often maximal on awakening
- EEG: generalized polyspike-wave burst

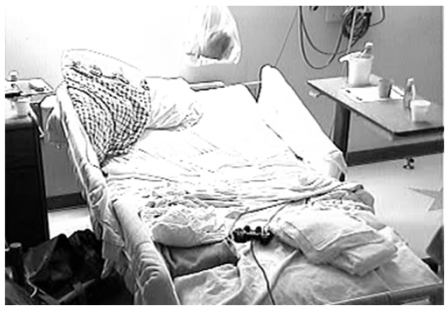
Tonic-Clonic Seizures

- Loss of Consciousness
- May have a focal or generalized onset
- Tonic Extension of limbs (about 20-40 sec)
- Evolves to rhythmic clonic jerking of extremities (about 30-50 secs)
- Cessation of breathing, tongue biting, incontinence
- Post-ictal sleep
- EEG: Variable, often obscured.

Focal Seizures

Focal Aware Seizures

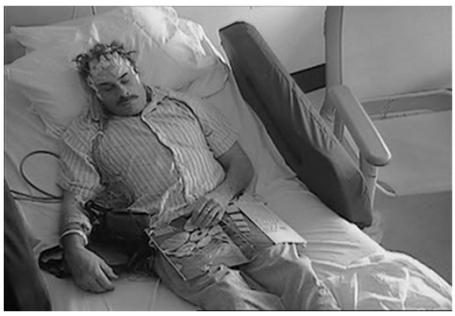
- Motor, sensory, psychic or autonomic signs or symptoms
- Preservation of consciousness & awareness
- May progress to focal impaired awareness or tonic-clonic seizures
- EEG: Interictal-focal sharp or slow; ictal-rhythmic discharge or often normal!



Abou Khalil & Misulis. Atlas of EEG and Seizure Semiology. Elsevier 2006.

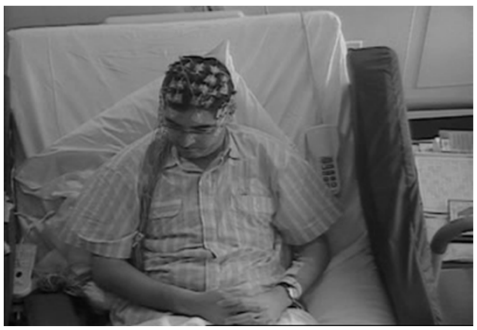
Focal Impaired Awareness Seizures

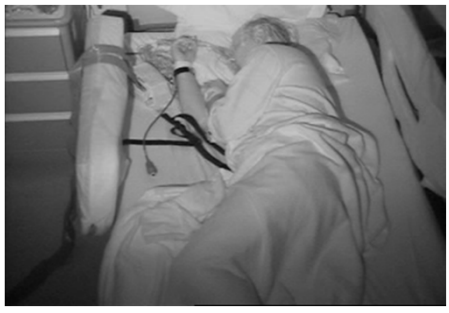
- Altered consciousness/awareness
- Duration 30 sec to 3 min
- Purposeless automatisms
  - Arms
  - Oral
- Amnesia
- Semiology varies with site of origin
- EEG: Interictal- sharp waves or spikes; Ictal- focal or bilateral rhythmic sharp

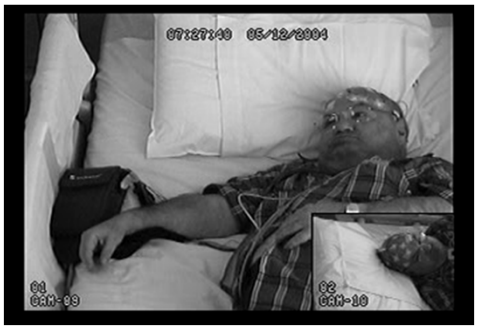


Abou Khalil & Misulis. Atlas of EEG and Seizure Semiology. Elsevier 2006.

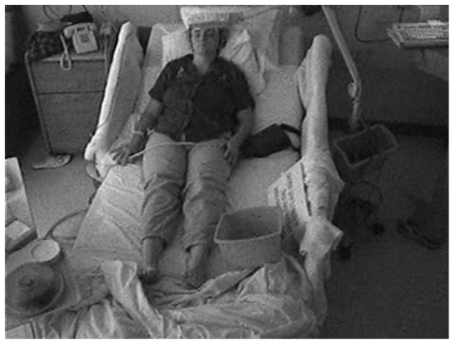
Guess the seizure type







Abou Khalil & Misulis. Atlas of EEG and Seizure Semiology. Elsevier 2006.



Abou Khalil & Misulis. Atlas of EEG and Seizure Semiology. Elsevier 2006.

Electro-Clinical Syndromes and Other Epilepsies

Samata Singhi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

ELECTRO-CLINICAL SYNDROMES AND OTHER EPILEPSIES

Samata Singhi, MD, MSc
Director, Epilepsy Monitoring Unit
Kennedy Krieger Institute
Assistant Professor, Neurology and Pediatrics
Johns Hopkins University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Abbreviations used

AED Anti epileptic drug	FCD Focal cortical dyplasia
ACTH Adrenocorticotrophic hormone	TSC Tuberous sclerosis complex
CBZ Carbamazepine	SWS Sturge Weber Syndrome
CZP Clonazepam	HIE Hypoxic Ischemic Encephalopathy
CBM Clobazam	NAT non accidental trauma
ESM Ethosuximide	AD Autosomal dominant
KD Ketogenic diet	M Male
LTG Lamotrigine	F Female
OXC Oxcarbazepine	GTCs Generalized tonic clonic seizure
PHT Phenytoin	EEG electroencephalogram
PHB Phenobarbital	DOL day of life
TPM Topiramate	Sec seconds
VPA Valproate	Min minutes
ZNS Zonisamide	Mos months
SE Status epilepticus	Yr years

Outline

Neonatal period
Infancy
Childhood
Adolescence
Adulthood

Approach to Electroclinical syndromes

3 key factors:
- age of the child
- neuro-developmental status
- seizure semiology

EEG, neuro-imaging, metabolic tests and genetic work-up for establishing the diagnosis.

Pediatric epilepsy syndromes by age of onset

Neonatal period
-Benign idiopathic neonatal seizures
-Benign familial neonatal epilepsy (BFNE)
-Ohtahara syndrome
-Early myoclonic encephalopathy (EME)

Infancy
-Benign infantile epilepsy
-Epilepsy of infancy with migrating focal seizures
-West syndrome
-Myoclonic epilepsy in infancy
-Dravet syndrome

Childhood
-Genetic epilepsy with febrile seizure plus (GEFS+)
-Benign epilepsy with centrotemporal spikes (BECTS)
-Panayiotopoulos syndrome

Childhood
-Late Childhood Occipital epilepsy (Gastaut type)
-Continuous spike and wave during sleep (CSWS)
-Landau Kleffner syndrome (LKS)
-Lennox Gastaut syndrome (LGS)
-Epilepsy with myoclonic-atonic (formerly astatic) seizures (Doose syndrome)
-Childhood Absence epilepsy (CAE)
-Epilepsy with myoclonic absences

Adolescence-Adult
-Juvenile Absence epilepsy (JAE)
-Juvenile Myoclonic epilepsy (JME)
-Epilepsy with generalized tonic clonic seizures
-Autosomal dominant nocturnal frontal lobe epilepsy
-Familial temporal lobe epilepsies
-Progressive Myoclonus epilepsies (PME)

Outline

Neonatal period
Infancy
Childhood
Adolescence
Adulthood

Benign Familial Neonatal Epilepsy

Etiology: Chromosomes 20 & 8 (KCNQ2 & 3, K+ channels, M-channel subunit); AD channelopathy; high degree of penetrance (85%)

Positive family history of benign neonatal seizures

Onset: Seizure onset often DOL 2-3 in healthy term neonate

Clinical: Frequent, brief clonic or tonic posturing, apnea/cyanosis, autonomic signs, face and limb clonus, may cluster lasting 1-3 min

EEG normal or bilateral spikes and sharp waves

Treatment: ezogabine binds to subunit on KCNQ2 ion channel pore and stabilizes membrane, alters M current; no longer available, PHB

Course: May last for 1-6 mos (10% incidence of later epilepsy). Neurodevelopment favorable.

Benign Neonatal Seizures or Idiopathic neonatal convulsions

Etiology: Family history is negative

Onset: Seizure onset often DOL 4-6 "fifth day fits" following an uneventful gestational and perinatal course

Clinical: Unifocal clonic, (rarely) focal tonic seizures, normal neurologic status between

Treatment: Acutely for seizure management

EEG: *theta pointu alternant*: a nonreactive, discontinuous focal, theta frequency rhythm with intermixed sharp waves may shift between hemispheres and persist days to weeks following cessation of clinical seizures

Course: Self limited, seizures usually dissipate after 2 days. Favorable outcome

Pearl PL. Epilepsy Syndromes in Childhood. Continuum (Minneap Minn). 2018

Early infantile epileptic encephalopathy (Ohtahara)

Etiology: Structural brain lesions most common, Hemimegalencephaly, porencephaly, Aicardi syndrome, olivary-dentate dysplasia,

Metabolic (cytochrome a oxidase deficiency, Leigh encephalopathy)

Genetics: **STXBP1**, CDKL5, ARX, **KCNQ2**, SCN2A, SLC25A22, SPTAN1, PNPO (B6 dependent), ALDH7A1 (PLP-dependent), etc

Onset in first 3 months

Clinical: tonic spasms in isolation or clusters, hundreds per day; Focal motor and generalized tonic seizures may also be seen

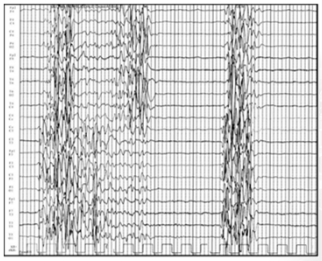
EEG: suppression burst waking and sleep (bursts >150 microvolts)

Treatment: Corticosteroids, LEV, KD, ZNS, PHB; surgery

Course: High mortality rate in infancy (50%), profound neurodevelopmental deficits in survivors , progression to West syndrome (75%), SMEI, LGS

EIEE EEG

Typical EEG bursts of high-amplitude slow waves and polyspikes interspersed with suppression phases that are isolectric.



Pavone P et al. Ohtahara syndrome with emphasis on recent genetic discovery. Brain Dev (2011)

EIEE EEG

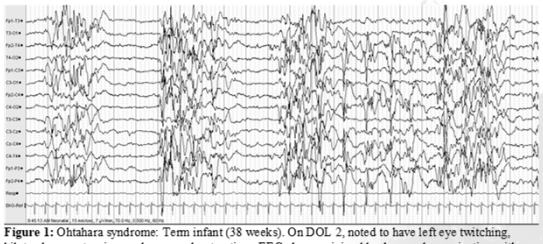


Figure 1: Ohtahara syndrome: Term infant (38 weeks). On DOL 2, noted to have left eye twitching, bilateral arm extension, and oxygen desaturation. EEG shows minimal background organization with excessive asynchrony.

Image courtesy of Dr. Phillip Pearl

Early myoclonic encephalopathy (EME)

Etiology: metabolic disorders (pyridoxine dependency, glycine encephalopathy, methylmalonic or propionic academia); SLC25A22 mutations (mitochondrial glutamate transporter)

Onset in first month of life

Clinical: Myoclonus in limbs, face predominant at onset ("fragmentary"); later evolution of tonic spasms and focal seizures

EEG: burst suppression, more marked in sleep, often persists

Treatment: Correct metabolic disorder, KD, ASMs: CLB, TPM, PHB

Course: Myoclonus: resolves weeks/ months; focal seizures persist; Mortality high in early ages; poor prognosis for seizures and neurodevelopment; evolution to West syndrome, LGS

EME EEG

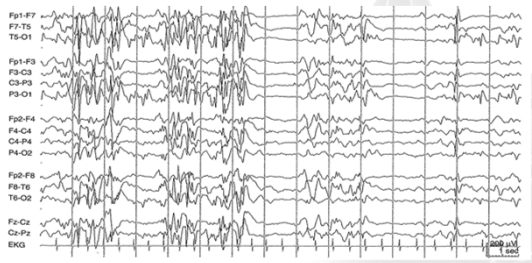


Image courtesy of Dr. Phillip Pearl

EEG: burst suppression in glycine encephalopathy

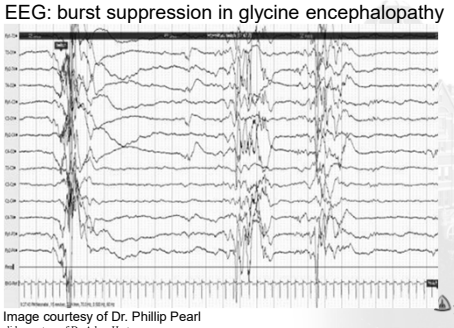


Image courtesy of Dr. Phillip Pearl
slide courtesy of Dr. Adam Hartman

EIEE

Age: within first 3 mos

Abnormal exam, asymmetrical findings

Main feature is early tonic spasms;

Later, focal seizures and Myoclonus

EEG: suppression-burst in sleep and wake, longer bursts; progress to hypsarrhythmia, then slow spike wave

Etiologies: cerebral dysgenesis, anoxia, cryptogenic

Static impairment

Severe neurological impairment, intractable epilepsy

EME

Age: within first 3 mos

Abnormal exam sometimes, hypotonia

Main feature is early fragmentary myoclonus; Later, focal seizures and tonic spasms

EEG: suppression-burst predominantly in sleep, longer suprresion, often persists

Etiologies: IEM, genetic

Progressive impairment

High mortality (early death), extremely poor prognosis

Metabolic etiologies of early onset epileptic encephalopathy)

Pyridoxine dependent/ folinic acid responsive epilepsy (ALDH7A1)

-Seizures in hrs or days after birth (range from in utero to months after birth)

-Frequent erratic myoclonus or convulsive incl SE

-Sleeplessness, irritability, abnormal eye movements, and facial grimacing.

-EEG: diffuse or focal discharges, or also burst-suppression

-Prompt response of seizures to IV pyridoxine (50-100 mg)

Pyridoxal 5-phosphate-dependent epilepsy/ deficiency of pyridoxamine 5'phosphate oxydase (PNPO)

-Refractory neonatal onset, often in preterm

-seizures typically involve myoclonus, abnormal eye movements, and convulsions.

-P5P 30mg/kg/day PO

Genetic/ Metabolic etiologies of early onset epileptic encephalopathy)

Serine deficiency disorders

Creatine deficiency

Cerebral folate deficiency (transportopathy)

Glycine encephalopathy

- Lethargy, hypotonia, hiccups, seizures, apnea in neonate/ infant
- Sodium benzoate 250-750mg/kg/day and dextromethorphan

Biotinidase deficiency (BTD gene variants; AR)

- Neonatal/ infantile seizures tonic-clonic or myoclonic or infantile spasms
- EEG background slowing, multifocal spikes, hypsarrhythmia, or burst-suppression
- irritability, conjunctivitis, cheilosis, alopecia, and in time optic atrophy
- 5-40 mg of biotin daily

Genetic/ Metabolic etiologies of early onset epileptic encephalopathy)

Glucose transporter 1 deficiency (SLC2A1, transportopathy)

- 90% have epilepsy (focal or generalized seizures), birth to early childhood
- Microcephaly, ataxia, psychomotor delay
- EEG: slowing or attenuation, or spike-and-wave discharges (generalized, focal, or multifocal)
- Rapid response to KD

Mitochondrial disorders (POLG1, Twinkle)

Amino acidopathies (glycine encephalopathy, phenylketonuria (PKU)

Organic acidurias (methylmalonic aciduria, maple syrup urine disease (MSUD) proprionic aciduria)

Urea cycle disorders (OTC deficiency, citrullinemia)

Neurotransmitter disorders

Outline

Neonatal period
Infancy
Childhood
Adolescence
Adulthood

Benign infantile seizures

Etiology: genetically heterogeneous: mutations in PRRT2 (same gene as paroxysmal kinesigenic dyskinesia), ASC-1 (amino acid transporter), SCN2A, SCN8A, etc.

Onset: 3-20 mos in a developmentally normal infant; Familial form onset typically is 4-7 mos, F>M

Clinical: focal onset (head, face, limbs) clonic seizures or unresponsiveness/motor arrest/blank look or version, may secondarily generalize, in clusters (5-10 per day for 1-3 days) with varying lateralization

Treatment: OXC, CBZ, PHB

Course: Usually seizures remit by 1 to 2 yrs of age, excellent prognosis; some may develop movement disorders.

Epilepsy of infancy with migrating focal seizures

Etiology: Genetics: KCNT1, SCN1A, SCN2A, SCN8A, SLC12A5 (KCC2), SLC25A22, TBC1D24, PNPO, KKCNQ2, KCNQ3, STXBP1,PRRT2, PLCB1; Imaging usually reveals non-specific atrophy

Seizure onset: 1 week – 7 mos (mean = 3 mos) in healthy infants

Clinical: Focal motor seizures prolonged or in clusters; may show bilateral spread; associated with autonomic features

EEG: multifocal origins & migration of seizure foci (incl rhythmical delta or sharp waves/spikes)

Treatment: SCN2A/ SCN8A – phenytoin; KCNT1 – quinidine, Corticosteroids, IVIG. Stiripentol, KD, Bromides, LEV, CLB (most AEDs ineffective)

Early intractability but seizure control may improve

Neurodevelopmental prognosis in survivors generally is poor

Infantile Spasms and West Syndrome

West syndrome triad: Spasms + Hypsarrhythmia (EEG) + DD

4 per 10,000 live births

Etiology: Symptomatic (80%) vs. asymptomatic

Polymicrogyria, Schizencephaly, FCD, TSC, SWS, Incontinentia pigmenti, TORCH, Down syndrome, Trauma, HIE, Meningitis, Encephalitis, ICH, PKU, Glycine encephalopathy, MSUD, Mitochondrial disorders, etc

Genetic (ARX, CDKL5 (X linked), FOXG1, STXBP1, TSC1/2)

Seizure onset: 4-8 mos typically; 90% <1 year

** Children>12 months of age may present w epileptic spasms not associated with hypsarrhythmia. Usually, structural malformation. M>F

Infantile Spasms and West Syndrome

Clinical: Flexor (50-60%): sudden flexion of neck, arms, legs

Extensor (20%): sudden extension of neck, arms and legs, like a

Mixed (40%): flexion of head, arms extension of the legs or vice versa.

Mild (head nod or shoulder shrug) or forceful flexion or extension.

Occur in clusters, generally on awakening; few to several times a day

Each cluster consists of 3-4 to several, even 100 spasms.

Crying or irritability or other behavioral changes during or soon

EEG: hypsarrhythmia, chaotic high voltage slow waves, multifocal spikes and sharp waves, may attenuate or disappear during REM sleep.

EEG hypsarrhythmia

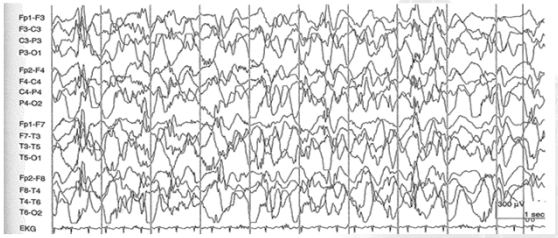


Image courtesy of Dr. Phillip Pearl

EEG spasm

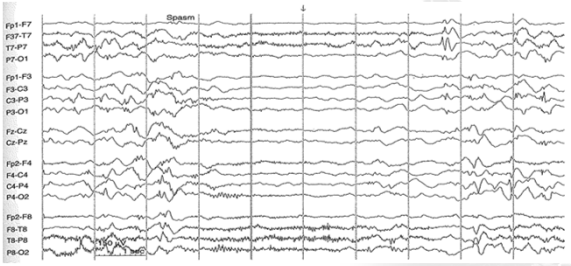


Image courtesy of Dr. Phillip Pearl

Infantile Spasms and West Syndrome

Treatment: Pyridoxine 100 mg IV trial with EEG monitoring (if no obvious source) →continue 50-100 mg PO/day until results of CSF/ genetic testing

ACTH (100 -150 IU/m^2 per day) better efficacy, but more side effects (response within 1-2 weeks; generally dramatic) taper x12wks

Low dose ACTH (20-30 IU IM/day) similar to prednisolone 2mg/kg/day.

Relapse of spasms after stopping steroids in a third

Vigabatrin 100-150 mg/kg/day divided into 2 doses (1st line TSC) x6mos

ICISS: Combination!

KD, TPM, ZNS, Rufinamide

Surgery

Outome: depends on etiology (best in cryptogenic) Intellectual disability: 75-90%, evolution to LGS; mortality is about 25%

Myoclonic epilepsy in infancy (MEI)

Etiology: Family history in 25-30%

Onset: 4 mos – 3 yrs in neurodevelopmentally normal

Clinical: Brief axial or upper extremity myoclonic jerks w/head drops; may see trunk flexion/extension (lower extremities involved rarely)

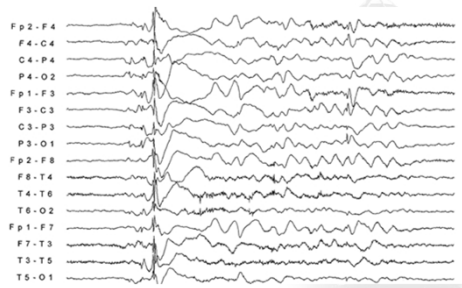
Reflex myoclonic seizures are a subgroup (auditory, tactile stimuli); some are photosensitive

Ictal EEG: generalized spike wave>3 Hz for 1-3sec. 20% photosensitive.

Treatment: VPA, LEV, CZP

Course: Seizures responsive to treatment, may develop other seizures later, Neurodevelopment generally normal

EEG in myoclonic epilepsy



EEG shows generalized spike/polyspikes lasting 1-3 sec

Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management 2005. Chapter 6, Idiopathic Epileptic Seizures and Syndromes in Infancy., Image courtesy of Dr. Hartman

Severe myoclonic epilepsy of Infancy SMEI (Dravet Syndrome)

Etiology: 70-80% with SCN1A mutations; similar phenotype with PCDH19 in females; family history in 20-50%

Onset: Usually in the 1st year in a developmental normal child

Clinical: (Prolonged) Hemiconvulsive seizures (alternating sides) in the 1st year often with fever → afebrile and febrile myoclonic, focal and atypical absence seizures emerge b/w 1-3yo w GTCs → intractable epilepsy; prone to status epilepticus ("obtundation status")

Sensitive to elevated temperature (fever, immersion in hot water, intense physical activity), photosensitive

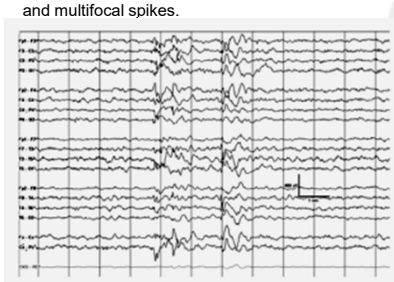
**Association with SUDEP

Treatment: VPA+CLB+stiripentol, LEV, TPM, KD, bromides, cannabidiol; Avoid Na channel blockers; seizures pharmacoresistant

Course: Development normal early → deteriorates 2yo w pyramidal signs ataxia → ID, crouch gait, myoclonic seizures resolve,

Dravet Syndrome

EEG: Background slowing, generalized spikes, polyspikes, spike-waves and multifocal spikes.



Korff et al, 2007. Image courtesy of Dr. Hartman

Outline

Neonatal period
Infancy
Childhood
Adolescence
Adulthood

Genetic epilepsy with febrile seizure plus (GEFS+)

Etiology: usually missense type mutations in SCN1A, SCN1B , GABRG2, and SCN2A genes, AD with incomplete penetrance.

Onset: 1st month to childhood (usually 6mos-6yrs), M=F

Clinical: Range from simple febrile seizures to mixed febrile and afebrile seizures such as focal seizures, generalized seizures, absences, myoclonic jerks, tonic seizures or rarely myoclonic atonic seizures.

Seizures may be prolonged or occur in clusters

Treatment: No prophylaxis for febrile seizures alone, rescue for prolonged or clusters. VPA, TPM, CLB Avoid sodium channel blockers

Course: Usually pharmacoresponsive epilepsy, remits by adolescence. Typically normal development

Benign Epilepsy with centro-temporal spikes (BECTS or Rolandic Epilepsy)

Etiology: GRIN2A, ELP4, BDNF, KCNQ2, KCNQ3, DEPDC5, RBFOX1/3, and GABAA-R, possibly others

Most common focal epilepsy in childhood (25%) M>F

Onset: 2-14 yrs (peak: 7-10 yrs) in developmental normal

Clinical: Infrequent (20% single seizure), focal facial or motor seizures with associated somatosensory symptoms; Unilateral or bilateral, usually shortly after falling asleep; GTC 25%

Sensory: tongue, lips, gums, cheek paresthesias; Motor: tongue, larynx, pharynx (difficulty with speech, gurgling, drooling and hypersialorrhea); preserved awareness 60%,

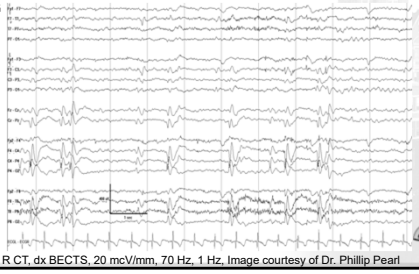
Treatment: LEV, CBZ, OXC for very frequent or disabling seizures

Course: Typically (99.8%) outgrow seizures by 16yo; in few, other types of seizures develop after 18yo (recurrence 1-2%; 7% atypical evolution)

Deficits in in language, auditory-verbal, visuo-spatial, attention, learning, behavior and executive functions MAY be seen

BECTS

High-voltage sharp or blunt spikes involving centrotemporal region (30%) with potentiation during drowsy and non-REM sleep. Unilateral 60%. Tangential electrical dipole (50%) with anterior positivity and centrotemporal negativity
**asymptomatic siblings may have characteristic centrotemporal spikes of BECTS on EEG



6 yo boy with R CT, dx BECTS, 20 mcV/mm, 70 Hz, 1 Hz, Image courtesy of Dr. Phillip Pearl

Early childhood onset occipital epilepsy (Panayiotopoulos syndrome)

Etiology: unknown; family history of seizures in 7% to 32%; Neuroimaging is normal

Peak onset: 3-6 yrs (range 1-14yrs), F>M

Clinical: Behavioral agitation, then headache, **autonomic symptoms** (**vomiting (60-80%)**, pallor, cyanosis, incontinence, pupillary changes, ictal syncope), eye deviation; tend to be prolonged (5min-hrs) with preserved consciousness, onset usually during sleep (2/3)

Visual symptoms (blindness, illusions, complex hallucinations)

Also motor (hemiclonic or GTC) seizures

EEG: sleep potentiated spikes, shifting and multifocal, occipital in half; no correlation between ictal discharges and clinical symptoms

Treatment:, Intermittent benzodiazepine (infrequent seizures); for frequent seizures OXC or LEV

Course: Prognosis good, seizures stop after one to two years in most

Panayiotopoulos Syndrome

EEG: Occipital spikes (increased in sleep) but spikes can be seen anywhere

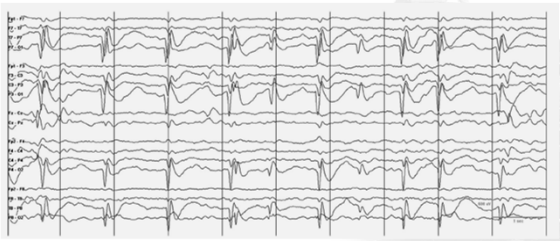


Fig: Sanchez Fernandez & Loddenkemper, J Clin Neurophys 2012;29:425

Late Childhood onset occipital epilepsy (Gastaut)

Etiology: unknown

Peak onset: 8-11 yrs

Clinical: Brief seizures with elementary visual auras (objects, shapes, colors, flashing), eye deviation; may progress to partial vision loss (50%) or eye pain; complex visual symptoms such as faces, figures, micropsia, pallinopsia, metamorphopsia in 10%; focal-onset seizures (rarely, generalize); Daytime occurrence in all but 1/3 in sleep also, Post-ictal headache 50%

EEG: bilateral occipital spike-and-wave discharges precipitated by eye closure and attenuated by eye opening ("fixation off phenomenon")

** if not present→suspicion for symptomatic occipital epilepsy**

Treatment: Seizures more frequent, CBZ, LEV

Outcome: >50% tend to remit 2-7 yrs after onset, few cases may continue to have seizures in adulthood

Continuous spikes and wave during sleep (CSWS)

Etiology: unknown, recently GRIN2A

Peak age of onset: 5-9 yrs (seizures start 3-5 yrs)

Clinical:

1. Slow spike wave activity occupying >85% of NREM sleep (Electrical status epilepticus of sleep or ESES)
2. Heterogeneous seizure types: focal, atypical absence, GTC
3. Neuropsychological regression characterized by decreasing IQ, language regression, hyperactivity, autism, and behavioral problems

Treatment: VPA, LEV, high dose DZP, steroids, possibly IVIG (target seizures and EEG); Avoid PHT, CBZ, PB, OXC

Course: Seizures and ESES remit by adolescence, neurocognitive sequelae persist (<50% normal intelligence); better if later age of onset and shorter time to treatment

CSWS

EEG shows high amplitude 1.5-2.5Hz spike and wave discharges predominantly bitemporal, at times multifocal or generalized occupying >85% of record in NREM sleep.

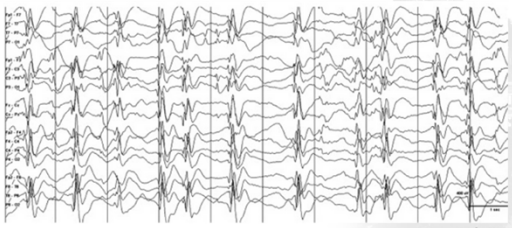


Fig: Sanchez-Fernandez et al., Pediatr Neurol 2012;47:390, image courtesy of Dr. Hartman

Landau Kleffner syndrome

Etiology: Imaging typically normal; PET unilateral or bilateral hypo or hyper metabolism.

Onset: 3-7 yrs (range 2-14yrs), M:F = 2:1

Clinical: Language regression (loss of previously acquired language skills); "verbal auditory agnosia" - then expressive aphasia;

70-80% have seizures usually focal or GTCs, atypical absence

Behavioral problems, irritability and poor attention span, are common

Treatment: VPA/ VPA+CLB, Prednisolone 2mg/kg/day x 1month, high dose DZP 1mg/kg max 40mg, foll by 0.5mg/kg x1-3mos

IVIG, ESM, Rufinamide, Felbamate, avoid PHT/CBZ/PB/OXC. Can try KD. Epilepsy surgery for lesional

Course: Language function problematic; seizures usually remit by 15 years

Lennox Gastaut Syndrome (LGS)

Etiology: Structural malformations, vascular (incl. HIE), inborn errors of metabolism, genetic syndromes, intrauterine infections, meningitis, encephalitis, neurophakomatoses, trauma (incl. NAT)

Infantile spasms precedes LGS in 10-25%; ~40% h/o DD Onset: 1-8 years of age (peak 3-5)

Clinical: Triad of ID, slow spike wave on EEG (plus paroxysmal fast activity during sleep) and multiple seizure types: Axial **tonic,** atypical absence, atonic; focal, myoclonic and GTCs less common

50-90% NCSE

Treatment: VPA, LMT; TPM, LEV, Felbamate, Rufinamide (atonic), CLB, (cannabidiol), amantadine, imipramine, KD, Callosotomy, Vagus nerve stimulator,

Course: "Catastrophic" ; ID, worse if onset<3yo, history of IS, recurrent SE

Lennox Gastaut Syndrome (LGS)

Periods of cognitive regression

Changes in seizure patterns

- Tonic seizures – debated
- Drop attacks
- Atypical absences

Predictors of seizure outcome

- Early dysphagia
- Developmental regression
- Predominance of atypical absences
- Persistently epileptiform EEGs

Lennox Gastaut

EEG: Slow background, with generalized slow spike / poly spike waves 1.5-2.5 Hz; Sleep activates bursts of fast activity (10 Hz) and attenuates paroxysmal activity

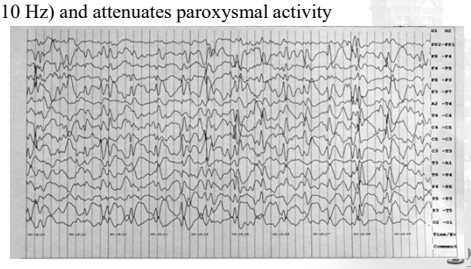


Image courtesy of Dr. P Singhi

Myoclonic-atonic epilepsy (Doose syndrome)

Etiology: Genetics: SCN1A/B, GABRG2, SLC6A1

Epilepsy in 37% of first and second degree relatives

Onset typically between 18mos-5yo (peak 2-4yo), M>F in a previously developmentally normal

24 % onset in first year of life followed by a latent period

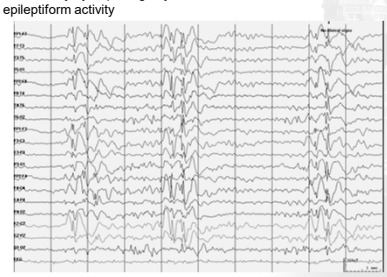
Clinical: Explosive onset. Brief and frequent large-amplitude symmetric jerks of the arms, legs, neck, and shoulders, result in head drop and upper limb flexion or abduction. Followed by loss of muscle tone and a fall.; **non-convulsive or myoclonic status epilepticus 40%

Treatment: VPA, ESM, CLB, TPM, LTG (may exacerbate myoclonus), Rufinamide (drop seizures), LEV, **KD**; avoid CBZ, Phenytoin, Vigabatrin

Course: 75 % spontaneous remission with 50% normal cognitive ability. Cognitive impairment associated with earlier onset, later myoclonic seizures and poor response to treatment.

Doose syndrome

EEG normal at onset → recurrent paroxysms of generalized spike waves, photosensitivity, 4-7 Hz theta rhythms with parietal accentuation and occipital 4 Hz rhythms blocked by eye opening. Myoclonic events are associated with bursts of 2 Hz to 4 Hz epileptiform activity



Kelley & Kossoff, Dev Med Child Neurol 2010;52:988 image courtesy of Dr. Hartman

Febrile Infection Related Epilepsy Syndrome (FIRES)

Etiology: ? immune-mediated disorder

Clinical: Explosive onset of seizures with fever mimicking an encephalitis-like illness followed by cognitive deterioration and continuing refractory epilepsy. Focal seizures at onset with secondary generalization, at times with facial myoclonia.

Treatment: Treatment of SE with benzodiazepines followed by AEDs such as valproic acid, phenytoin, levetiracetam, lacosamide. Seizures in FIRES typically do not respond. Steroids, IVIG might be helpful. KD.

Outome: poor, 30% mortality, refractory epilepsy and cognitive deficits

Childhood Absence epilepsy

15% of childhood epilepsy; concordance in monozygotic twins 75%

Etiology: GABRG2, GABRA1, Ca channels, GLUT1/ SLC2A1 (10% of early onset CAE <4yo); Microdeletion: 15q13.3 in 1% of IGEs

Abnormality of thalamocortical interaction:

- abnormal oscillatory rhythms caused by abnormalities of the T type Ca channels or enhanced GABA-B activity

Onset: 80% 2.5 – 9 yrs (peak 5-7yo); F>M in developmentally normal

Clinical: Short (5-30sec) with abrupt impairment of consciousness, associated behavioral arrest, staring, eye fluttering, or automatisms; no post-ictal confusion, occur 10-100/day

Motor automatisms in 23% (Increased during HV or with prolonged seizures); 40-50% have GTCs, myoclonus

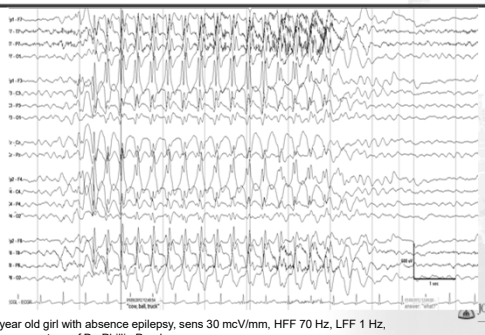
Childhood Absence epilepsy

EEG shows paroxysms of bilaterally synchronous and symmetric regular 3 Hz spike wave:

- Abrupt onset and offset
- SW slows from 3 Hz/4.5 Hz to 2 Hz/2.5 Hz.
- One hemisphere may show onset a few milliseconds before other
- Fragmentary spike or polyspike discharges confined to one region common in non-REM sleep.
- May use a 3-second cutoff to distinguish run vs ictal event.
- Runs of occipital intermittent rhythmic delta activity (OIRDA)

Pearl PL. Epilepsy Syndromes in Childhood. Continuum 2018

Childhood Absence epilepsy



8 year old girl with absence epilepsy, sens 30 mcV/mm, HFF 70 Hz, LFF 1 Hz, Image courtesy of Dr. Phillip Pearl

Childhood Absence epilepsy

Treatment: First line: ESM (53%), VPA (58%) then LTG (29%) Avoid CBZ, OXC, VGB, Tiagabine

Refractory: Zonisamide, combinations (ETX/VPA, VPA/LTG); for SLC2A1 related → ketogenic diet

Course: 90% remit if absence sz only; however GTCs may occur 5 -10 years after onset, infrequent and easily controlled

Favorable features incl early age at onset, early response to treatment

Unfavorable prognosis includes presence of GTCs, status epilepticus

Poor outcomes in academics, social, unplanned pregnancies, psychological/emotional difficulties, behavior problems, legal convictions, substance abuse

Accidental injuries are well reported during absence seizure

Other "absence" epilepsies

Eyelid myoclonia with Absences (Jeavons syndrome)

Often familial

Clinical: Brief absences always accompanied by myoclonia, but myoclonia can occur independent of absences; Prominent eye blinking and upward eye deviation, often triggered by eye closure., Retropulsion (of neck) may occur, photosensitive epilepsy

EEG: Diffuse 3 Hz to 6 Hz polyspike-and-wave complexes; may be precipitated by eye closure

Treatment: VPA, ESM, blue-colored or polarized lenses

Outcome: Photosensitivity and absences decline with age, myoclonias persist generalized tonic-clonic seizures may occur

Myoclonic Absence Epilepsy (Tassinari syndrome)

Etiology: Family history positive for epilepsy in 20%, abnormal imaging in ~15%, baseline cognitive impairment

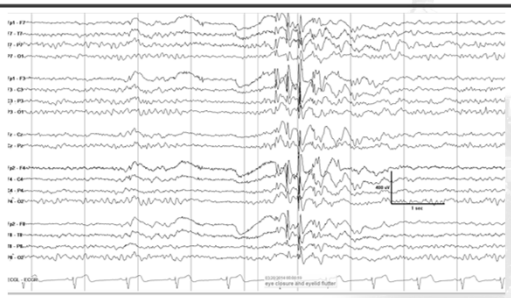
Onset: Peak 7yo, M:F = 2:1

Clinical: Prominent rhythmic myoclonic or clonic activity during absence seizures Absences (10-60 sec) with axial hypertonia (myoclonic absence); ~40% have other seizure types before MA; may see GTCS and drops; Myoclonic jerks may be severe and occur with spikes at 3 Hz frequency

Treatment: VPA, LMT

Outcome: tend to be pharmacoresistant

Jeavon's Syndrome



11 year old boy with Jeavons syndrome shows generalized spike-wave upon eye closure. Sens 30 mcV/mm, HFF 70 Hz, LFF 1 Hz, Image courtesy of Dr. Phillip Pearl

Outline

Neonatal period
Infancy
Childhood
Adolescence
Adulthood

Juvenile Absence Epilepsy (JAE)

Etiology: Genetics: EFHC1, CLCN2, others

Onset 7-17 years, peak 10-12 years

Clinical: GTCs (80% vs 40% CAE), often precede absences, usually on awakening; rare, longer absences with automatisms,speech arrest, and loss of awareness; absence status epilepticus, Myoclonic seizures in 15-20%

EEG: paroxysms of generalized 3 Hz to 4 Hz spike- or polyspike-and-wave activity

Treatment: VPA and LTG

Course: typically pharmacoresponsive syndrome (60%), although lifelong requirement for medication is expected

Juvenile Myoclonic Epilepsy (JME)
impulsive petit mal of Janz

Most common generalized epilepsy in adolescents

Etiology: Genetics: GABRG1, CLCN2, EFHC1 (myoclonin); family history of epilepsy in 40-50%

Onset typically 12-20 years; F:M=2:1

Clinical: Myoclonic jerks (>95%), Absences (18-38%), GTCs (80-95%); classic: upon awakening

Very photosensitive, common precipitants incl sleep deprivation, EtOH,

Facial or lingual and perioral jerks may be precipitated by talking.

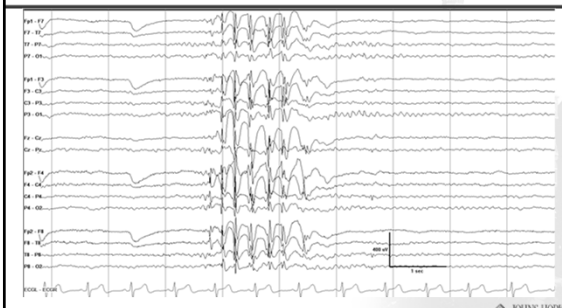
'Typical' JME (72%)

JME preceded by childhood absence (18%)

JME with copious absences (7%)

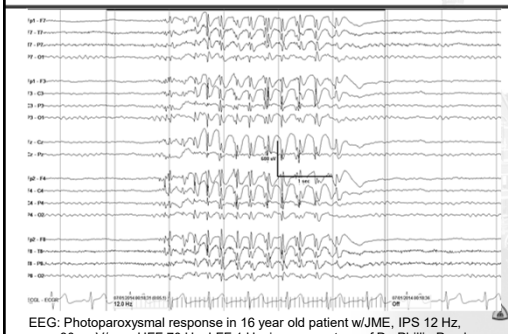
JME with astatic seizures (3%)

JME



16 year old boy with JME, sens 20 mcV/mm, HFF 70 Hz, LFF 1 Hz
EEG: 4-6 Hz generalized spike-and-wave, image courtesy of Dr. Phillip Pearl

JME



EEG: Photoparoxysmal response in 16 year old patient w/JME, IPS 12 Hz, sens 30 mcV/mm, HFF 70 Hz, LFF 1 Hz, image courtesy of Dr. Phillip Pearl

Juvenile Myoclonic Epilepsy

EEG: Myoclonic seizures w 10Hz -16 Hz polyspikes or >3Hz spike-and-wave activity

Treatment: VPA (teratogenicity and polycystic ovary syndrome), LTG (may exacerbate myoclonic seizures), TPM, ZNS, lifestyle modification including avoidance of triggers

Course: 16% pharmacoresistant; most patients easily treated but 80% relapse if drug stopped. Prognosis for complete resolution poor, associated with:

- presence of all 3 seizure semiologies,
- absences at onset,
- psychiatric illness (high rate, especially mood and anxiety disorders)

Canadian cohort: 17% seizure-free off meds

German cohort: 59% seizure-free x 5 yrs (28% off meds)

Epilepsy with Generalized Tonic Clonic seizures alone

Etiology: Familial: mutations in PRRT2 (same gene as paroxysmal kinesigenic dyskinesia), ASC-1 (amino acid transporter), SCN2A, SCN8A, probably others

Onset: 6-28 yrs (typically 16yrs)

Clinical: Subtypes

Epilepsy with GTCS on awakening (30%) , GTCS in sleep (50%)

EEG shows 3 Hz to 4 Hz generalized spike-and-slow-wave paroxysms.

Triggers: sleep deprivation, alcohol, photic stimulation, stress

Treatment: VPA, LTG, LEV

Outome: pharmacoresponsive, but a lifelong predisposition to seizures

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

Etiology: Genetics: nicotinic cholinergic receptors (CHRNA4, CHRNB2, CHRNA2 nicotinic acetylcholine receptor subunits), KCNT1, DEPDC5; AD with variable penetrance

Onset: 7-12 years.

Clinical: Brief (20-50 seconds) dystonic or tonic motor seizures manifest as arousal from sleep (NREM2) with hyperkinetic movement (thrashing, rolling, bizarre movements); may retain awareness, occur in clusters, may have aura

Vocalizations may be prominent

Interictal EEG often normal; Ictal EEG: bilateral frontal epileptiform activity

Treatment: oxcarbazepine, lamotrigine at night

Course: 1/3 remain pharmacoresistant

Familial temporal lobe epilepsies

FMTLE with febrile seizures

Etiology: rarely see SCN1A/B mutations

Clinical: Onset 1st/2nd decade

Benign FMTLE without hippocampal sclerosis or febrile seizures

Etiology: complex genetics

Clinical: Onset 1st/2nd decade, psychic and autonomic auras, mild clinical course

Mesial temporal lobe epilepsy with hippocampal sclerosis

Etiology: Atrophy and gliosis of the hippocampus as well as the amygdala, parahippocampal gyrus, and entorhinal cortex (unilateral or bilateral 60%)

Onset: 4-16 years

Clinical: 90% of children have complex febrile seizure then afebrile focal seizures with autonomic or abdominal auras, such as déjà vu or jamais vu, fear, rising epigastric sensations, or experiencing bad odors or tastes. Behavioral arrest with a vacant stare and impaired responsiveness 30 to 60 seconds. Automatisms lip smacking, swallowing, chewing, or picking or fidgety movements. Ipsilateral hand automatisms and postictal nose wiping.

Interictal EEG: intermittent focal and even rhythmic temporal slowing as well as anterior temporal spike or sharp discharges. Ictal EEG: nearly monomorphic rhythmic discharge in the 5 Hz to 9 Hz theta to alpha frequency range, maximally anterior temporal region.

Treatment: CBZ, LEV, epilepsy surgery for drug resistant

Course: Unlikely to respond to pharmacotherapy but seizure up to 90% of selected patients undergoing temporal lobectomy.

Autosomal dominant partial epilepsy with auditory features

"Familial lateral temporal lobe epilepsy"

Etiology: Genetics: LGI1 point mutation 30-50%, AD, variable penetrance, Normal imaging

Onset typically 1st/2nd decade but can be 4-50 yrs

Clinical: Simple auditory hallucinations (buzzing, clicking, ringing) .When lateralized, contralateral temporal lobe. Accompanying visual, autonomic, psychic, or olfactory phenomena

EEG: intermittent midtemporal slowing, rare temporal discharges

Outcome: tends to be pharmacoresponsive.

Progressive Myoclonus Epilepsies (PME)

Disorders manifesting as myoclonus (cortical and subcortical) along with cognitive regression, onset usually during adolescence

Etiology: Variable

Unvericht-Lundborg disease

Lafora disease

Neuronal ceroid lipofuscinosis

Myoclonic epilepsy with ragged red fibers (MERRF)

Also: other mitochondrial disorders (Alpers), sialidosis, dentatorubral-pallidoluysian atrophy, biotinidase deficiency, Huntington disease, pantothenate kinase-associated neurodegeneration, subacute sclerosing panencephalitis, Creutzfeld-Jacob disease, Gaucher,

Clinical: Myoclonus (epileptic and non epileptic), GTCs, absence seizures, ataxia (distinguishing feature)

Treatment: VPA, clonazepam, LEV, TPM, ZNS, CLB

Course: Cognitive decline

PME

NCL	Skin, rectal, conj bx; AR (several genes)	Infancy to adulthood	Progressive seizures, ataxia, myoclonus, dementia, visual loss	Death within 1-15 years
Sialidosis 1	Alpha neuraminidase, urine OLS	8-15 yrs	Decreased vision, cherry red spot, burning extremity pain, progressive myoclonus, mild cognitive impairment	Death in 3rd or 4th decade
Sialidosis 2		0-10 mos or adolescence	As above plus coarse features, dementia	
Unverricht-Lundborg	EPM (21q22.3)	6-18 yrs	Ataxia, mild cognitive, GTCs (presenting sign 50%), absences; EEG: generalized → VPA, CLB, LEV	Slow progress, stabilizes
Lafora	Axillary bx EPM2A/B, AR	6-19 yrs	GTCs and occipital sz, absence, astatic sz, rapid cognitive decline EEG: spikes, occ slow waves	Rapid to death 2-10yrs
MERRF	Muscle Bx, Mito testing	3- 65yrs	Focal or generalized seizures, deafness, myopathy, lactic acidosis, ataxia and optic atrophy EEG: bl SW, occ spikes, slowing	Variable

Wirrell, Continuum 2016 and Wyllie's Treatment of Epilepsy

PME: EEG

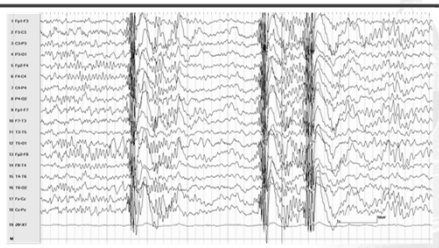


Figure 26: 15 year old boy with Lafora body disease presents with increased generalized seizures. Sleep EEG shows significant activation of epileptiform activity in sleep characterized by generalized polyspike and wave activity (as shown) and fragmentary spike discharges. Sensitivity 7uV/mm, TC 0.1s, HF 70Hz.

Image courtesy of Dr. Phillip Pearl

Multiple Choice Questions

1. 7 year old boy presents to your clinic with a short seizure characterized by left side facial contraction, drooling while watching a baseball game in the evening. The boy remembers the episode. You decide to obtain an EEG but stress on the need for:
   a. Photic Stimulation
   b. Sleep
   c. Hyperventilation
   d. Wakefulness
   d. Neuroimaging

Multiple Choice Questions

1. 7 year old healthy boy presents to your clinic with a short seizure characterized by left side facial contraction and drooling while watching a baseball game in the evening. The boy remembers the episode. You decide to obtain an EEG but stress on the need for:
   a. Photic Stimulation
   b. Sleep
   c. Hyperventilation
   d. Wakefulness
   d. Neuroimaging

The age and description of seizures is suggestive of BECTS. EEG classically shows spikes in the central or centrotemporal regions that are potentiated or activated in drowsiness and sleep. Therefore, EEG is highest yield if sleep is captured. Neuroimaging is typically not needed once the diagnosis of BECTS is made by EEG and clinical symptoms.

Multiple Choice Questions

2. A 6 year old girl presents to your office with staring spells. You do hyperventilation and elicit a classic spell. In counseling the family about potential treatment options, what is your best choice:
   a. Ethosuximide has best efficacy and tolerability
   b. Ethosuximide and Valproate are equally effective and tolerable
   c. Lamotrigine has best efficacy
   d. Valproate is first line with best efficacy and tolerability
   e. Lamotrigine is the best choice because risk of generalized tonic clonic seizures is high

Multiple Choice Questions

2. A 6 year old girl presents to your office with staring spells. You do hyperventilation and elicit a classic spell. In counseling the family about potential treatment options, what is your best choice:
   a. Ethosuximide has best efficacy and tolerability
   b. Ethosuximide and Valproate are equally effective and tolerable
   c. Lamotrigine has best efficacy
   d. Valproate is first line with best efficacy and tolerability
   e. Lamotrigine is the best choice because risk of generalized tonic clonic seizures is high

A double blinded RCT comparing ESM, VPA and LTG in CAE found that ESM provided the best combination of seizure control and fewest side effects making it the optimal initial therapy. While ESM and VPA had comparable seizure control, side effects were more significant with VPA. LTG was not as effective in seizure control as either ESM or VPA. Risk of GTCs is lower in CAE (405) as compared to JAE (60%).

Multiple Choice Questions

3. A 1 year old infant presents with an afebrile generalized tonic clonic seizure. On history, you find that he had febrile seizures starting at age 6 months, consisting of hemiconvulsive movements. He is developmentally appropriate. Which of the following is the best choice:
   a. Siezures are benign and will likely resolve without further intervention
   b. He needs follow up and genetic testing for mutations in the sodium channel
   c. He is not at risk of status epilepticus
   d. He should not receive vaccines
   e. Since he is developmentally appropriate, he will likely have easy to control seizures.

Multiple Choice Questions

3. A 1 year old infant presents with an afebrile generalized tonic clonic seizure. On history, you find that he had febrile seizures starting at age 6 months, consisting of hemiconvulsive movements. He is developmentally appropriate. Which of the following is the best choice:

a. Seizures are benign and will likely resolve without further intervention

b. He needs follow up and genetic testing for mutations in the sodium channel

c. He is not at risk of status epilepticus

d. He should not receive vaccines

e. Since he is developmentally appropriate, he will likely have easy to control seizures

The case description should raise caution for SCN1A related epilepsy, particularly Dravet syndrome. It is important to note that infants are often developmentally normal initially but after onset of GTCs and myoclonic seizures, this deteriorates including pyramidal signs and ataxia. Seizures are difficult to control medically. While hyperthermia can provoke seizures, vaccines are not contraindicated.

Multiple Choice Questions

4. Which of the following is true about CSWS?

a. It can be seen with migrational disorders, shunted hydrocephalus and thalamic lesions

b. It is most commonly seen in children with sodium channel mutations

c. Treatment is aimed at seizure control alone

d. Trileptal is an appropriate choice of AED

e. There are usually no neuropsychological sequalae

Multiple Choice Questions

4. Which of the following is true about CSWS?

a. It can be seen with migrational disorders, shunted hydrocephalus and thalamic lesions

b. It is most commonly seen in children with sodium channel mutations

c. Treatment is aimed at seizure control alone

d. Trileptal is an appropriate choice of AED

e. There are usually no neuropsychological sequalae

CSWS is an electroclincial syndrome characterized by neuropsychological regression: decreasing IQ, language regression, hyperactivity, autism, and behavioral problems. EEG shows ESES in NREM sleep. CSWS is sometimes associated with identifiable pathology including polymicrogyria, shunted hydrocephalus. Treatment options include VPA, LEV, high dose DZP, steroids and IVIG (target seizures and EEG). Avoid PHT, CBZ, PB, OXC. Seizures and ESES remit by adolescence, neurocognitive sequelae persist (<50% normal intelligence);

Multiple Choice Questions

5. Which of the following is true about familial lateral temporal lobe epilepsyh with auditory features?

a. It is autosomal recessive

b. Seizures usually start in infancy

c. Hippocampal sclerosis is the pathological finding in majority of cases

d. It is related to mutations in the LGI1 gene

e. It is usually medical refractory and surgery is curative

Multiple Choice Questions

5. Which of the following is true about familial lateral temporal lobe epilepsy with auditory features?

a. It is autosomal recessive

b. Seizures usually start in infancy

c. Hippocampal sclerosis is the pathological finding in majority of cases

d. It is related to mutations in the LGI1 gene

e. It is usually medical refractory

Autosomal dominant partial epilepsy with auditory features is characterized by Simple auditory hallucinations (buzzing, clicking, ringing) with onset typically in the first or second decade of life. Point mutations in LGI1 are found in 30-50%, and it is inherited in an AD manner with variable penetrance. Imaging is usually normal. Seizures tend to be pharmacoresponsive.

References

1. Pearl PL. Epilepsy Syndromes in Childhood. Continuum (Minneap Minn). 2018 02; 24(1, Child Neurology):186-209
2. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676-85
3. Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome; its overview referring to our 16 cases. Brain Dev. 2002;24(1):13–23.
4. Ohtahara S, Yamatogi Y. Ohtahara syndrome: with special reference to its developmental aspects for differentiation from early myoclonic encephalopathy. Epilepsy Res 2006;70(suppl 1): S58–S67.
5. Pavone P et al. Ohtahara syndrome with emphasis on recent genetic discovery. Brain Dev (2011)
6. Saitsu H, Kato M, Tohyama J, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet. 2008;40(6):782–8.
7. Archer HL, Evans J, Osborne J, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. J Med Genet. 2006;43(9):729–34.
8. Claes L, Del-Favero J, Ceulemans B, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001;68(6):1327–32.
9. Depienne C, Bouteiller D, Poirier K, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. PLoS Genet. 2009;5(2):e100038
10. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011–2020
11. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. The Cochrane database of systematic reviews. 2013;2:CD003277
12. Arzimanoglou A, French J, Blume WT, et al. Lennox–Gastaut syndrome: a consensus approach on diagnosis, assessment, man-agement, and trial methodology. Lancet Neurol. 2009;8(1):82–93

References

13. Hughes JR. A review of the relationships between Landau–Kleffner syndrome, electrical status epilepticus during sleep, and continuous spike-waves during sleep. Epilepsy Behav. 2011; 20(2):247–53.
14. Trivisano M, Specchio N, Cappelletti S, et al. Myoclonic astatic epilepsy: an age-dependent epileptic syndrome with favorable seizure outcome but variable cognitive evolution. Epilepsy Res. 2011;97(1–2):133–41.
15. Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology.Epilepsia 2009;50
16. Kramer U, Chi CS, van Baalen A, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and out-come: a multicenter study on 77 children. Epilepsia. 2011; 52(11):1956–65.
17. Stockler S, Plecko B, van Karnebeek C, et al. Pyridoxine depen-dent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab. 2011;104(1–2):48–60.
18. Glauser TA et al, Ethosuximide, Valproic acid and lamotrigine in Childhood Absence Epilepsy. NEJM 2010;362:790-9.
19. Holmes GL et al, Absence seizures in Children: clinical and EEG features. Ann Neurol 1987;21:268-273.
20. Byrne S et al, Refractory absence epilepsy associate with GLUT-1 DS. Epilepsia 2011
21. von Stulpnagel C, Coppola G, Kluger G, et al. First long-term experience with the orphan drug rufinamide in children with myoclonic-astatic epilepsy (Doose syndrome). Eur J Paediatr Neurol. 2012;16(5):459–63.
22. Glauser T, Kluger G, Arroyo S, et al. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology. 2008;70(21):1950–8.
23. Glauser TA. Topiramate in the catastrophic epilepsies of child-hood. J Child Neurol. 2000;15(Suppl. 1):S14–21.
24. Camfield CS, Berg A, Stephani U, Wirrell EC.Transition issues for benign epilepsy with centrotemporal spikes, nonlesional focal epilepsy in otherwise normal children, childhood absence epilepsy, and juvenile myoclonic epilepsy. Epilepsia 2014;55

References

25. Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology 2013: 81:2128-2133
26. Betul Baykan, Iris E. Martínez-Juárez, et al. Lifetime prognosis of juvenile myoclonic epilepsy, Epilepsy & Behavior,Volume 28, Supplement 1,2013, S18-S24
27. Combi R, Dalprà L, Tenchini ML, Ferini-Strambi L. Autosomal dominant nocturnal frontal lobe epilepsy—a critical overview. J Neurol 2004;251(8): 923–934.
28. Shahwan a et al. Progressive Myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurol 2005; 4:239-48
29. Pearl PL. Amenable Treatable Severe Pediatric Epilepsies. Semin PediatrNeurol 2016 23:158-166
30. Sanchez Fernandez & Loddenkemper. Pediatric Focal Epilepsy Syndromes, J Clin Neurophys 2012;29:425,

Less Age-Specific Relationship

Samata Singhi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

LESS AGE-SPECIFIC RELATIONSHIP

Samata Singhi, MD, MSc
Director, Epilepsy Monitoring Unit
Kennedy Krieger Institute
Assistant Professor, Neurology and Pediatrics
Johns Hopkins University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Outline

Reflex epilepsies
Gelastic seizures with hypothalamic hamartoma
Rasmussen syndrome
Hemiconvulsion–hemiplegia–epilepsy
Familial focal epilepsy with variable foci
MELAS
Angelman Syndrome

Epilepsy with reflex seizures

An epilepsy characterized by specific mode of seizure precipitation; predominantly or exclusively triggered seizures.

Etiology: may be lesional but often AD with incomplete penetrance

Seizures induced by visual triggers:

- Recurrent visually induced seizures (incl TV, flickering light, strobe lights, reflection of sunlight in water/ snow); Seizures are GTC in 84%, absence 6%, myoclonic 2.5%; females overrepresented; Rx = valproate
- Seizures induced by patterns (stripes, usually need binocular view); Rx eyepatch
- Seizures induced by television and other screens (Pokemon)
- Self induced (wave hand → pleasure/ relief, patients unwilling to stop); Primarily myoclonic seizures, Rx VPA

Epilepsy with reflex seizures

Seizures induced by complex nonvisual activity

- Thinking and concentration/ manipulation of spatial activity (chess, cards, complex decisions)
- Praxis induced seizures
- Seizures induced by reading; 12-15yrs; jaw jerks/ clicks → GTC if reading continues; Rx valproate/ benzodiazepine or LTG
- Language induced epilepsy (speaking/ reading/writing/ typing) → jaw jerks
- Seizures induced by music (specific per patient) or ringing/ whirring (phone/ vacuum); adulthood often in the context of symptomatic focal epilepsy (R temporal predominance on functional imaging).

Epilepsy with reflex seizures

Seizures induced by complex nonvisual activity

- Seizures induced by eating (India/ Lanka): almost always related to symptomatic focal epilepsy (frontal, anterior temporal and parietoinsular region implicated)
- Proprioceptive induced seizures (teeth or hair brushing, walking)
- Touch evoked seizures
- Seizures induced by hot water (Japan, India): Boys around 13 yrs, focal with altered awareness or GTCs

Gelastic seizures-Hypothalamic Hamartoma

Note: HH can occur without gelastic seizures and vice versa

Etiology: Hypothalamic Hamartoma (epileptogenic); sporadic but may be associated with Pallister Hall syndrome

Clinical: Gelastic seizures usually start at 11mos but not identified until later; <30s, Laughter like vocalization combined with facial contraction in the form of smile; autonomic features and epigastric sensation can be present, Mirth is not frequent, coexist dacrystic sz

75% typically progress to multiple sz types (focal 50%, GTC 40%) by age10; incl IS.

Intellectual disability, ODD, ADHD,

EEG: ictal recordings may show no change or nonlocalizing (flattening of background or generalized paroxysmal fast activity or absence of interictal spikes).

Gelastic seizures-Hypothalamic Hamartoma

Treatment: Gelastic seizures do not respond to AEDs. Zonisamide anecdotal evidence. Surgical resection of hamartoma when development at risk or GTCs.

Timing is key: risks of surgery if seizures not disabling vs. secondary epileptogenesis

Outcome: Seizure freedom 86% - 93% at 9mos-1yr using laser ablation; 50% with other surgical techniques;

Cognitive deficits visual and verbal learning and memory ; ADHD (75%), ODD (83.3%), conduct disorder and learning problems (33% each), mood and anxiety problems (17%)

Rasmussen Syndrome

Rare, chronic inflammatory CNS disorder characterized by frequent and severe seizures, progressive hemiplegia and neurological deterioration, and inflammation.

Etiology: immune mediated, T cell dominated encephalitis w/activated microglial cells and reactive astrogliosis; perivascular lymphocyte cuffing (?viral vs viral mediated immune vs primary autoimmune)

MRI: White matter increased signal →Unihemispheric focal cortical atrophy

Onset: 3-14 years, 80% have seizures by age 10.

Clinical: SE presenting symptom in 20%. At onset focal seizures, epilepsia partialis continua (56%), hemiclonic or GTC seizures → progressive hemiparesis, hemianopia, hemi-hypoasthesia, cognitive decline, language deficits and refractory epilepsy.

Rasmussen's Encephalitis/ Syndrome

3 stages:

- Prodromal: motor seizures
- Acute: EPC, frequent seizures, progressive hemiplegia, neurological deterioration (intellectual 85%, visual 49%, sensory 29%, dysarthria 23%)
- Residual: seizures, end stage hemispheric failure

Variants: bilateral (children<2yo), late onset (less severe), basal ganglia involvement (chorea/ athetosis), double pathology (FCD, Glu3 Ab, Parry Romberg, SLE, narcolepsy)

EEG: Unihemispheric slowing and deterioration of background + epileptiform activity (multifocal but lateralized) & Unilateral seizure onset

Rasmussen's Encephalitis/ Syndrome

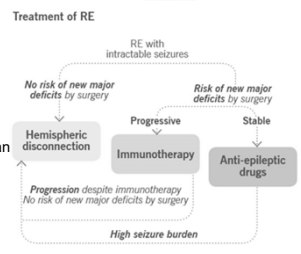
Treatment: conventional ASMs

Hemispherectomy (best)

- 71% seizure free at CCF, 91% at JHH

Immune modulators (case reports)

- Interferon intraventricular – 2/2 improvement
- Corticosteroids + IVIG/PLEX or cytoxan = 11/15 time limited improvement
- IVIG: initial benefit
- Cytoxan no effect
- Tacrolimus PO w superior neuro outcome but no better sz outcome
- Rituximab
- TMS



Treatment algorithm from the Cleveland Clinic
https://consultqd.clevelandclinic.org/immune-modulatory-therapy-can-be-right-choice-when-surgery-is-not-indicated-in-rasmussen-epilepsy/

Hemiconvulsion-hemiplegia syndrome

Etiology: SCN1A and CACNA1A mutations; inflammation as well as hyperthermia (follows CNS infection) Acute imaging: edema involved hemisphere, abnormal signal subcortical white matter and diffusion restriction in ipsilateral basal ganglia, thalamus, and internal capsule.

Onset in infancy or childhood, usually <4yo, M=F

Clinical: sudden onset hemi-convulsions following a febrile illness → prolonged unilateral clonic seizures (>24hrs) → ipsilateral hemiplegia, progressive cerebral hemiatrophy

EEG: bilateral acutely →background activity improves contralateral hemisphere. Ictal EEGs lateralize to involved side.

Course: Prognosis variable, from resolution of hemiplegia and good intellectual outcome to pharmacoresistant epilepsy and permanent hemiparesis. Focal sz in 80%, learning difficulties. Hemispherectomy may be required for pharmacoresistant.

Familial focal epilepsy with variable foci

- AD form of epilepsy characterized by focal seizures arising from different cortical regions in different family members
- Etiology: mutations of the (mTOR) pathway inhibitor gene DEPDC5; NPRL2/3 (GATOR1 complex); AD w incomplete penetrance and phenotypic variability within families; FCDs may be present
- Onset from childhood to early adulthood (1st or 2nd decades),
- Clinical: daytime seizures are characteristic manifested by an initial, albeit nonspecific, aura, followed by motoric activity as well as automatisms and sometimes secondary generalization; mostly temporal or frontal onset
- Course: Most will have normal development, although some with ID and autism

Mitochondrial Encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS)

- Etiology: Mitochondrial tRNA-Leu point mutation (80%)
- Clinical: Stroke-like episodes, migraine headaches, sensorineural hearing loss, epilepsy, lactic acidosis, exercise intolerance, muscle weakness, peripheral neuropathy, recurrent vomiting, and dementia, short stature.
- Seizures initially with metabolic disarray then later due to structural lesions; focal seizures and status epilepticus (EPC), myoclonic
- EEG: multifocal discharges (41%), followed by focal (39%) and generalized (39%) discharges
- Treatment: IV L-Arginine to prevent strokes

MELAS

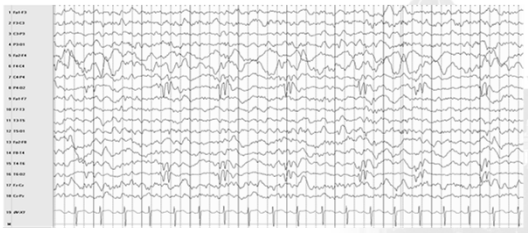


Figure 28: 14-year-old girl with a history of MELAS presents with epilepsia partialis continuans manifest by clonic activity of the left fingers, wrist and arm. EEG is most notable for right hemispheric polymorphic slowing and PLEDS maximally involving the right occipital lobe. Sensitivity 7uV/mm, TC 0.1s, HF 70Hz.

Image courtesy of Dr. Phillip Pearl

MELAS

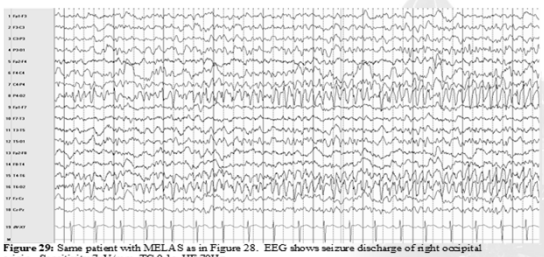


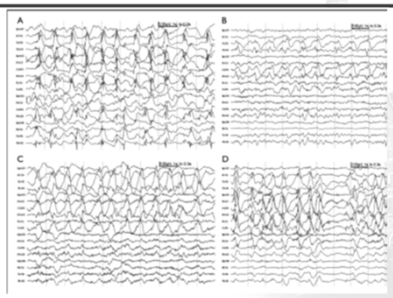
Figure 29: Same patient with MELAS as in Figure 28. EEG shows seizure discharge of right occipital origin. Sensitivity 7uV/mm, TC 0.1s, HF 70Hz.

Image courtesy of Dr. Phillip Pearl

Alpers disease

- Etiology: Mutations in the gene POLG1 (nuclear gene for DNA polymerase gamma) which facilitates mitochondrial DNA replication, AR
- Clinical: Intractable seizures, developmental arrest, liver dysfunction
- Rapidly progressive encephalopathy, causing intractable epilepsy and diffuse neuronal degeneration. Focal and myoclonic seizures most common
- Treatment: Supportive, Avoid VPA (fulminant hepatic failure)
- Outcome: Poor, death within first decade of life

Alpers' disease



RHADS: Rhythmic High-Amplitude Delta with (Poly)Spikes, usually unilateral and occipital.

Wolf et al: Status epilepticus in children with Alpers' disease caused by POLG1 mutations: EEG and MRI features. Epilepsia 2009; 50:1596-1607.

Angelman Syndrome

Etiology: loss of function of the maternally inherited UBE3A gene that codes for the ubiquitin protein ligase: maternal deletion of chromosome 15q11.2-13.1 (68–75%), mutations in the UBE3A gene (UBE3A: 8–11%), uniparental disomy (UPD: 2–7%)

Clinical: Intellectual disability, ataxia, hypotonia, inappropriate laughter, absence of speech, microcephaly

Epilepsy in 85%, within first 3 years of life; Myoclonic seizures most frequent at onset, atonic seizures, GTCs and atypical absences

Treatment: VPA alone or w CZP. ESM, LEV, LTG, CLB. **KD/ LGI**.

Angelman Syndrome

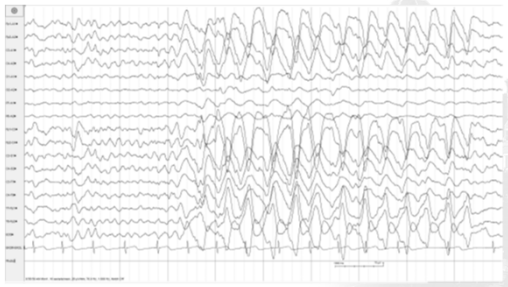


Image courtesy of Dr. Phillip Pearl

References

1. Pearl PL. Epilepsy Syndromes in Childhood. Continuum (Minneap Minn). 2018 02; 24(1, Child Neurology):186-209
2. Taliano D,Striano P, Russo E,et al.Genetics of reflex seizures and epilepsies in humans and animals. Epilepsy Res 2016;121:47–54.
3. Wilfong A and Curry D. Hypothalamic hamartomas: optimal approach to clinical evaluation and diagnosis. Epilepsia, 54(Suppl. 9):109–114, 2013
4. Curry D, Raskin J, Ali I et al. MR-guided laser ablation for treatment of hypothalamic hamartomas. Epilepsy Research; Volume 142, May 2018, Pages 131-134
5. Bein CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain 2005; 128; 454-71
6. Yu JY and Phillip PL (2013) Metabolic Causes of Epileptic Encephalopathy. Epilepsy Res Treat. 2013: 124934
7. Shaaya EA, Grocott OR, Laing O, et al. (2016) Seizure treatment in Angelman syndrome: A case series from the Angelman Syndrome Clinic at Massachusetts General Hospital. Epilepsy Behav. 60:138-141.

Multiple choice questions

1. Which of the following genes is associated with familial focal epilepsy with variable foci
   a. SCN1A
   b. DEPDC5
   c. SCN8A
   d. CACNA1A
   e. SLC2A1

Multiple choice questions

1. Which of the following genes is associated with familial focal epilepsy with variable foci
   a. SCN1A
   b. DEPDC5
   c. SCN8A
   d. CACNA1A
   e. SLC2A1

Most cases of FFEVF are caused by mutations in the DEPDC5 gene with fewer cases caused by mutations in NPRL2 or NPRL3 genes. These three genes provide instructions for making protein complex GATOR1 (regulates cell proliferation).

Multiple choice questions

2. Pallister Hall syndrome is associated with which of the following
   a. Hemiconvulsion hemiplegia syndrome
   b. Familial focal epilepsy with variable foci
   c. Hypothalamic hamartoma
   d. Autosomal dominant temporal lobe epilepsy
   e. None of the above

Multiple choice questions

2. Pallister Hall syndrome is associated with which of the following
   a. Hemiconvulsion hemiplegia syndrome
   b. Familial focal epilepsy with variable foci
   c. Hypothalamic hamartoma
   d. Autosomal dominant temporal lobe epilepsy
   e. None of the above

Pallister Hall syndrome is a pleiotropic autosomal dominant disorder comprising of HH, pituitary dysfunction, central polydactyly, and visceral malformations. Caused by mutations of the GLI3 gene

Multiple choice questions

3. Which of the following is false about Rasmussen's encephalitis
   a. EPC may be a presenting symptom
   b. Corticosteroids, intravenous immunoglobulin and other immunomodulatory treatments have shown limited success
   c. Seizures are typically responsive to conventional AEDs
   d. MRI shows progressive unihemispheric focal cortical atrophy
   e. Functional hemispherotomy or hemispherectomy may reduce frequency of seizures and halt progression

Multiple choice questions

3. Which of the following is false about Rasmussen's encephalitis/ syndrome
   a. EPC may be a presenting symptom
   b. Corticosteroids, intravenous immunoglobulin and other immunomodulatory treatments have shown limited success
   c. Seizures are typically responsive to conventional AEDs
   d. MRI shows progressive unihemispheric focal cortical atrophy
   e. Functional hemispherotomy or hemispherectomy may reduce frequency of seizures and halt progression

Typically seizures in Rasmussen syndrome become refractory to anti seizure medications, and most patients benefit from disconnection of affected hemisphere.

Multiple choice questions

4. Which of the following AEDs should be avoided in Alpers syndrome
   a. Levetiracetam
   b. Oxcarbazepine
   c. Clobazam
   d. Valproate
   e. None of the above

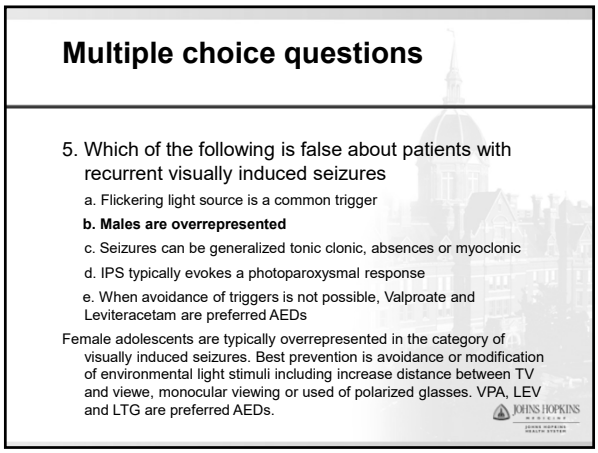
Multiple choice questions

4. Which of the following AEDs should be avoided in Alpers disease
   a. Levetiracetam
   b. Zonisamide
   c. Clobazam
   d. Valproate
   e. None of the above

Valproate has been associated with fulminant hepatic failure in Alpers disease and should be avoided in mitochondrial disease

Multiple choice questions

5. Which of the following is false about patients with recurrent visually induced seizures
   a. Flickering light source is a common trigger
   b. Males are overrepresented
   c. Seizures can be generalized tonic clonic, absences or myoclonic
   d. IPS typically evokes a photoparoxysmal response
   e. When avoidance of triggers is not possible, Valproate and Keppra are AEDs are typically used



Epilepsies Attributed to and Organized by Structural-Metabolic Causes

Amar B. Bhatt, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

EPILEPSIES ATTRIBUTED TO AND ORGANIZED BY STRUCTURAL-METABOLIC CAUSES

Amar B. Bhatt, MD
Assistant Professor of Neurology, Epilepsy Section
Rush University Medical Center
Program Director, Neurology Residency

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None
- Thanks to Dr. Inati for slides/images

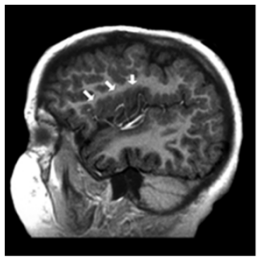
Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

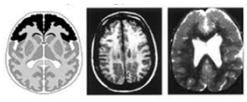
Malformations of Cortical Development (MCDs)

- Cortical neurons and glia originate from germinal matrix
  - must develop AND migrate
  - Any disruption in development = MCD (abnormal neuronal and glial proliferation or apoptosis, neuronal migration, or cortical organization)
- normal cells in the wrong place OR abnormal cells in the correct place
- important cause of refractory epilepsy, resection often needed beyond imaging margins

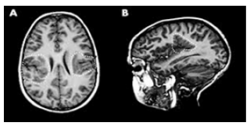
Polymicrogyria (PMG)



www.germaco.net/pmg_gb.html



www.peds.ufl.edu



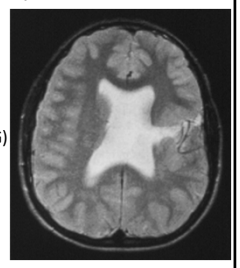
jmg.bmj.com

Polymicrogyria (PMG)

- Excessive, small convolutions/gyri
- Pathology:
  - Midcortical laminar necrosis in layer 5, likely postmigratory ischemic mechanism
  - Associated with intrauterine CMV infection
- Bilateral perisylvian polymicrogyria syndrome
  - bihemispheric pre- and post-central PMG
  - Seizures
  - Intellectual disability with aphasia
  - **Unique finding: oromotor dysfunction (tongue, face, pharyngeal, speech difficulties)

Schizencephaly (SCZ)

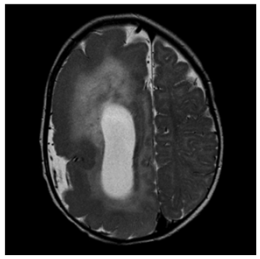
- Parenchymal clefts from lack of cortical development
  - Closed lip / type I: clefts are fused
  - Open lip / type II: clefts are separated (filled with fluid)
- schizencephaly = grey matter along cleft (often PMG)
- porencephaly = white matter along cleft
- Septo-optic dysplasia (deMorsier syndrome)
  - SCZ
  - agenesis of septum pellucidum
  - optic nerve hypoplasia
  - hypopituitarism



http://emedicine.medscape.com/article/413051-overview

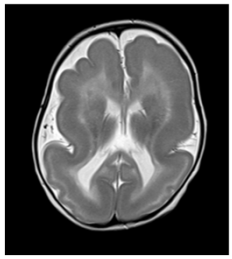
Hemimegalencephaly

- Triad of intractable partial seizures in infancy, progressive hemiparesis or unilateral deficits, and developmental delay
- Variable pathology, including other MCDs
  - often isolated
  - associated with tuberous sclerosis, neurofibromatosis, linear nevus sebaceous syndrome, hypomelanosis of Ito
- May need functional hemispherectomy (consider this early!)

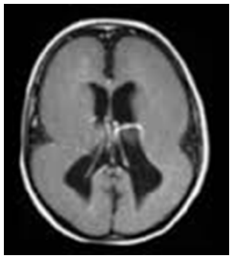


http://radiopaedia.org/articles/emimegalencephaly

Lissencephaly



http://radiopaedia.org/cases/agyria-pachygyria



doctordecides.com

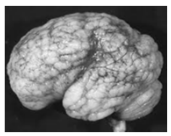
Lissencephaly (LIS)

- "Smooth brain"
- Developmental delay, hypotonia, spasticity, seizures (esp. epileptic spasms), and difficulty feeding
- Genetics
  - LIS1: AD, more occipital / posterior
  - DCX*: X-linked dominant, more frontal / anterior
  - ARX: X-linked dominant (lissencephaly with ambiguous genitalia and anomalies of the corpus callosum)

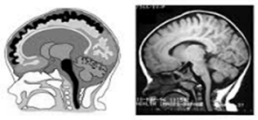
*also causes subcortical band heterotopia

Cobblestone lissencephaly complex

- Pebbled cortical surface due to leptomeningeal neuronal and glial heterotopias
- Also enlarged ventricles, atrophic brainstem and cerebellum; agenesis of corpus callosum
- Associated with Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome
- Mutations: FKRP (Fukutin-related protein)

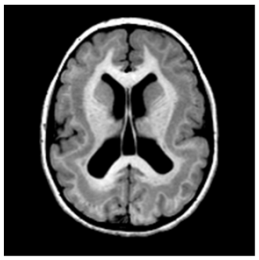


neuropathology-web.org



lookfordiagnosis.com

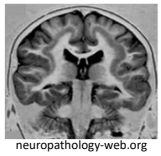
Subcortical Band Heterotopia



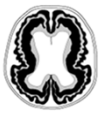
radiopaedia.org/articles/band-heterotopia

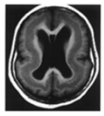
Subcortical band heterotopia (double cortex)

- Bands of neurons located midway between brain surface and lateral ventricles
- Genetics:
  - X-linked dominant inheritance
  - Due to X-inactivation, only some neurons lose function, unaffected neurons migrate normally
  - Usually only in females; males don't survive or have lissencephaly
  - Carrier females: 50% sons will have lissencephaly; 50% daughters band heterotopia
- Clinical:
  - Mild-moderate developmental delay; spasticity
  - Refractory epilepsy in ~2/3



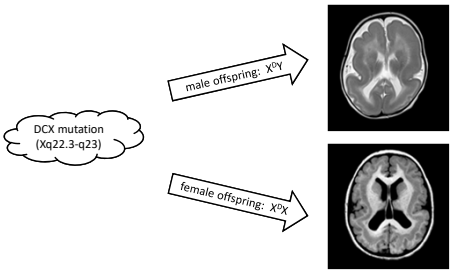
neuropathology-web.org





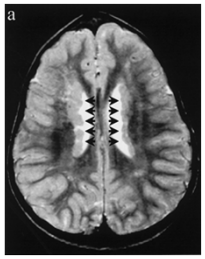
www.peds.ufl.edu

Doublecortin (DCX)



Periventricular Nodular Heterotopia (PVNH)

- Periventricular gray matter (failed migration)
- Seizures beginning in adolescence (usu. normal development)
- Bilateral PVNH is associated with the FLNA (filamin A) gene at Xq28 (usu. lethal in males)



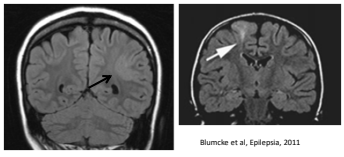
http://www.gfmer.ch/genetic_diseases_v2/gendis_detail_list.php?cat3=591

Subependymal Nodules?

Tuberous Sclerosis	Periventricular Nodular Heterotopia
smaller	larger
less in number	more in number, often bilateral
heterogeneous	homogeneous
calcified	not calcified
white matter intensity on MRI	gray matter intensity on MRI

Focal Cortical Dysplasia (FCD)

- Typically has refractory partial seizures (childhood or adolescent onset)
- Typical MRI findings
  - blurred gray-white junction
  - cortical thickening
  - "transmantle sign": abnormal T2 signal extending from cortex to the superolateral margin of the lateral ventricle



Blumcke et al, Epilepsia, 2011

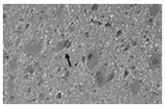
QUESTION

Both dysmorphic neurons and balloon cells are found in what type of focal cortical dysplasia?

A. Type I
B. Type IIa
C. Type IIb
D. Type III
E. Type IV

FCD classification and prognosis

- ILAE neuropathological classification*
  - type I – abnormal cortical lamination/layering
  - type II – dysmorphic neurons (+ balloon cells in Type IIb)
  - type III – associated lesions (e.g., hippocampal sclerosis, tumors, vascular malformations)
- "Milder" type often has normal MRI (may be found on interictal PET or SPECT)
- "Severe" pathology (Type IIb) may have better prognosis – easier to find on MRI and resect



Source: Lerner et al, Epilepsia, Jun. 2009

*Source: epilepsydiagnosis.org/aetiology/focal-cortical-dysplasia-overview

Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

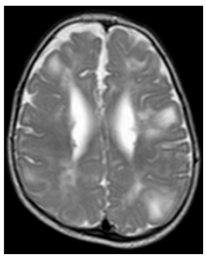
QUESTION

What is the most likely diagnosis in a patient with refractory epilepsy, subependymal nodules on brain MRI, and hypomelanotic macules on skin examination?

A. Tuberous Sclerosis
B. Neurofibromatosis type 1
C. Neurofibromatosis type 2
D. Hypomelanosis of Ito
E. Sturge-Weber Syndrome

Tuberous Sclerosis

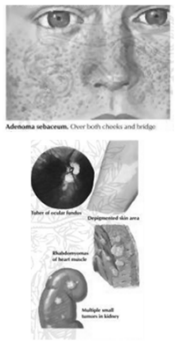
- TSC1 and TSC2 mutations
  - Hamartin and tuberin proteins
  - AD with high penetrance, variable expression
  - Dysregulation in mTOR pathway
- Pathology:
  - Cortical tubers at gray-white interface
  - Subependymal nodules projecting into the ventricles
  - Subependymal giant cell astrocytomas (SEGA)
  - Frequent calcifications



en.wikipedia.org

Tuberous Sclerosis

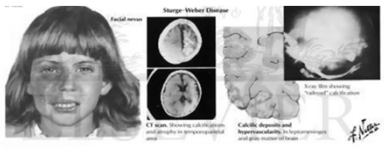
- Clinical (non-CNS):
  - Renal angiomyolipomas or cysts
  - Dermatologic features (hypomelanotic macules, facial angiofibromas, shagreen patches)
  - Retinal hamartomas
- Treatment:
  - Unlike infantile spasms otherwise, Vigabatrin FIRST LINE over ACTH



www.netterimages.com

Other neurocutaneous disorders

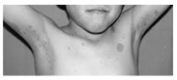
- Sturge-Weber:
  - Venous angioma of leptomeninges with congenital homolateral skin hemangioma usually on upper face (port-wine stain)
  - Gyriform intracranial calcifications (train-track appearance)
  - High incidence of epilepsy, mental retardation, hemiparesis and glaucoma
    - Unilateral convulsive status epilepticus in 50%
  - Can see good outcomes with hemispherectomy

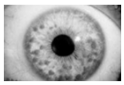


www.netterimages.com

Other neurocutaneous disorders

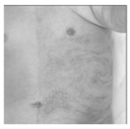
- Neurofibromatosis 1:
  - One of the most common neurocutaneous syndromes
  - Seizures in 3-7%
  - Clinical:
    - café au lait patches
    - skinfold freckling
    - benign peripheral nerve sheath tumors (neurofibromas)
    - iris - Lisch nodules
    - optic pathway gliomas
    - sphenoid wing bony dysplasia

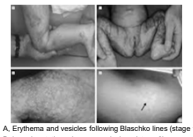




Other neurocutaneous disorders

- Hypomelanosis of Ito:
  - Irregular hypopigmented skin lesions with white or gray hair
  - 50-70% have seizures and mental retardation
    - Often due to neuronal migration disorders
    - Can have hemimegalencephaly
  - Mosaicism is common
- Incontinentia pigmenti:
  - Affects skin, hair, teeth, CNS
  - Erythematous bullous lesions in neonatal period, verrucous patches, hyperpigmentation, and dermal scarring
  - May have seizures (13-25%), mental retardation, spasticity





A, Erythema and vesicles following Blaschko lines (stage 1)
B, hyperkeratotic and verrucous lesions (stage 2)
C, linear hyperpigmentation (stage 3)
D, pale, atrophic, hairless linear lesions (arrow) (stage 4)
Arch Dermatol

Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

What tumors are epileptogenic?

- Adult-onset
- Lower grade tumors
- Tumors close to cortex or sensitive networks (hippocampal, primary motor)
- Parietal tumors have strongest association with seizures, followed closely by temporal

Peritumoral, non-neoplastic tissue often causes seizures (tumor core often silent, necrotic)

Tumor pathology and seizures

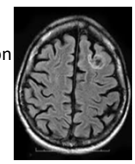
- Nearly 100% of dysembryoplastic neuro-epithelial tumors (DNET) have seizures
- 60-90% of oligodendrogliomas
- 70-80% of gangliogiomas and astrocytomas
- 30-60% of meningiomas and GBMs
- <20% of primary CNS lymphomas
- Hypothalamic hamartomas – gelastic seizures

<u>Meningiomas</u>

- Complete surgical resection often curative (63% seizure free)
- BUT 20-40% develop new seizures after resection
  - prolonged brain retraction
  - interruption of cortical arteries or veins
  - parietal meningiomas
  - severe peritumoral edema

<u>DNETs</u>

- T1 hypointense
- May enhance (heterogeneous or mural nodule)
- Bright on T2 (bubbly appearance)
- Bright rim on FLAIR
- Can have calcification



Treatment

- Must balance tumor treatment goals with epilepsy treatment goals
  - seizure freedom is a goal with operable tumors
  - first-line anticonvulsants fail in 60-70% of patients
- Older drugs can interact with chemo/steroids, can compound risk of bone marrow suppression

Prophylaxis Guidelines

- **NO strong evidence** that anticonvulsants can prevent first seizure in a known brain tumor
- AAN guidelines against their use in primary or metastatic brain tumor patients who never had a seizure
- Can be given for the **first week postop**, but should not be continued

Surgical Evaluation

- Is this "tumor surgery" (curative) or "epilepsy surgery" (palliative)?
- Poor epilepsy prognostic factors
  - longer epilepsy duration
  - low grade tumor
  - subtotal resection (e.g., positive margins)

Surgical Evaluation

- Imaging alone should not guide surgery
- Assess peritumoral or even distant epileptogenic focus (may need invasive EEG)
- Assess for dual pathology (hippocampal sclerosis and tumor); consider resecting both
- Functional mapping (electrocorticography, fMRI) is important, if tumor is near eloquent cortex

Seizure Evaluation in Neuro-Onc Patients

- Recurrence/Expansion
- Metabolic disturbances (Mg, Ca, Na)
- Drug-induced (MTX, cisplatin, ifosfamide, BCNU, IL-2, VP-16, changes in AEDs,
- ICH (coagulopathy)
- Radiation necrosis
- Infectious meningitis (esp. Listeria)
- Leptomeningeal carcinomatosis
- Limbic encephalitis (infectious or paraneoplastic)

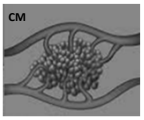
Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

Vascular Malformations

	Arterio-Venous Malformation (AVM)	Cavernous Malformation / Cavernoma (CM)	Developmental Venous Anomaly / Angioma (DVA)
Description	direct connection between arteries and veins (no capillaries)	small bundles of brittle vascular endothelium (not true vessels)	collection of veins that drain into a larger feeding vein
MRI Findings	collection of signal void on MRI	heterogeneous core of mixed signal (popcorn") with T2 or GRE hypointense hemosiderin rim (halo)	T1 post-contrast enhancing "caput medusa" or "palm tree" appearance
Seizure risk	30-66%	50%	rare
Bleed risk	4% per yr	0.7-3% per yr	rare

chw.org



weillcornellbrainandspine.org

Vascular Malformations

- AVMs and CMs
  - surrounding hemorrhage and gliosis usually epileptogenic
  - vascular lesions themselves electrically silent
  - Surgery (resection, radiosurgery) has goals of seizure and hemorrhage prevention
  - ECoG guided resection may have better outcomes
- DVAs – usually incidental and not epileptogenic
  - Resection should probably be avoided
- Familial CM syndromes
  - autosomal dominant inheritance
  - some patients have cutaneous and retinal involvement

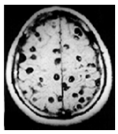
Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

QUESTION

A 32 year old previously healthy patient has recent onset of seizures and is found to have intraparenchymal cysts on MRI. Based on current evidence, what is NOT a recommended treatment for both the seizures and the cysts?

A. Albendazole
B. Dexamethasone
C. Levetiracetam
D. Praziquantel
E. Proguanil

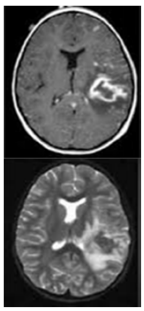


Neurocysticercosis

- Most common cause of adult onset (acquired) epilepsy in developing countries
- Parasitic infection with Taenia solium
  - May remain vesicular/cysts, may degenerate to inflammatory nodule/granuloma, then to calcified lesion
  - Can cause episodic edema, reactive gliosis, hydrocephalus
- Often presents only as seizures, but can have focal deficits, cognitive decline, elevated intracranial pressure
- *AAN Practice Parameter 2013: in patients with symptomatic disease, improved seizure control and decreased active lesions with anticysticercal drugs and steroids*

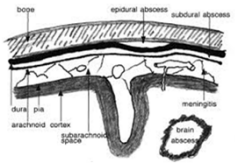
CNS Tuberculosis

- Can spread into subarachnoid space to cause meningoencephalitis or grow in brain parenchyma to form tuberculomas
- Cerebral tuberculoma:
  - Very rare in Western countries; 20-40% intracranial tumors in developing countries
  - Can appear even after apparently successful treatment of systemic or CNS tuberculosis
  - Seizures can be the 1st manifestation
  - Tx: anti-TB therapy, steroids, AEDs if seizures


Slideshare.net

Bacterial Infections

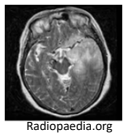
- Brain abscess
  - Presents with fever, elevated intracranial pressure, focal deficits
  - Acute symptomatic seizures in ~50%
  - Chronic epilepsy in ~40%, highest risk if in temporal lobe
- Empyemas
  - Collections of purulent material at the subdural and epidural spaces
  - Can cause septic thrombosis of dural sinuses +/- cortical veins leading to cortical infarctions
  - Can see intracranial hypertension, seizures, focal deficits
  - Look for infectious process of paranasal sinuses, orbits or ears
  - Tx: surgical drainage + antibiotics + AEDs (at least acutely)
- Pyogenic meningitis
  - Acute symptomatic seizures in <=40%
  - Few patients develop chronic epilepsy (2-7%), usually with permanent focal neurologic deficits



Neuropathology-web.org

Viral Infections


Idiva.com


Radiopaedia.org

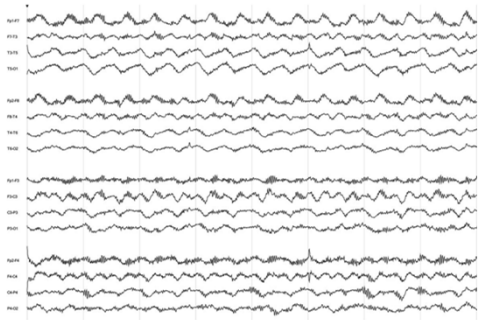
- Viral encephalitis:
  - Clinical:
    - Fever, seizures, behavioral changes, cloudiness of consciousness, rigidity, focal neurologic deficits related to infarctions
    - Can also have myalgias, sore throat, conjunctivitis, skin rash, bleeding diathesis, respiratory dysfunction
  - HSV is most commonly associated with seizures
- HIV:
  - Varied pathologies can lead to seizures:
    - Most often toxoplasma abscesses, lymphomas, or PML
      - Can also be due to HIV itself, metabolic abnormalities
  - 10 X risk of seizures vs general population

Inflammatory

- SLE:
  - Seizures with CNS lupus, hypertensive or metabolic encephalopathy, due to cerebrovascular or infectious complications
  - Seizures in ~25-30% patients
- Cerebral vasculitis:
  - Seizures occur as complications of cerebral infarction, metabolic encephalopathy (hepatic/renal failure)
  - Primary CNS angiitis / granulomatous angiitis
    - Seizures in 20-44%, not just due to stroke
  - Secondary vasculitides
    - Connective tissue diseases (Wegener's, Behcet, Neurosarcoidosis) – seizures in 1-10%
    - Infections (CMV, TB, HSV, VZV, aspergillosis)
    - Vasoactive drugs (phenylpropanolamine, ergotamine, amphetamines, cocaine)
    - Malignancies (lymphoma)
    - Drug hypersensitivity reactions

Autoimmune Epilepsy Overview

- Strongly suspect in new-onset refractory epilepsy, or new-onset status epilepticus
- Clinical signs include, encephalopathy, amnestic syndrome, cognitive decline, personality changes, psych features (e.g., psychosis, catatonia, agitation), movement disorder
- Look for autoimmune stigmata (type 1 diabetes, thyroid disease, celiac disease, B12 deficiency)
- Look for cancer (or strong risk factors for cancer)


Adapted from Schmitt et al, Neurology, 2012

Workup

- MRI, EEG, LP, serum and CSF antibody screening
- Divide antibodies into cytoplasmic (onconeural) vs. cell membrane
  - onconeural are more often paraneoplastic
  - cell membrane are more often responsive to immunotherapy
- Cancer screening
  - PET-CT brain and body
  - select cases – testicular ultrasound, colonoscopy, mammogram, prostate or gynecologic exam

Select Onconeural Antibodies

Antibody	Associated Cancer	Symptoms (other than seizures / limbic encephalitis)
ANNA-1 (Hu)	**Small cell carcinoma**	Brainstem encephalitis, autonomic or sensory neuropathy
Ma1, Ma2	**Testicular**	Brainstem encephalitis
CRMP-5	Small cell carcinoma Thymoma	Dementia, personality change, chorea, ataxia, neuropathy
Amphiphysin	Small cell carcinoma Breast adenocarcinoma	Dementia, myelopathy, neuropathy
GAD	**None** Thymoma Breast adenocarcinoma	**Stiff-person syndrome**, ataxia, brainstem encephalitis, ophthalmoplegia, parkinsonism, **diabetes (DM-1)**

Adapted from McKeon and Pittock, Acta Neuropathol, 2011.

Select Neuronal Membrane Antibodies

Antibody	Associated Cancer	Symptoms (other than seizures / limbic encephalitis)
VGKC-complex*	**None** Small cell carcinoma	Executive dysfunction, personality changes, brainstem encephalitis, myoclonus **(CJD-like picture)**, neuropathy, **hyponatremia**
NMDA	**None** **Ovarian teratoma**	Psychosis, **extrapyramidal disorders (e.g., choreoathetosis), dysautonomia**
AMPA	Thymic, Lung, Breast	–
GABA-B	Neuroendocrine tumors incl. small cell carcinoma	Orolingual dyskinesias

*multiple antibody targets in this complex (LGI-1, CASPR2, Contactin-2)

Adapted from McKeon and Pittock, Acta Neuropathol, 2011.

Treatment

- No controlled trials, no strong evidence basis
- First line
  - find / treat cancer
  - IVIg and/or IV methylprednisolone daily x3-5 days
  - continue weekly for 6-12 weeks
  - plasma exchange used if severe symptoms
- If successful
  - gradual taper + addition of mycophenolate or azathioprine
- If failed
  - consider cyclophosphamide, rituximab

Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

QUESTION

Which of the following factors is associated with an increased risk of developing epilepsy after head trauma?

A. Amnesia for 25 minutes at the time of injury
B. Severe post-concussion headaches
C. Seizure at the time of injury
D. Intracerebral hematoma
E. Non-displaced skull fracture

Severity of Head Trauma

- Mild: LOC < 30 min, no skull fracture
- Moderate: LOC 0.5-24 hrs, no parenchymal injury
- Severe: LOC > 24 hrs, contusion, ICH, or dural penetration

- Increased risk of developing epilepsy
  - Severe head trauma
  - Early seizures PLUS moderate or severe trauma

Early Seizures After Head Trauma

- Early seizures = within first week
  - 10% will develop late seizures (multivariate analysis has shown that early seizures are predictive but not an independent risk factor)
  - Early status has higher risk for late seizures
- Late seizures = epilepsy
  - Only one unprovoked late seizure necessary for diagnosis
  - 70-90% develop epilepsy within 2 years

Seizure Prophylaxis

- Strong evidence for prophylaxis in adults with severe brain injury **for the first week only**
  - Cochrane review – NNT is 10
  - AAN recommendations – phenytoin x 1 week
- **No evidence** that prevention of early seizures prevents late seizures / epilepsy

Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

Pediatric Stroke

- Neonatal stroke
  - Usually large vessel arterial disease
  - Up to 80% have seizure as presenting symptom
- Childhood stroke
  - Usually small vessel arterial disease
  - Up to 30% have seizure as presenting symptom
- Epilepsy risk is approximately 15-25%

Adult Stroke

- Post-stroke seizures: 7-11% incidence (but wide range)
  - Acute symptomatic seizures (within 24 hrs)
  - Early seizure (within 1 week)
  - Late seizure / epilepsy (after 1 week)
- Post-stroke epilepsy: 2-4% prevalence
  - High recurrence after first late seizure (50-90%)
  - Consider treatment after first late seizure

Predictors of Post-stroke Epilepsy

- Cortical location
- Stroke severity (exam / NIHSS)
- Hemorrhage
- PLEDs/LPDs may be predictive (uncommon)
- Focal slow activity is not predictive
- Seizure-free rates up to 70%

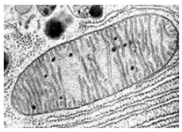
Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

Mitochondrial Disorders

- Decreased ATP production -> unstable membrane potential
- Look for elevated blood, CSF lactate
- Can be mitochondrial or nuclear mutations

- Maternal inheritance:
  - Derived exclusively from oocyte
  - Mother may be oligosymptomatic – few symptoms if lower % mutations



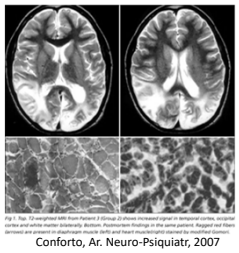
users.rcn.com courtesy of Keith Porter

MERRF (Myoclonic Epilepsy with Ragged Red Fibers)

- Progressive myoclonus epilepsy (may be photosensitive), myopathy, slowly progressive dementia
  - Often with hearing loss, ataxia, neuropathy, short stature
- Onset childhood to late adulthood; variable severity in same families
- Mutation in mt gene for tRNA-lysine in 80-90% of patients
  - Decreased cytochrome C oxidase activity
- Ragged-red fibers on muscle biopsy

MELAS (Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes)

- Stroke-like episodes typically <40 years old, most often occipital
- Encephalopathy (seizures, dementia)
  - Seizures initially with metabolic disarray, later due to structural lesions
- Mitochondrial dysfunction
  - Lactic acidosis, ragged-red fibers, or both
- Other clinical features:
  - Migraines, myopathic weakness, myoclonus, ataxia, hearing loss, short stature
- Mutation in mt gene for tRNA-leucine in 80-90% patients



Conforto, Ar. Neuro-Psiquiatr, 2007

Other Mitochondrial Disorders:

- Leigh's Syndrome:
  - Subacute necrotizing encephalomyelopathy
  - Often acute onset following seizure or febrile illness
  - Psychomotor regression, hypotonia, optic neuropathy or pigmentary retinopathy, progressive external ophthalmoplegia, hearing loss, nystagmus, ataxia +/- GI, respiratory problems
  - Myoclonic or tonic-clonic seizures (~30%)
  - Genetically variable:
    - Mutations in mt or nuclear subunits of complex I of mitochondrial respiratory chain
    - Mitochondrial, AR, or X-linked inheritance (X-linked PDHA1 gene)
- Alpers Syndrome:
  - Presents in infancy or early childhood (up to 25yo)
  - Intractable seizures, episodic neurodegeneration with regression; liver dysfunction
  - AR, nuclear DNA polymerase gamma (POLG1) gene
  - Avoid VPA – can precipitate fulminant hepatopathy

Objectives

- Malformations of Cortical Development
- Neurocutaneous Syndromes
- Tumors
- Vascular Malformations
- Infections and Autoimmune Diseases
- Trauma
- Stroke
- Mitochondrial Disorders
- Metabolic Disorders

Pyridoxine-dependent epilepsy

- AR, mutation in ALDH7A1
- Elevated pipecolic acid in the blood, urine or CSF
- Refractory neonatal seizures, EEG with unusual bursts of diffuse asynchronous high-voltage delta with intermixed spikes
- IV pyridoxine 75-100mg treats seizures; may need respiratory support; can show effect after several days of po

Glucose Transporter Type 1 Deficiency Syndrome (GLUT-1)

- Encephalopathy, developmental delay
- Seizures: multifocal, myoclonic, atypical absence
- Diagnosis: low CSF glucose and lactate, normal blood sugar, SCL2A1 mutation
- EEG: multifocal, generalized spike and wave
  - IEDs enhanced when fasting, improve after a meal
- Treat with ketogenic diet; refractory to AEDs

Metabolic disease evaluation

Finding	Differential diagnosis
Acquired microcephaly	Defect of energy metabolism, infantile NCL, Rett syndrome
- Dislocated lenses; seizure then stroke - Macular cherry red spots - Abnormal hair - Peculiar fat distribution over flanks - Gelastic cataplexy	- Homocystinuria - Tay-Sachs - Menkes - Carbohydrate-deficient glycoprotein - Niemann-Pick type C
Bone marrow depression	Ketotic hyperglycinemia syndromes
Chemistry profile (including Ca and Mg)	Carbohydrate, electrolyte disturbances, specific organ dysfunction
Low uric acid	Molybdenum cofactor deficiency
Low BUN	Urea cycle defect
Plasma and urinary amino acids	Aminoacidopathies
Biopsy	Skin (NCL, Lafora) Muscle (MELAS, MERRF) Nerve (neuroaxonal dystrophy)

Metabolic disease evaluation: CSF

Finding	Differential diagnosis
Elevated protein	- Metachromatic leukodystrophy - Globoid cell encephalopathy
Low glucose	Defect of gluconeogenesis or GLUT-1 deficiency
Low folate	Folate metabolism defect
Amino acid alterations (Glycine, glutamate or GABA)	- Nonketotic hyperglycinemia - Pyridoxine-dependent epilepsy
Elevated lactate, pyruvate	Disorders of cerebral energy metabolism (pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, respiratory chain disturbances, Menkes)
Low lactate	GLUT1 deficiency
Biogenic amines	Hyperphenylalaninemic state

Metabolic disease evaluation: EEG

Finding	Differential diagnosis
Suppression burst	- Nonketotic hyperglycinemia - PKU - Maple syrup urine disease - Molybdenum cofactor deficiency - Neonatal citrullinemia - Propionic acidemia (and others)
Central 7-9Hz comb-like activity:	- Maple syrup urine disease - Propionic acidemia
Vertex positive spikes	Sialidosis type 1
Bioccipital polymorphic delta	X-linked adrenoleukodystrophy
14-22Hz invariant activity	Infantile neuroaxonal dystrophy
Diminished spikes during sleep	PME
Giant SSEPs	PME
Marked photosensitivity	PME NCL, particularly type II

Metabolic disease evaluation: MRI

Finding	Differential diagnosis
Progressive atrophy	Neuronal Ceroid Lipofuscinosis
White matter signal abnormalities	Metachromatic leukodystrophy, globoid cell encephalopathy, phenylketonuria, some mitochondrial diseases, Canavan disease, some organic acidurias
Cortical and basal ganglia calcifications	Common to many
MRS elevated lactate	Mitochondrial diseases
MRS elevated NAA	Canavan disease

Metabolic diseases: Treatment

- Correct hypoglycemia, electrolyte disturbances
- Use AEDs, but beware of valproate

Treatment	
Ketogenic diet	- GLUT1 deficiency - Pyruvate dehydrogenase deficiency
Restriction - Phenylalanine - Protein - Fat	 - Phenylketonuria - Urea cycle defects - Fatty acid oxidation
Supplementation - Vitamin/cofactors - Enzyme replacement	 - Pyridoxine-dependent seizures, etc. - Gaucher
Bone marrow transplantation	- Mucopolysaccharidoses - Adrenoleukodystrophy

References

Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011 Jan;52(1):158-74

Britton JW. Autoimmune Epilepsy. J Kiffin Penry Epilepsy Minifellow Symposium XXV, AES Annual Meeting, San Diego, CA. 3 Dec 2012.

Chang BS and Lowenstein DH, Practice parameter: Antiepileptic drug prophylaxis in severe traumatic brain injury. Neurol. 2003;60:10-16.

Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG. Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neurol. 2000;54;1886-1893.

Irani SR, Bien CG, Lang B. Autoimmune epilepsies. Curr Opin Neurol. 2011;24:146-53.

Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R; SAVMs steering committee and collaborators. Seizure risk from cavernous or arteriovenous malformations: prospective population-based study. *Neurol.* 2011;76(18):1548-1554.

Krsek P, Maton B, Korman B, Pacheco-Jacome E, Jayakar P, Dunoyer C, Rey G, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. Different features of histopathological subtypes of pediatric focal cortical dysplasia. *Annals of Neurology*. 63(6):758-69, 2008 Jun.

Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, Sankar R, Donald Shields W, Engel J Jr, Fried I, Cepeda C, Andre VM, Levine MS, Miyata H, Yong WH, Vinters HV, Mathern GW. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia*. 50(6):1310-35, 2009 Jun.

Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. *Dialogues in Clinical Neuroscience*. 10(1):47-62, 2008.

McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011,122:381–400.

Quek AM, Britton JW, McKeon A, So E, Lennon VA, Shin C, Klein C, Watson RE Jr, Kotsenas AL, Lagerlund TD, Cascino GD, Worrell GA, Wirrell EC, Nickels KC, Aksamit AJ, Noe KH, Pittock SJ. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol. 2012 May,69(5):582-93.

Schierhout G, Roberts I. Antiepileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane review, 2010.

Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurol. 2012 Sep 11;79(11):1094-100.

Wyllie E, Cascino GD, Gidal BE, Gookin HP. Wyllie's Treatment of Epilepsy: Principles and Practice, Fifth ed. Philadelphia: Lippincott Williams and Wilkins, 2011.

Non-Epileptic Paroxysmal Disorders in Pediatric Age Group

Dewi Depositario-Cabacar, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

NON-EPILEPTIC PAROXYSMAL DISORDERS IN PEDIATRIC AGE GROUP

Dewi Depositario-Cabacar, MD
Assistant Professor, Neurology and Pediatrics
Children's National Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Definitions

- Seizure: abnormal excessive or synchronous neuronal activity in the brain.
- Epilepsy: a condition characterized by the tendency for recurrent unprovoked seizure.
- Nonepileptic paroxysmal disorders can produce recurrent, paroxysmal changes of movement, consciousness or behavior.

Nonepileptic Paroxysmal Disorders

- can produce recurrent, paroxysmal changes of movement, consciousness or behavior.
- Heterogenous group (both neurological and nonneurological conditions).
- 25% in monitoring units have no epilepsy (Uldall et 2006, Hindley et al 2006, Bye et al 2000).
- Many are benign, require no treatment and can resolve spontaneously.

Nonepileptic Paroxysmal Disorders

Infancy and Neonates

- Jitteriness, Head banging/Body rocking
- Benign neonatal myoclonus
- Self Gratification phenomena
- Reflux and Sandifer syndrome
- Benign myoclonus of early infancy
- Startle disease or hyperekplexia
- Shuddering attacks
- Spasmodic Torticollis
- Apnea
- Breath-holding

Nonepileptic Paroxysmal Disorders

Older Children

- Breath-holding spells
- Movement disorders (motor tics, paroxysmal kinesogenic choreoathetosis etc)
- Parasomnias and sleep disorders (night terrors, sonambulism, narcolpesy, cataplexy)
- Migraine Headaches
- Nonepileptic seizures
- Behavioral disorders (rage attacks, inattentiveness)
- Syncope
- Attention deficits
- Stereotypies

Nonepileptic Paroxysmal Disorders

Adolescence/Adult

- Syncope
- Tremor
- Panic attacks and hyperventilation
- Nonepileptic seizures (pseudoseizures)
- Migraines
- Parasomnias and Sleep Disorders (narcolepsy, cataplexy)
- Attention Deficits

EXAMPLES OF SOME NONEPILEPTIC PAROXYSMAL DISORDERS

Sandifer syndrome

- Intermittent abnormal posturing such as stiffening and opisthotonic posturing.
- Gastroesophageal reflux
- associated with feedings
- Tx : Anti-reflux medications

Shuddering attacks

- Spells of tremor of head, arms, trunk with adduction and flexion of elbows.
- last a few seconds
- starts at 4 months; most improve by 10 years of age.
- pptd by anger, fear, frustration
- Family hx of essential tremor (Holmes et.al. Am J Dis Child 1986)
- EEG: normal

Self gratification behavior

- Infantile masturbation
- variant of normal behavior
- Rubbing of thighs together, rocking of the pelvis against hard surface
- Associated with sweating or flushing of face
- Distracting stimuli – stop these movements
- Tx: reassurance

Yang M L et al. Pediatrics 2005;116:1427-1432

Self gratification behavior

Spasmodic/paroxysmal torticollis

- Sudden, repetitive episodes of head tilting or turning to one side with rotation of the face to opposite side.
- Minutes to days
- child is responsive
- etiology unknown.
- family hx of torticollis or migraine
- ddx: neoplastic conditions of the posterior fossa, cervical cord, neck

Spasmodic/paroxysmal torticollis

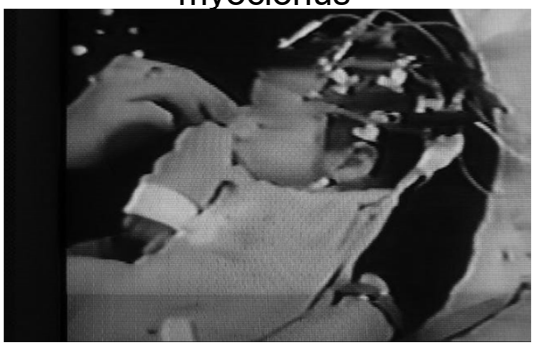
Movement Disorders

- Benign neonatal sleep myoclonus
- Benign myoclonus of early infancy
- Spasmus nutans
- Hyperekplexia
- Paroxysmal dystonia
- Tics

Benign neonatal sleep myoclonus

- Healthy newborns
- Onset within 15 days of life
- repetitive myoclonic jerks of the extremities during sleep (occur q2-3 secs and may last as long as 30 mins).
- bilateral, asynchronous and asymmetric movements (migrate from one muscle group to another and occur bilaterally)
- EEG: normal
- Spontaneously resolves by 3 mos. of age

Benign neonatal sleep myoclonus



Spasmus nutans

- Triad: head nodding, head tilt (torticollis), nystagmus
- 4 – 12 months of age
- Pathophysiology: unknown
- MRI: r/o mass lesion of optic chiasm or 3rd ventricle
- Usually remits spontaneously within 1-2 years at onset.

Spasmus nutans

Benign myoclonus of infancy

- First year of life (3 to 8 months)
- Brief tonic or myoclonic contractions involving the axial muscles
- Spasms occur in cluster, usually mealtime
- Resolves by 2 years old
- EEG: normal
- Tx: reassurance

Hyperekplexia

- "Stiff baby syndrome or startle disease"
- rare
- hyperactive startle reflex (falling)
- triad: *generalized stiffness*
  nocturnal myoclonus
  tonic spasms with auditory/tactile stimuli
- gene mutations affecting glycine receptor (GLRA1, GLRB)
- can dominant or recessive
- Tx: clonazepam; valproic acid (Andermann F et.al. Brain Dev 1988)

Hyperekplexia video 1

Paroxysmal dyskinesia

Paroxysmal kinesogenic dyskinesia (PKD)

- Repetitive attacks of dystonia or choreoathetosis
- precipitated by movement.
- Can be sporadic or familial
- Chromosome 16p11.2
- EEG: normal
- Tx: carbamazepine, phenytoin

Benign paroxysmal vertigo

- Sudden or repeated attacks of dysequilibrium usually < a minute.
- child unable to walk, associated with nystagmus, diaphoresis, nausea and vomiting.
- child alert and responsive.
- EEG: normal
- (+) family history of migraine.
- Subsequently develop typical migraines (Drigo P, et al. Brain Dev. 2001)

Stereotypies

- Patterned repetitive movements that recur frequently.
- more common in children with autism and with mental retardation; can be seen in normal children.
- Head banging, head rolling, body rocking.
- Movements stops when distracted.
- Treatment: behavioral modification techniques.

Stereotypies

Breath holding spells

- 6 mos to 6 years (peak 2-3 years)
- cyanotic and pallid

Cyanotic

- Provocation ⟶ cries ⟶ then holds breath in expiration ⟶ cyanosis ⟶ LOC/ loss of tone
- precipitating event: mild injury/upset.
- if apnea prolonged ⟶ opisthotonus or clonic jerks.
- Treatment: behavioral modification of parents response
  Iron deficiency screening (if recurrent)

Breath holding spells

Pallid breath holding

- induced by minor trauma ⟶ stops breathing, pale, +/- brief cry ⟶ then followed by loss of consciousness
- bradycardia or asystole may occur
- Tx – most no treatment;
  some studies: atropine

Migraines

- Dilemma: acute neurologic events without significant headaches.

Confusional migraine

- confusion, hyperactivity, partial or total amnesia, disorientation, lethargy, vomiting
- several minutes to hours
- Clears up following sleep
- Headache +/- visual sxs before.
- r/o encephalitis, substance abuse, metabolic causes, and vasculitis

Migraines

Alice in Wonderland

- distortions of perception, change in size and shape of body parts, distortion of surroundings.
- confused with temporal lobe or occipital seizures; encephalitis, vasculitis

Parasomnias and Sleep Disorders

- **Night terrors** – usual onset: 4 years old
  wakes up from sleep, agitated, inconsolable; no recollection of event; r/o frontal lobe seizures
- **Cataplexy** *- sudden loss of muscle tone precipitated by a stimuli; r/o atonic seizures
- **Narcolepsy** * - excessive daytime sleepiness, sudden sleep attacks; hypnagogic hallucinations; sleep paralysis.

** Multiple sleep latency (short latency from sleep onset to REM); video EEG

Cataplexy

Syncope

- Transient interruption of cerebral blood flow resulting in loss of consciousness.
- Majority are neurally mediated (Mcleod KA 2003).

Syncope - Causes

A. Secondary to known precipitating events.
1. Neurocardiogenic
a. Vasovagal – fear, pain, unpleasant sights
b. Reflex – cough, micturition, carotid sinus pressure, swallowing.
2. Decreased Venous return
- Orthostatic, soldier's syncope, Valsalva
B. No clear precipitating event.
1. Cardiac – arrhythmia, obstructive outflow
2. Cerebrovascular insufficiency
3. Psychogenic

Pellock's Pediatric Epilepsy 2017.

Syncope versus seizures

	Syncope	Seizures
Setting	usually provoked	unprovoked
Prodrome/aura	presyncope	déjà vu, olfactory
EEG	high voltage delta flattening of EEG	spike waves
Recovery	fast, back to baseline	prolonged confusion/ lethargy

*** **Convulsive Syncope** - occurs in more prolonged cerebral hypoperfusion.

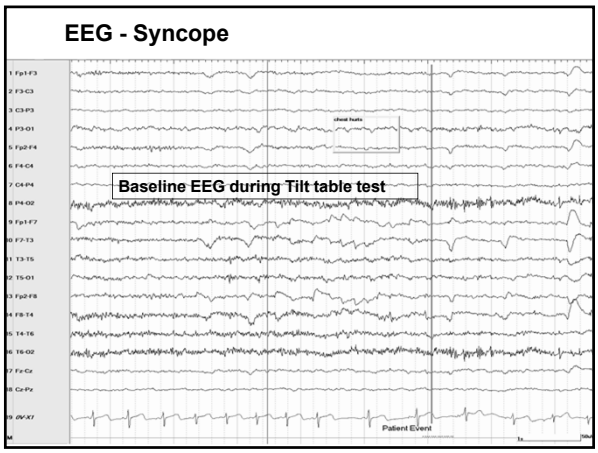
Syncope

Neurocardiogenic syncope

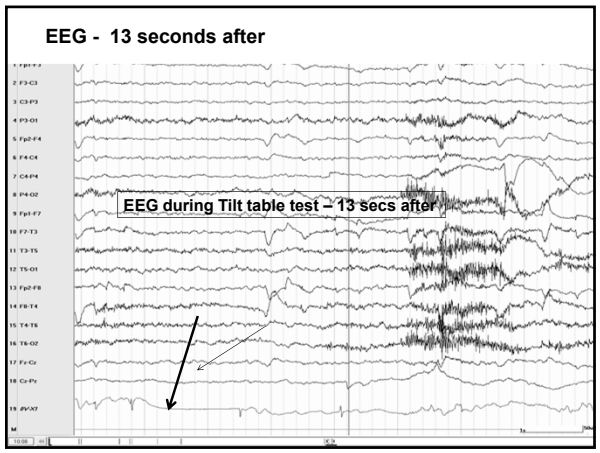
- a. Vasovagal syncope
  - Most prevalent
  - Occurs in response to an emotion or setting (blood drawing, hot weather, anxiety).
  - Prodome: warmth, nausea, tunnel vision

***Decreased venous return: Autonomic activation → parasympathetic cardioinhibitory response → vasodepression.*

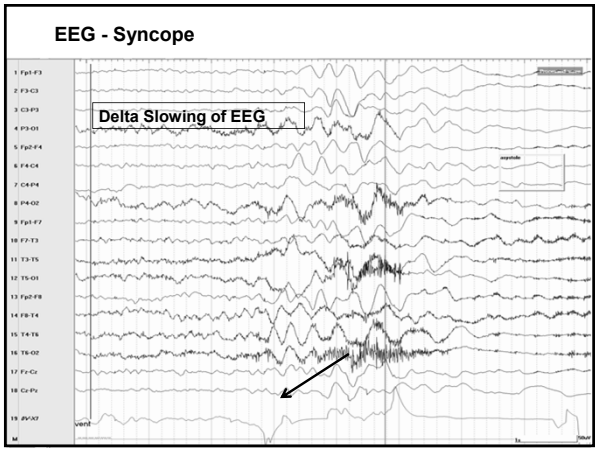
EEG - Syncope



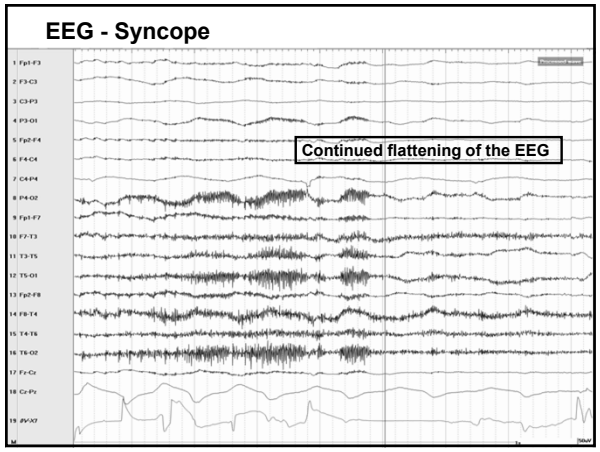
EEG - 13 seconds after



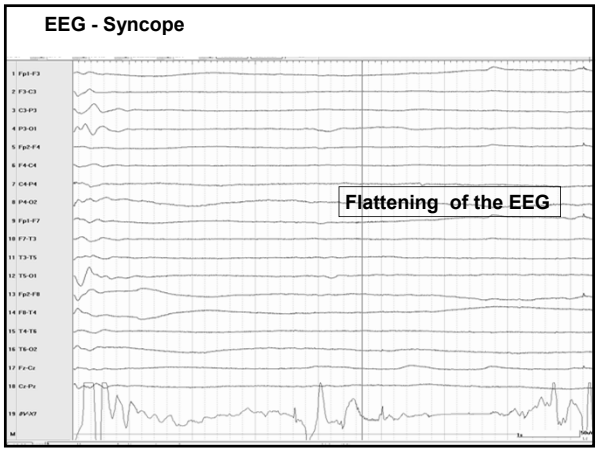
EEG - Syncope



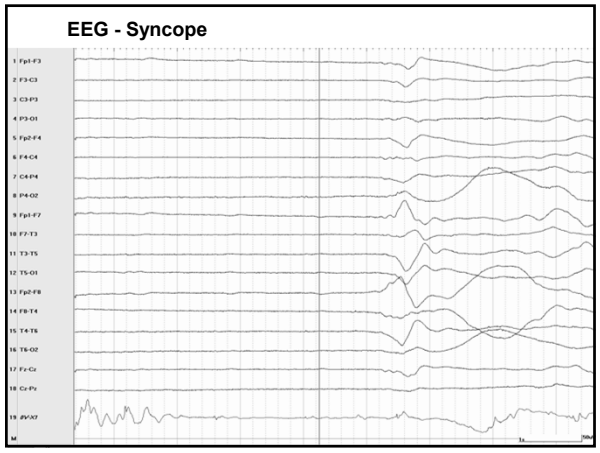
EEG - Syncope



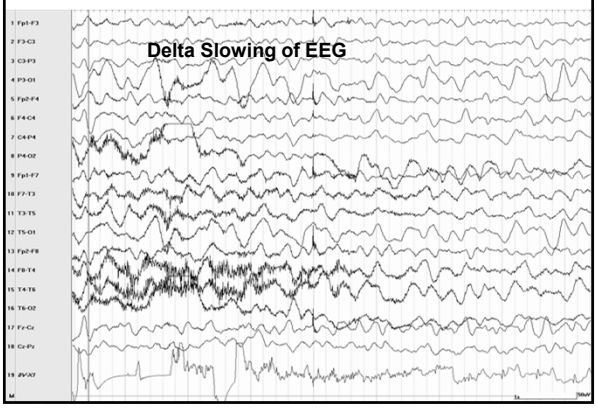
EEG - Syncope



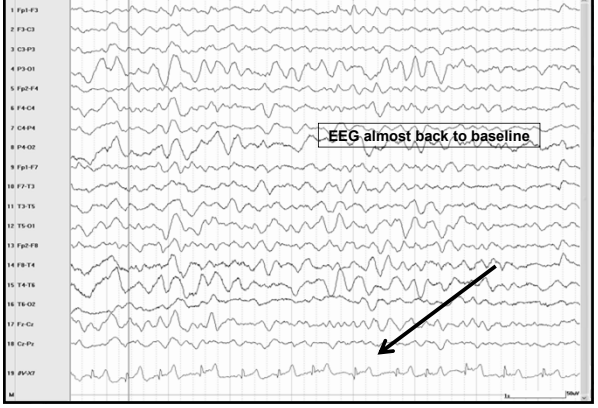
EEG - Syncope



EEG - Syncope



EEG - Syncope



Syncope

Neurocardiogenic syncope

- **Reflex syncope**
  - transient disturbance autonomic control of HR and BP.
  - common triggers: coughing, micturition, swallowing

***Autonomic activation -- → parasympathetic cardioinhibitory response --→ vasodepression.*

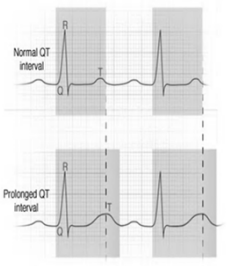
Syncope

- Dx: check orthostatic blood pressure
  Tilt table test (if recurrent)
  EEG: diffuse slowing and flattening
- Tx: reassurance
  avoidance of precipitating factor
  increase H20 and salt intake
  if recurrent : beta blockers, alpha adrenergic agonists, mineralocorticoids,

Syncope

Cardiogenic syncope

- Rare; life threatening
- Usually without warning
- Cardiac dysrhythmias:
  prolonged QT syndrome



Psychogenic nonepileptic seizures (PNES)

- Events that resemble an epileptic seizure but unaccompanied by EEG abnormalities .
  (Wichaidit BT et.al., 2015; Bhatia MS, 2005).
- Based on several poplation studies, the estimated incidence are at ranges from 1.5 to 5 per 100,000 persons per year.
  (Szaflarski JP et al, Neurology 2000; Reuber et al. Epilepsy and Behav. 2003; Duncan R et al. Epilepsy and Behav 2011)
- Related to a psychological process (Crompton and Berkovic 2009; Patel H, et al Epilepsia 2007; Kutluav E et al Epilepsy Behav 2010).
- Video EEG is the gold standard for diagnosis

Psychogenic nonepileptic seizures (PNES)

- Video EEG is the gold standard for diagnosis

- Yield of monitoring is high; 73 to 96 percent of patients will have typical PNES within the first 48 hours of recording
  (Woollacott IO, et al Epilepsy Behav. 2010; Perrin MW, et al.Epilepsy Behav. 2010; Parra J, et al. Epilepsia. 1998.)

Psychogenic nonepileptic seizures (PNES)

Danish hospital national survey (n=64)

- 5 historical characteristics
  - psychosocial stressors/trauma
  - sexual abuse
  - paroxysmal events occur in stressful situations.
  - no effect of antiepileptic meds
  - physical abuse

Wachaidit BT et al. Diagnostic practice of psychogenic nonepileptic seizures (PNES) in the Pediatric setting. Epilepsia. 2015; 56 (1):58-65.

Psychogenic nonepileptic seizures (PNES)

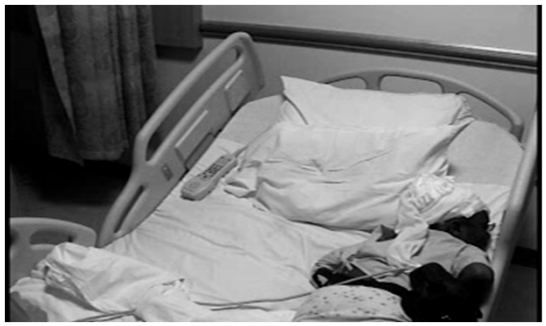
- 6 paroxysmal event characteristics
  - resistance to eyelid opening.
  - avoidance/guarding behavior
  - paroxysmal events occurring in the presence of others
  - closed eyes
  - rarely injury related to paroxysmal event.
  - absence of postictal change (Freeman 2005)

Wachaidit BT et al. Diagnostic practice of psychogenic nonepileptic seizures (PNES) in the Pediatric setting. Epilepsia. 2015; 56 (1):58-65.

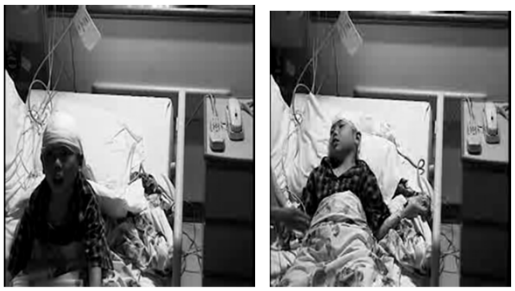
Psychogenic nonepileptic seizures (PNES)

- **Treatment**: cognitive behavioral therapy
- **Prognosis**:
  - In general, only a minority (25 to 38%) of patients achieve “seizure freedom”.
  - Children with better prognosis than adults, 70 to 80% achieve “seizure remission” [n= 18 pediatric, n=20 adult] (Wylie R et al, Neurology 1991).

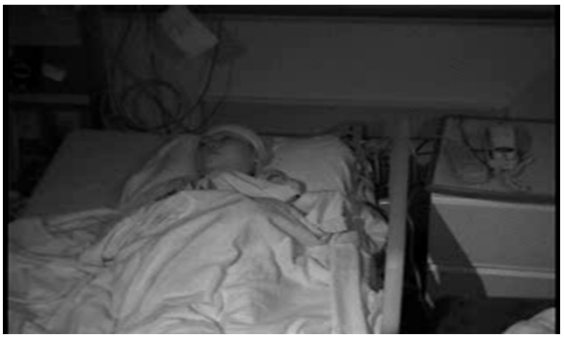
Psychogenic nonepileptic seizures



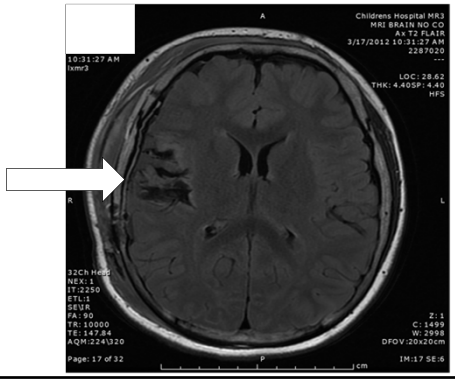
Psychogenic nonepileptic seizures



But……



MRI



Conclusion

"The differential diagnosis of epileptic seizures includes a variety of benign, physiologic phenomena as well as pathologic conditions."

- thorough clinical history and examination
  - patient's age
  - description of event
  - time of occurrence
- Video EEG helpful
- *** dual diagnosis is possible

Board Questions

Question 1

- A 2 year old girl has been having spells consisting of rubbing of the thighs together, thrusting of the pelvis with sweating, grunting and flushing of the face. The child goes back to baseline after the event. Which work up is warranted?

a. electroencephalogram
b. Magnetic resonance imaging
c. No work up needed
d. Sleep study

Question 2

- These are spells of intermittent abnormal posturing such as stiffening associated after feeding.

a. Infantile spasms
b. Paroxysmal dystonia
c. Tonic seizures
d. Sandifer syndrome
e. Stereotypy

Question 3

- Which is a common finding in an EEG of a patient having syncope?

a. Spike waves
b. High voltage delta and flattening of the EEG
c. Preservation of the alpha rhythm
d. Beta activity

Question 4

- A 10 year old girl has been having spells of confusion, disorientation, lethargy, vomiting lasting for 3 hours and usually resolves following sleep. Which is the likely diagnosis?

a. Focal seizures
b. Confusional migraines
c. Psychogenic nonepileptic seizure
d. Neurocardiogenic syncope

Question 5

Which is not a typical characteristic of PNES?

a. resistance to eyelid opening.
b. paroxysmal events occurring in the presence of others
c. psychosocial stressors/trauma.
d. Some postictal change.
e. lack of response to antiepileptic meds.

Thank you

Non-Epileptic Seizures in Adults

Amar B. Bhatt, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

NON-EPILEPTIC EVENTS

Amar B. Bhatt, MD
Assistant Professor of Neurology, Epilepsy Section
Rush University Medical Center
Program Director, Neurology Residency

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Overview

- Differential Diagnosis of Seizures
- Non-epileptic events (physiologic)
- Non-epileptic events (psychogenic)
- Frontal Lobe Seizures and Simple Partial Seizures

Differential Diagnosis of Seizures

- Detailed history is crucial (in lay person terms)
- Cell phone home videos are extremely helpful
- Non-epileptic ≠ Psychogenic

Non-epileptic Events

- Physiologic
  - Cerebrovascular
  - Sleep disorders
  - Cardiac/Syncope
  - Movement disorders
  - Migraine
  - Behavioral
- Psychogenic
  - Conversion disorder / PTSD
  - Panic attacks / Anxiety
  - Factitious disorder and malingering

Cerebrovascular

- TIA and stroke → negative symptoms
- Epileptic seizures → positive symptoms
- Both may be stereotyped
- Both may be new onset in elderly
- Both may present with limb shaking (esp. in setting of critical carotid stenosis)

Sleep Disorders

- Hypnic Jerks (Benign Myoclonus of Sleep)
- Narcolepsy
- Parasomnias
- Sleep paralysis
- OSA
- Hypersomnia

In the differential diagnosis of nocturnal events, which of the following parasomnias are more likely to occur much later during a night of sleep?

A. Somnambulism
B. Confusional Arousals
C. Nightmares
D. Night Terrors
E. Sleep Related Eating Disorder

Parasomnias

- Early in the night (NREM)
  - Sleepwalking
  - Sleep Related Eating Disorder
  - Confusional Arousals
  - Night terrors
- Late in the night (REM sleep)
  - REM Behavior Disorder
  - Nightmares

Cardiac/Syncope

- Arrhythmia
- Valvular Disease
- Vasovagal Syncope
- Orthostasis

Syncope vs. Seizure

Convulsive Syncope	**Generalized Tonic Clonic Seizure**
"Aura" of lightheadedness, palpitations, tunnel vision, tunnel hearing	Aura with typical epileptic semiology (or no aura, if primarily generalized)
Brief duration (<1 min)	Longer duration (2-3 min)
May respond to sitting / lying down (orthostasis)	Usually not positional
Possibly decreased tone	Increased tone
Generalized or multifocal myoclonus	Synchronous clonic activity
No post-event confusion*	Post-event confusion

*post-event (situationally appropriate) disorientation is common in any LOC

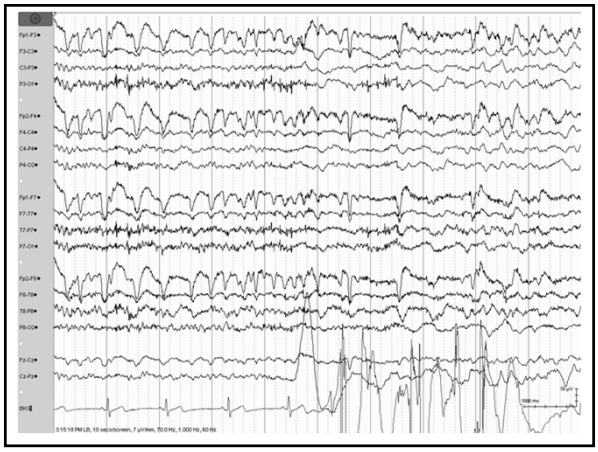
Shaking in syncope is common!

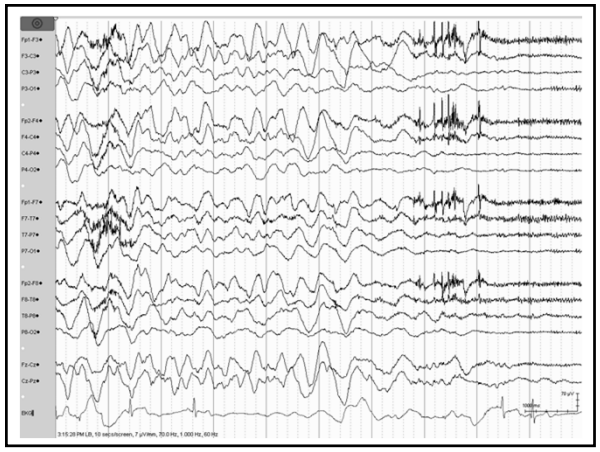
- 56 healthy volunteers had syncope induced using hyperventilation, orthostasis and valsalva
- 90% had myoclonic activity
  - –Usually multifocal
  - –Less commonly was generalized
- 79% had other movements

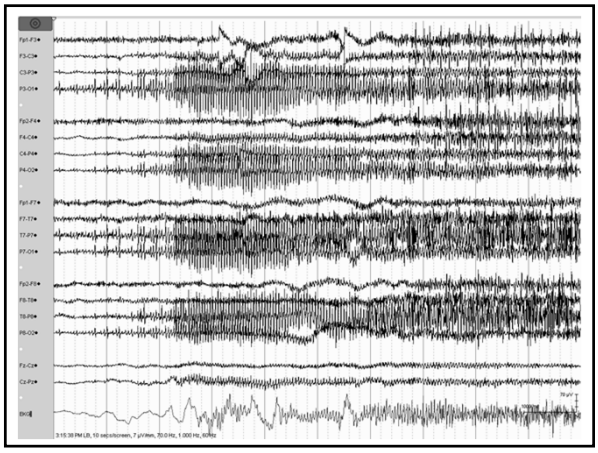
Lempert et al, Ann Neurol, 1994

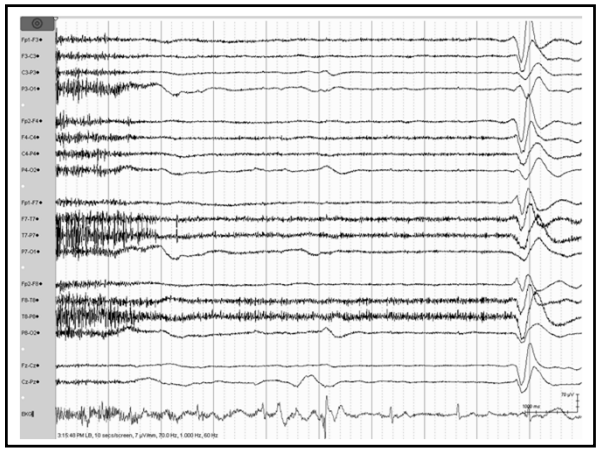
The EEG findings in syncope are best characterized by:

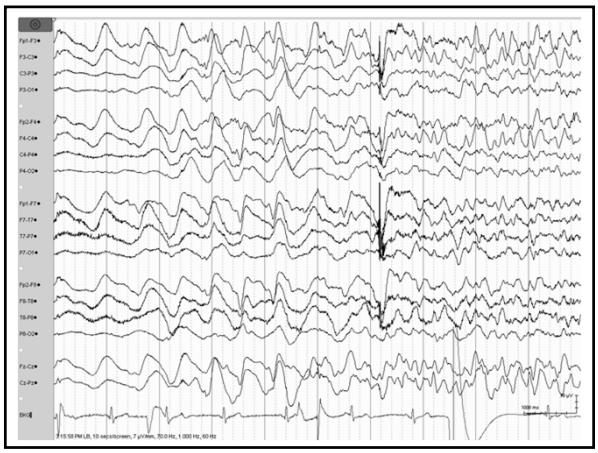
A. Burst suppression
B. Normal background with abnormal EKG
C. Generalized slow activity, then attenuation
D. Focal slow activity, then attenuation
E. Focal attenuation, then slow activity

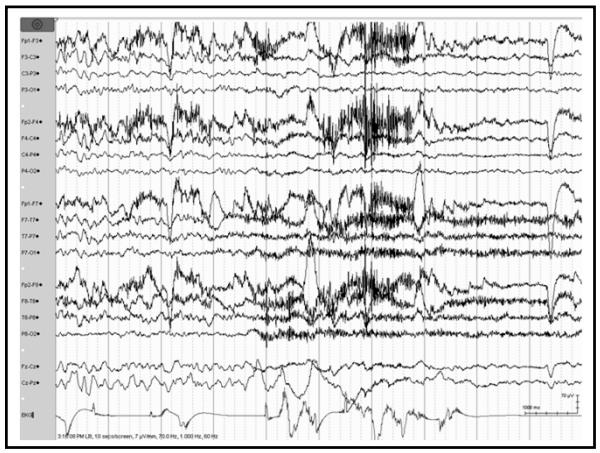












Psychogenic pseudosyncope (PPS)

- In "idiopathic syncope," psychogenic causes are not necessarily investigated
- Video-EEG (or TCDs) usually required; often performed with Tilt Table Testing
- Eyes may be open during true syncope (and closed during PPS)
- Patients typically have increase in HR and BP with PPS

Raj et al, Autonomic Neuroscience, 2014

Non-epileptic Events

- Physiologic
  - Cerebrovascular
  - Sleep disorders
  - Cardiac/Syncope
  - Movement disorders
  - Migraine
  - Behavioral
- Psychogenic
  - Conversion disorder / PTSD
  - Panic attacks / Anxiety
  - Factitious disorder and malingering

Psychogenic non-epileptic events

- Also called psychogenic non-epileptic seizures (PNES) or pseudoseizures
- The words "pseudo" or "seizure" or "spell" have negative connotations and should be avoided
- Includes "seizures" starting from "sleep" (i.e., pseudo-sleep)

Psychogenic non-epileptic events

- Video is as important as EEG correlation
- Detailed history and correlation with typical events is key
- Pathology usually is PTSD / conversion disorder (NOT malingerers or factitious)*

*though secondary gain may perpetuate it

Etiology and Predisposing Factors

- Trauma (Combat, Abuse)
- Personality Disorders (esp. borderline)
- Poor Coping Skills
- Comorbidities (PTSD, Anxiety, Depression)
- Illness Perception
  - Alexithymia (inability to name/express emotions)
  - External locus of control

Reuber, Epilepsy and Behavior, 2008

PNES: Patient education

- Avoid "pseudo-seizure" or "seizure" ("non-epileptic" may be too technical)
- Use easy-to-understand examples that patients may understand
  - stress-induced migraines, ulcers, fainting
  - PTSD in veteran and victims of abuse/violence
- Validate the diagnosis
  - Clearly state that the patient ***is not faking it*** and ***is not doing it on purpose***
  - Not saying this implies the opposite, in most cases
  - Written brochure on PNES will help validate it as a "real" diagnosis (patients assume we give this diagnosis because "we can't really figure it out")
- Do not abandon patient
  - Establish clear follow up with neurology and psychiatry
  - Assess patient's understanding and insight at the follow-up visit

PNES: Provider education

- Provide clear education and documentation to other providers
- Many neurologists, psychiatrists, and PCPs still believe these patients are malingering / factitious (which is WRONG)
- Psychiatrists will be hesitant to treat without clear statement of:
  - confirmed diagnosis of PNES
  - normal EEG without any evidence of seizures or epilepsy
  - neurologist's opinion that AEDs are not indicated
  - neurologist managing AEDs (and tapering them off, if appropriate)
- Lack of neurology follow up often results in "neurologist shopping" and restarting of AEDs inappropriately

Characteristic PNES Semiology

- gradual onset or termination
- occurrence during "pseudosleep"
- discontinuous movements
- asynchronous (out-of-phase) activity
- side-to-side head movement
- pelvic thrusting
- opisthotonic posturing
- stuttering
- weeping
- preserved awareness during bilateral motor activity
- postictal whispering
- eye closure of long duration
- less severe physical injuries - controversial

Gedzelman and LaRoche, Neuropsychiatr Dis Treat, 2014

Which of the following symptoms are commonly seen in psychogenic non-epileptic events (but NOT typically seen in generalized tonic clonic seizures)?

A. Synchronous limb jerking
B. Post event confusion
C. Tip of the tongue bite
D. Urinary incontinence
E. Bowel incontinence

PNES vs. Seizure

Convulsive PNES	Generalized Tonic Clonic Seizure
Variable or multiple symptom types	Stereotyped symptoms
Prolonged duration (>5 minutes)	Duration usually 2-3 minutes
Waxing and waning intensity	Tonic activity → Clonic activity that slows down and stops
May have explosive frequency (without apparent functional interference)	Usually infrequent
Asynchronous or variable shaking (flailing, flopping, or lateral movements)	Synchronous clonic activity
Post event confusion minimal in comparison to event	Post-event confusion
Keeping eyes closed (or resisting opening)	Eyes open
Rapid, shallow (or normal) breathing (during or after event)	Slow, deep stertorous respiration (post-ictal)
Medial/anterior/tip tongue bite	Lateral/posterior tongue bite

Predictive Value of PNES Semiology

- Prospective study of eyewitness reports of 48 PNES and ES signs, compared to (EEG-blinded) epileptologist video review
- Eyewitness reports not reliable (equivalent to guessing)
- Reliable for PNES (high spec, low sens):
  - Preserved awareness
  - Eye flutter
  - Bystanders can intensify or alleviate
- Reliable for ES (high sens, low spec):
  - Abrupt onset
  - Eye-opening/widening at onset
  - Postictal confusion/sleep

Syed et al, Ann Neurol, 2011

courtesy of Dr. Koubeissi

Post-event breathing pattern

	GTCS	PNES
Inspiratory and expiratory phases	Long	Short
Respiratory rate	Regular	Increased and irregular
Duration of altered breathing	Long (mean 347 s)	Short (mean 94 s)
Snoring (stertor)	Loud	Absent
Post-event agitation	Possible	Rare

Azar et al, Epilepsia, 2008

Treatment trials in PNES

- CBT effective (series of 21 patients, 12 weeks)
  - 17 completed program, 11 became event free
  - Statistically significant improvement in multiple surveys/scales of depression, trauma, impulsivity, and psychosocial functional status
- Pilot RCT (34 patients, 16 weeks)
  - CBT vs. sertraline vs. both vs. treatment as usual
  - [CBT] and [CBT + sertraline] arms showed significant improvement in event frequency and some psychosocial scales

Lafrance et al, Epilepsy Behav, 2009
Lafrance et al, JAMA Psychiatry, 2014

courtesy of Dr. Koubeissi

Good Prognostic Factors*

- Short duration (mean dx delay 7-16 yrs)
- Minimal psych comorbidities
- Identifiable trauma
- Living independently
- Normal IQ
- Less dramatic event symptoms
- No ICU / "status epilepticus" admissions
- Female gender
- No ongoing AED use

*Prognosis Variable (not systematically studied)
1/3 of patients become event free
1/4 or more become chronic
Many will relapse after 2-5 years

Bodde et al., Seizure, 2009
Reuber, Epilepsy and Behavior, 2008

Frontal Lobe Seizures

- Semiology "too" bizarre to be psychogenic
- May have normal ictal and interictal EEG

- Typically short and stereotyped
- Often nocturnal (out of real sleep, not pseudosleep)
- May have pelvic thrusting and hypermotor activity

- Medication response and progression to (secondarily) generalized tonic clonic seizures useful in diagnosis

What percentage of simple partial seizures have scalp EEG correlate?

A. 0%
B. 25%
C. 50%
D. 75%
E. 100%

Simple Partial Seizures (SPS)

- Focal seizures without alteration of awareness (includes isolated auras)

- 70-90% do not have scalp EEG correlate

- Predominantly subjective events without EEG change should be interpreted with caution

Verma and Radtke, J Clin Neurophysiol, 2006

Summary

- History and video-EEG monitoring are crucial in differentiating epileptic seizures from non-epileptic events

- Not all non-epileptic events are psychogenic
- Most psychogenic patients are conversion disorder
- Neurologists must not abandon psychogenic patients

- Lack of EEG changes <u>not</u> enough to diagnose non-epileptic events
  - video as important as EEG
  - be cautious about frontal lobe and simple partial seizures

References

Azar NJ, Tayah TF, Wang L, Song Y, Abou-Khalil BW. Postictal breathing pattern distinguishes epileptic from nonepileptic convulsive seizures. Epilepsia. 2008 Jan;49(1):132-7. Epub 2007 Jul 25. PubMed PMID: 17651411.

Bodde NM, Brooks JL, Baker GA, Boon PA, Hendriksen JG, Mulder OG, Aldenkamp AP. Psychogenic non-epileptic seizures--definition, etiology, treatment and prognostic issues: a critical review. Seizure. 2009 Oct;18(8):543-53. doi: 10.1016/j.seizure.2009.06.006. Epub 2009 Aug 13. Review. PubMed PMID: 19682927.

Gedzelman ER, LaRoche SM. Long-term video EEG monitoring for diagnosis of psychogenic nonepileptic seizures. Neuropsychiatr Dis Treat. 2014 Oct 15;10:1979-86. doi: 10.2147/NDT.S49531. eCollection 2014. Review. PubMed PMID: 25342907; PubMed Central PMCID: PMC4206377

LaFrance WC Jr, Baird GL, Barry JJ, Blum AS, Frank Webb A, Keitner GI, Machan JT, Miller I, Szaflarski JP; NES Treatment Trial (NEST-T) Consortium. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. JAMA Psychiatry. 2014 Sep;71(9):997-1005. doi: 10.1001/jamapsychiatry.2014.817. PubMed PMID: 24989152.

LaFrance WC Jr, Miller IW, Ryan CE, Blum AS, Solomon DA, Kelley JE, Keitner GI. Cognitive behavioral therapy for psychogenic nonepileptic seizures. Epilepsy Behav. 2009 Apr;14(4):591-6. doi: 10.1016/j.yebeh.2009.02.016. Epub 2009 Feb 20. PubMed PMID: 19233313.

Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol. 1994 Aug;36(2):233-7.

Raj V, Rowe AA, Fleisch SB, Paranjape SY, Arain AM, Nicolson SE. Psychogenic pseudosyncope: diagnosis and management. Auton Neurosci. 2014 Sep;184:66-72. doi: 10.1016/j.autneu.2014.05.003. Epub 2014 May 16. Review. PubMed PMID: 24882462.

Reuber M. Psychogenic nonepileptic seizures: answers and questions. Epilepsy Behav. 2008 May;12(4):622-35. doi: 10.1016/j.yebeh.2007.11.006. Epub 2007 Dec 27. Review. PubMed PMID: 18164250.

Verma A, Radtke R. EEG of partial seizures. J Clin Neurophysiol. 2006 Aug;23(4):333-9. Review. PubMed PMID: 16885707.

Epidemiology of Epilepsy

Dewi Depositario-Cabacar, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

EPIDEMIOLOGY

Dewi Depositario-Cabacar, MD
Assistant Professor, Neurology and Pediatrics
Children's National Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Epidemiology - Outline

- Incidence and prevalence
- Natural history of epilepsy
  - recurrence after a single seizure
  - intractability
  - remission
  - relapse after medication withdrawal
  - mortality (SUDEP)

Statistics

- Epilepsy is the 4th most common neurological condition
- Approximately 2.2 million people in the US have epilepsy
- Epilepsy affects more than 65 million people worldwide (0.5-1%)
- These numbers are increasing (better diagnostic tools, aging), but may still be underestimates.

(IOM 2012)

The first seizure

- Acute symptomatic – 29-39/100,000 per year
- Single unprovoked – 23-61/100,000 per year.
- Lifetime risk of developing epilepsy by 80 years old = 1.4 - 3.3%.

Hauser WA. 2008 Epilepsia.

The first seizure

- 2 year recurrence risk – 25% to 66%
- Risk of recurrence: increases
  1. neurologic deficit
  2. focal seizures +/- Todd palsy
  3. abnormal EEG
  4. status epilepticus
  5. multiple seizures
  6. prior acute symptomatic seizures

Shinnar S et al 1990 Pediatrics; Lindsten H et al 2001 Acta Neurol Scand

The first seizure

- 20 people per 100,000
- 25,000 – 40,000 children per year in US

(Camfield et al Epilepsia 1996; Hauser et al Epilepsia1993; Jallon et al Epilepsia 1997)

- at **2 years**, recurrence risk:
  idiopathic first seizure: 32%
  remote symptomatic: 57%

The first seizure

- Prospective , population-based studies (Olafsson et al Neurol 2005; Loiseau P et al Epilepsia 2005)
  33 - 42% remote symptomatic
  21 – 53% cryptogenic**
  14 – 37% idiopathic**

* *Commission on Classification and Terminology of the ILAE (Berg 2010)*

Does treatment with AED after a first seizure change the long term prognosis for seizure remission?

- Class II (RCT, prospective, not placebo-controlled)

N=419, 114 (between 2-16 yold)

	1 or 2 year seizure remission
Pts treated after 1st sz	⟹ 68% , n= 215
Pts treated after 2nd sz	⟹ 60%, n = 204

risk of recurrence [RR]=1.04, 95% CI=1.3-0.82

Musicco et al. Treatment of first tonic clonic does not improve the prognosis of epilepsy. Neurology 1997;49:991-998.

Prediction of Risk of Seizure Recurrence after a single and early epilepsy: Further results from the MESS Trial

- Multicenter trial for Early Epilepsy and Single Seizures (MESS) Trial
  n=722
  Randomized to immediate and deferred tx

***Same conclusions obtained.

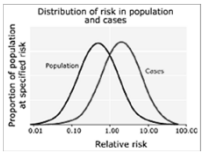
Kim LG et al Lancet Neurol 2006

Frequency Measures of Incidence and Prevalence

Incidence – number of new cases occurring in a given time. e.g. no. of cases per 100,000 population/year.

- **Epilepsy – 50 / 100,000 per year**
  higher in infants and older person
- About 40% develop epilepsy < 16 yold
  20% epilepsy > 65 yold

* Higher in low and middle income countries

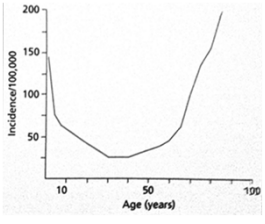


Hirtz et al 2007 Neurology 68:326-337

Age-specific incidence rate

Bimodal peaks in age-specific incidence (Forsgren 1996, Granieri 1983, Hauser 1996, Olafsson 2005, Sidenvall 1993)

- High in the first year of life
- Low throughout adult years
- Incidence increases > 55 years
- Over time, a trend for a decrease in childhood epilepsy, but an increase in older adults with epilepsy in developed countries.



Age-specific incidence rates based on combined results from studies in the USA, Iceland, and Sweden.

Frequency Measures of Incidence and Prevalence

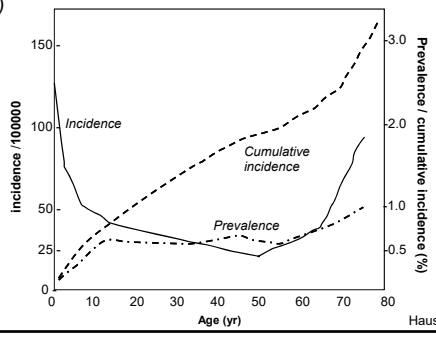
- **Prevalence** – current number of <u>active</u> cases at a specific moment in time.

  - no. of persons with epilepsy /1000 population.

  - 4-10 cases /1000 population
  * Higher in developing countries

Incidence and Cumulative Incidence of Epilepsy

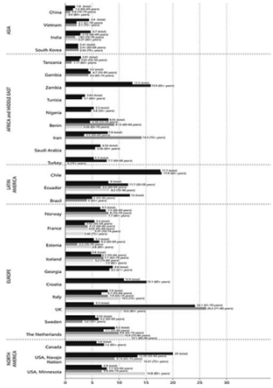
Age-specific incidence rate, cumulative incidence rate and prevalence rate of epilepsy in Rochester, Minnesota (1983-1974)



Hauser *et al*, 1983

Incidence of Epilepsy

- The incidence in high-income countries ranges from 24 to 71.0 per 100,000 per year.
- In low/middle-income countries, the incidence is higher and can be up to 190 per 100,000



Beghi, E and Giussani, G . Neuroepidemiology 2018;51:216–223

Distribution by Seizure Type and epilepsy syndrome

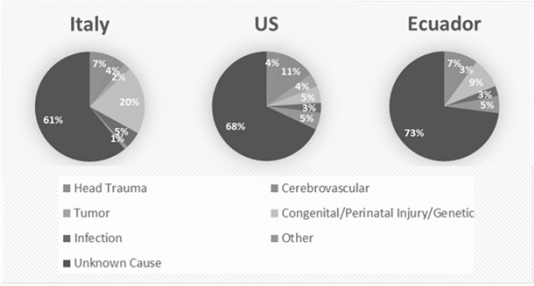
- Absence epilepsy
  incidence: 0.7 -8/ 100,000
  prevalence: 0.1 to 0.7/ 1000
- Juvenile myoclonic epilepsy
  incidence: 1 /100,000 persons
  prevalence: 0.1 – 0.2 /1000 (Jallon and Latour, 2005)
- Infantile spasms:
  incidence: 2-4.5/ 100,000 per year (Trevathan 1999)
- Lennox Gastaut :
  incidence: 1-2 / 100,000
  prevalence: 1.3 – 2.6 / 1000
  (Cowan, 2002)

Etiology by age

<15 years	15-34 years	35-64 years	≥65 years
• Congenital conditions	• CNS infection • Neoplasm • Head trauma • Birth injury/lesions	• **Cerebrovascular disease – 35%** • Neoplasm • Head trauma	• **Cerebrovascular disease – >60%** • Degenerative disease – 20%

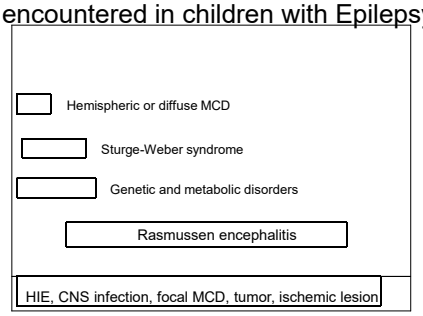
Hauser 1996

Etiology



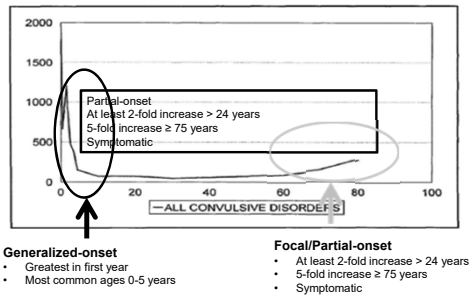
Hauser 1975, Placencia 1992, Granieri 1983

Usual age of onset and common etiologies/pathologic substrates often encountered in children with Epilepsy



Gupta A, Wylie E. Presurgical assessment of the Epilepsies with Clinical Neurophysiology and Functional Imaging. 2004

Common seizure type varies by age



Generalized-onset
- Greatest in first year
- Most common ages 0-5 years

Focal/Partial-onset
- At least 2-fold increase > 24 years
- 5-fold increase ≥ 75 years
- Symptomatic

Epilepsy risk in special populations

- 25.8% with mental retardation (MR)
- 13% with cerebral palsy (CP)
- 50% with both CP and MR
- 10% with Alzheimer
- 22% with stroke
- 33% with single unprovoked seizure

Definitions

- **Active epilepsy** – 1 seizure has occurred in the preceding period (2-5 years).
- **Remission** - no seizure has occurred in the preceding period (2-5 years).

Remission of Treated Epilepsy

- Community-based study Rochester, MN
  - 75% had 5 year remission
- The National General Practice Study of Epilepsy in United Kingdom (prospective study)
  - 60% had 5 year remission (9 years follow up)

**** Nearly 70% expected to enter remission.

Shafer SQ et al Epilepsia 1988; Cockerell OC et al Epilepsia 1997

Remission of Treated Epilepsy

Terminal remission data from selected studies

Reference	Study setting	Special study features	No. of patients	Median follow-up (years)	Years in remission	% in remission at median follow-up
Elwes et a. (32)	Hospital		106	5.5	2	79
Shafer et al. (29)	Community		432	17	5	66
Collaborative Group (33)	Hospital		280	4	1	70
Cockerell et al. (14)	Community	Definite epilepsy	564	7	5	68
Sillanpaa et al. (34)	Hospital	Children only	176	40	1	93
Lindsten et al. (35)	Community	≥1 baseline seizure ≥2 baseline seizures	107 89	9 9	5 5	64 58

From Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry. 2004; 75: 1376-1381.

Relapse

High risk of relapse:

- unrecognized minor seizure
- long history of seizure before remission
- structural brain lesion
- abnormal neurologic signs
- Learning disability
- past history of relapse
- more than one seizure type

MRC Antiepileptic drug withdrawal group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet 1991

Intractable Epilepsy

- 5-10% of epilepsy cases become refractory.
- 60% with focal seizures.

- etiology
- younger age at onset (<1 year old)
- high initial seizure frequency
- mental retardation

Intractable Epilepsy

- Prospective study: 613 children with newly diagnosed epilepsy
  10% met criteria for intractable epilepsy
  (failure of > 2 seizure meds, >1 seizure /month, over 18 month period)
- Increased risk of developing intractable epilepsy
  cryptogenic/symptomatic generalized syndromes
  high initial seizure frequency
  focal slowing on EEG

Berg, AT et al. Early development of intractable epilepsy in children: a prospective study. Neurology 2001.

The New England Journal of Medicine

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

PATRICK KWAN, M.D., AND MARTIN J. BRODIE, M.D.

- 63% become seizure-free
- More likely if idiopathic and ≤ 20 seizures prior to treatment
- AED #1: 47% seizure-free
- AED #2: 13% seizure-free
- AED #3: 1% seizure-free
- 3% seizure-free with two AEDs in combination
- Reason for failure is important predictor

Mortality

- **Standardized mortality rate (SMR)**
  observed no. of deaths in an epilepsy population to that expected based on the age and sex – specific mortality in a population
- SMR - 2-3 x higher in patients with epilepsy.
- Highest in children and >75 years old.
- Increased in remote symptomatic cases

Lhatoo et al Mortality in epilepsy Ann Neurol 2001

Mortality

- **Major causes**:
  a. Epilepsy- related deaths
  SUDEP, Status epilepticus, accidents and suicide

  b. Deaths related to the underlying cause

  c. Deaths unrelated to the underlying cause

Causes of Death in Epilepsy

Unrelated deaths

- Neoplasms outside the central nervous system
- Ischemic heart disease
- Pneumonia
- Others

Related to underlying disease

- Brain tumors
- Cerebrovascular disease
- Cerebral infection-abscesses and encephalitis
- Inherited disorders, e.g., Batten's disease

Nashef L, Shorvon SD. Mortality in epilepsy. Epilepsia. 1997; 38: 1059-1061.

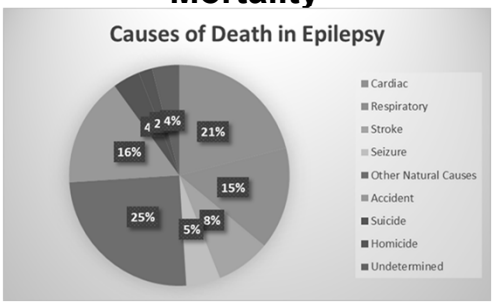
Causes of Death in Epilepsy

Epilepsy-related deaths

- Suicide
- Treatment-related deaths
- Idiosyncratic drug reactions
- Medication adverse effects
- Seizure-related deaths
- Status epilepticus
- Trauma, burns, drowning
- Asphyxiation, aspiration
- Aspiration pneumonia after a seizure
- Sudden unexpected death in epilepsy (SUDEP)

Nashef L, Shorvon SD. Mortality in epilepsy. Epilepsia. 1997; 38: 1059-1061.

Mortality



Barooni 2007

- SUDEP is the cause of death in 4-17% of unselected cases, 50% of refractory epilepsy
- SUDEP most common with recurrent generalized seizures, polypharmacy, coexisting neurologic disease

Mortality

- The true incidence of epilepsy- related deaths is unknown

  - U.S. national mortality records provide grossly incomplete data on epilepsy.

Mortality

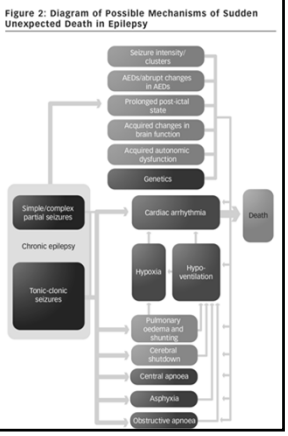
Sudden unexpected death in epilepsy (SUDEP)

- occurs from a nontraumatic death with no obvious cause of death by postmortem examination.
- Mechanism not fully understood.

(proposed: cardiac arrhythmia, respiratory depression, cerebral autonomic dysfunction)

SUDEP - Mechanism

- **Mechanism not fully understood**
- Possibly multifactorial proposed:
  - cardiac arrhythmia,
  - respiratory depression
  - cerebral autonomic dysfunction
    (dysregulation of systemic or cerebral circulation)
  - seizure-induced hormonal and metabolic changes
    (during and after seizures)



Genes associated with sudden unexpected death in epilepsy (SUDEP).

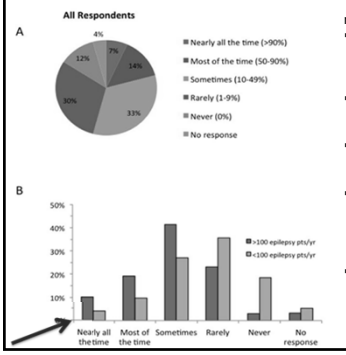
Gene	OMIM disease	Evidence for association with SUDEP
KCNA1	Episodic ataxia/myokymia syndrome	Animal model; variant found in SUDEP case
SCN1A	Dravet syndrome	Animal model; *de novo* variants found in SUDEP cases
SCN2A	Early-infantile epileptic encephalopathy 11	*De novo* variants found in SUDEP cases
SCN8A	Early-infantile epileptic encephalopathy 13	Animal model; *de novo* variants found in SUDEP cases
DEPDC5	Familial focal epilepsy with variable foci	*De novo* variants found in SUDEP cases
KCNQ1	Long QT syndrome type 1	Variants found in SUDEP cases
KCNH2	Long QT syndrome type 2	Variants found in SUDEP cases
SCN5A	Long QT syndrome type 3	*De novo* variant found in SUDEP case

Bagnall et al. Genetics Basis of Sudden Unexpected Death in Epilepsy. Neurology 2017

Epilepsy Behav. 2014 Jun;35:13-8. doi: 10.1016/j.yebeh.2014.03.022. Epub 2014 May 3.

Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists.

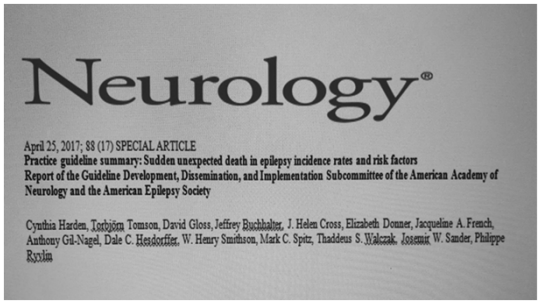
Friedman D[1], Donner EJ[2], Stephens D[3], Wright C[4], Devinsky O[5].



n= 1200 respondents

- U.S. and Canadian neurologists rarely discuss SUDEP with all patients with epilepsy/caregivers.
- Only 6.8 % discussed SUDEP nearly all the time.
- Nearly 60% of the respondents stated that rxn was negative.
- assessment of SUDEP risk factors revealed that most neurologists (82.8%) have limited knowledge about this subject.
- Surveys of physicians in the UK and Italy: most physicians do not discuss SUDEP

Practice guideline summary: Sudden expected death in epilepsy incidence rates and risk factors



Harden C et al. Neurology April 2017

SUDEP -incidence

SUDEP risk in children with epilepsy:
0.22/1,000 patient-years
(95% CI 0.16-0.31)

SUDEP risk in adults with epilepsy:
1.2/1,000 patient-years
(95% CI 0.64-2.32)

Harden C et al. Neurology April 2017

SUDEP Incidence
(Based on twelve Class 1 studies)

Population	SUDEP/1,000 patient-years (confidence interval)	Confidence
Overall	0.58 (0.31-1.08)	Low
Childhood	0.22 (0.16-0.31)	Moderate
Adulthood	1.2 (0.64-2.32)	Low

Harden C et al. Neurology April 2017

Incidence recommendation 1: SUDEP incidence in children

Level B

- There is a rare risk of SUDEP.
- In 1 year, SUDEP typically affects 1 in 4,500 children with epilepsy; in other words, annually, 4,499 of 4,500 children will not be affected by SUDEP.

Harden C et al. Neurology April 2017

Incidence recommendation 2: SUDEP incidence in adults

Level B

- There is a small risk of SUDEP.
- In 1 year, SUDEP typically affects 1 in 1,000 adults with epilepsy; in other words, annually, 999 of 1,000 adults will not be affected by SUDEP.

SUDEP Risk factors (Based on 6 Class I and 16 Class II articles

Factor	Odds Ratio (CI)	Confidence level
Presence of GTCs vs lack of GTCS	10 (17-14)	Moderate
Frequency of GTCS	OR 5.07 (2.94-8.76) for 1-2 GTCS per year and OR 15.46 (9.92-24.10) for >3 GTCS per year	High
Not being seizure-free for 1-5 y	4.7 (1.4-16)	Moderate
Not adding an AED when patients are medically refractory	6 (2-20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2-0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0.0.3)	Moderate

SUDEP Risk factors (Based on 6 Class I and 16 Class II articles)

- Major risk factor:

  Presence and frequency of GTCS.

  - if with >3 GTCS per year, with 15-fold increased risk of SUDEP.
  - moderate confidence in the evidence from 2 Class II studies.

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is low that the following factors are associated with altering SUDEP risk:

- Nocturnal seizures (associated with increased risk)
- Any specific AED (none associated specifically with increased risk)
- LTG use in women (associated with increased risk)
- Never having been treated with an AED (associated with increased risk)
- Number of AEDs used overall (associated with increased risk)
- Heart rate variability (not associated with increased risk)
- Extratemporal epilepsy (associated with increased risk)
- Intellectual disability (associated with increased risk)
- Male gender (associated with increased risk)
- Anxiolytic drug use (associated with increased risk)

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low that the following factors are associated with altering SUDEP risk:

- Overall seizure frequency when evaluated by using all seizure types
- Medically refractory epilepsy vs not having well-controlled seizures defined as no seizures for the past year
- Monotherapy vs polytherapy
- CBZ, PHT, or VPA levels that are above, below, or within the reference range
- Psychotropic drug use
- Mental health disorders, lung disorders, or alcohol use

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:

- LTG use in people with highly refractory epilepsy
- Frequent changes in AEDs
- Therapeutic drug monitoring
- Undergoing a resective epilepsy surgical procedure**
- Engel outcome of epilepsy surgery**
- VNS use for more than 2 years**

**Although current research does not rule out the possibility of a beneficial effect or, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing SUDEP risk.

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:

- Epilepsy etiology - idiopathic or localization related
- Structural lesion on MRI
- Duration of epilepsy
- Age at epilepsy onset
- Postictal EEG suppression

SUDEP – Practice Guidelines Recommendations (AAN, AES)

- Level B: Epilepsy with GTCS – physicians should actively manage epilepsy therapies to reduce seizures.
- Level C: with frequent GTCS and nocturnal seizures, physicians should advise (if permitted) to use nocturnal supervision or nocturnal precautions.
- Level B: Clinicians should tell patients that seizure freedom particularly from GTCS, strongly associated with decreased risk of SUDEP.

Mortality

- **Status Epilepticus fatalities**
  estimates vary widely
  median estimate: 0.94/100,000 annually
  (Rosenow F et al, Epilepsia 2007)
- **Accidental deaths**
  drowning, traffic accidents, trauma, falls, burns, aspiration
  1.2% - 6.5 % in community based studies.

Mortality

Suicides

- Suicides per 100,000 population in US is 12.4*
- Suicide increased risk with:
  1. mental illness
  2. drug addiction
  3. Temporal lobe epilepsy
  4. personality disorder
  5. early onset epilepsy (adolescence)

* Calculated from data from U.S. Centers for Disease Control and Prevention.

Conclusion: Epidemiology

- Incidence and prevalence
- Natural history of epilepsy
  - recurrence after a single seizure
  - intractability
  - remission
  - relapse after medication withdrawal
  - mortality

Board Questions

Question 1

The incidence of epilepsy is the number of new cases occurring in a given time. What is the incidence of epilepsy?

a. 4-10 cases/1000 population

b. 50 cases/100,000 per year

c. 250 cases/100,000 per year

d. 200,000 cases

Question 2

Which one of the following is not an epilepsy related death:

a. Cerebrovascular accident

b. Sudden unexpected death in epilepsy

c. Suicides

d. Drowning

e. Adverse drug effects

Question 3

The risk for SUDEP is higher in which of the following patient with epilepsy?

a. A 24 year old female with history of GTCs on 3 seizure medications with no seizures for a year.

b. A 17 year old male with depression with 4-6 focal seizures per month.

c. A 6 year old girl with once a month GTCs on Valproic acid.

d. A 10 year old boy with a right frontal focal cortical dysplasia on Lamotrigine, Oxcarbazepine with 2 focal seizures per month being worked up for epilepsy surgery.

Question 4

Risk of suicide is highest in association with the following except:

a. Substance abuse

b. Temporal lobe epilepsy

c. Frontal lobe epilepsy

d. Mental illness

e. Adolescence

Question 5

5. Which of the following statement is correct:

a. In 1 year, SUDEP typically affects 1 in 4,500 children with epilepsy.

b. In the practice guidelines for SUDEP, clinicians should tell patients that seizure freedom particularly from focal seizures are strongly associated with decreased risk of SUDEP.

c. The number of AEDs used overall is a major risk factor for SUDEP.

d. The age of epilepsy onset is a major risk factor for SUDEP.

Normal EEG

Amar B. Bhatt, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

NORMAL EEG

Amar B. Bhatt, MD
Assistant Professor of Neurology, Epilepsy Section
Rush University Medical Center
Program Director, Neurology Residency

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

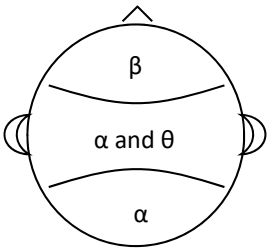
- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

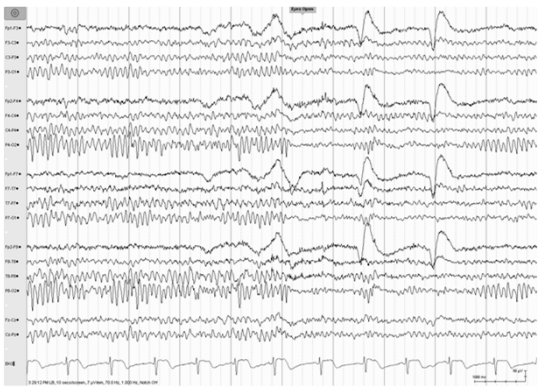
Overview

- Awake EEG
- Drowsy EEG
- Normal / Benign Variants
- Sleep EEG

Major waking rhythms

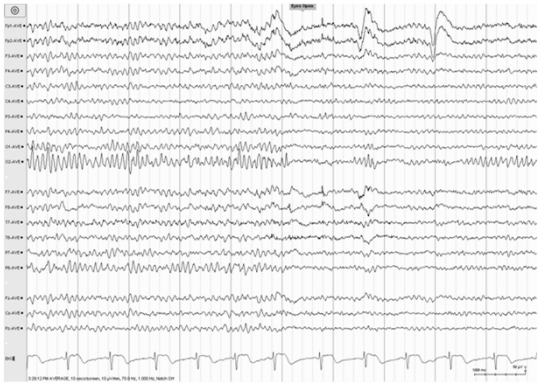
- Posterior Dominant Rhythm
- Mu rhythm
- Third rhythm





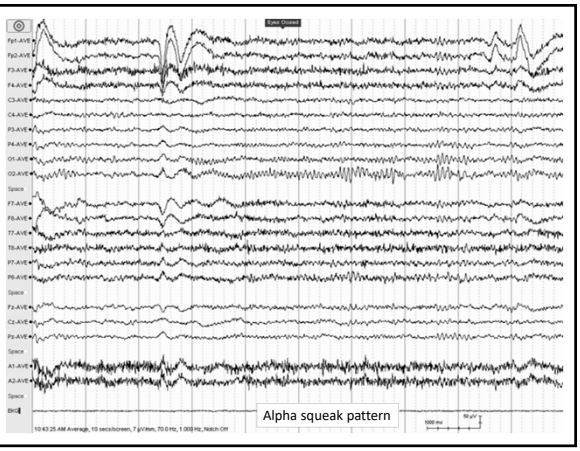
Posterior Dominant Rhythm

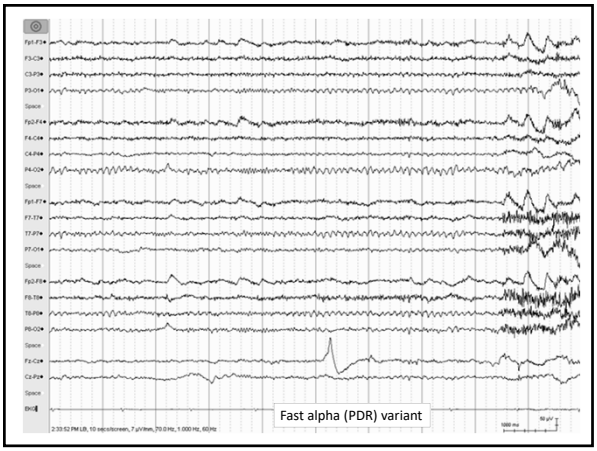
- "the Alpha rhythm" (resting rhythm of occipital cortex)
- Variants
  - alpha squeak
  - slow and fast variants
  - paradoxical alpha – increases with alertness
- Bancaud's phenomenon (abnormal) – failure to attenuate with eye closure (ipsilateral pathway lesion)
- Should be symmetric…?

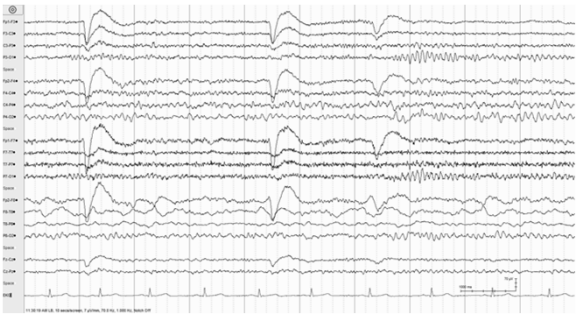


What is the allowable, normal asymmetry regarding the posterior dominant rhythm (alpha rhythm)?

A. Up to 35% higher amplitude on the right, and up to 35% higher amplitude on the left.
B. Up to 50% higher amplitude on the right, and up to 35% higher amplitude on the left.
C. Up to 35% higher amplitude on the right, and up to 50% higher amplitude on the left.
D. Up to 50% higher amplitude on the right, and up to 50% higher amplitude on the left.
E. Any asymmetry is considered abnormal

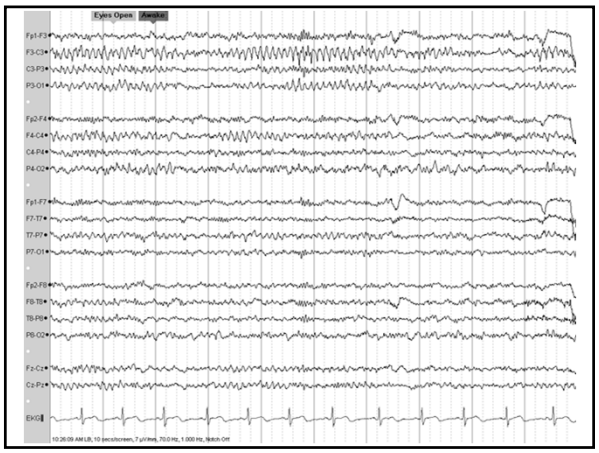






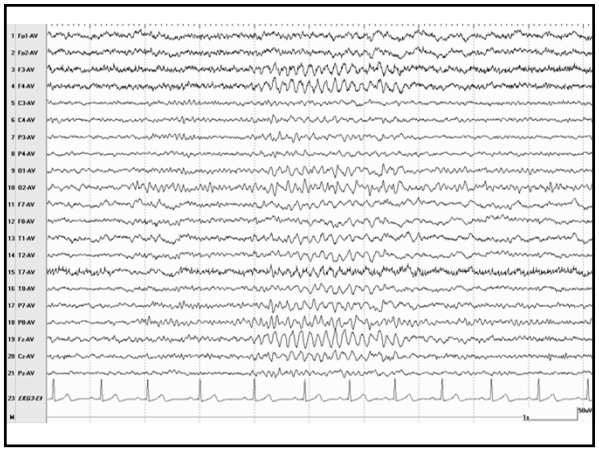
Mu rhythm

- resting rhythm of central (premotor) cortex
  - Alpha or theta (7-11 Hz) spiky rhythm
  - Looks like the letter "μ"
- Attenuates with contralateral limb movement (or even thinking about movement)
- Often enhanced in presence of breach rhythm



Midline theta

- a.k.a. Ciganek rhythm
- 5-7 Hz sinusoidal activity maximal at Cz or Fz
- may be spiky or arciform (mu-like)
- Present in awake and drowsy states
- Unrelated to eye opening, alerting, limb mvmt
- May enhance with concentration (midline frontal theta)

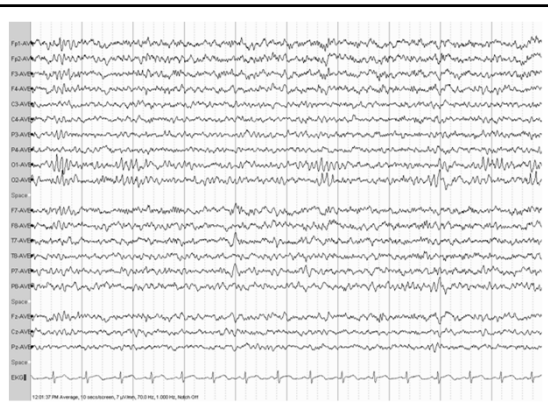


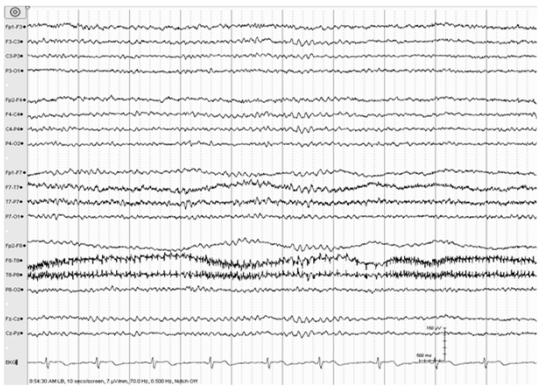
Which of the following is NOT a characteristic of Stage N1 Sleep?

A. Slow lateral eye movements
B. Attenuation of posterior dominant rhythm
C. Emergence of sleep spindles
D. Emergence of vertex waves
E. Emergence of theta activity

Drowsy EEG

- Changes in PDR
  - Attenuation without eye opening
  - May slow by up to 1 Hz
  - May become anteriorly projected
- Slow lateral eye movements
- Emergence of theta activity (often bursts)
- Emergence of frontal beta activity



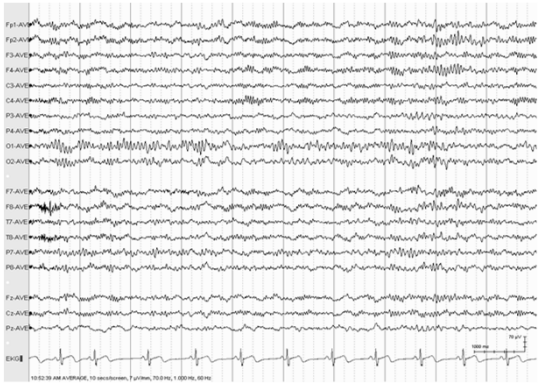


Frontal Beta Activity

- Resting rhythm of the frontal lobes
- Best seen in drowsiness

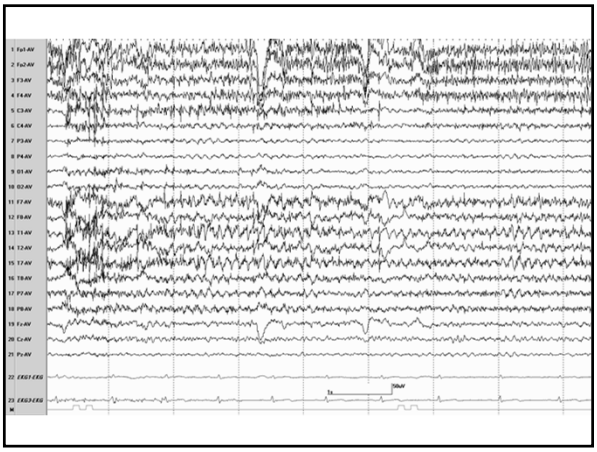
- Abnormal*
  - Generalized
  - High voltage (>30 μV)
  - Persistent in sleep or awake states

*think benzodiazepines, barbiturates, and propofol



Third rhythm

- Resting rhythm of temporal cortex
- Alpha or theta (7-11 Hz) sinusoidal rhythm
- May be asynchronous or unilateral
- Can be seen in waking or drowsiness
- If not seen, EEG may still be normal



Benign Variants

- May be rhythmic or occur in isolation
- May be high or low voltage (typically low)
- May be quite “sharp” or “spiky”

- Usually in drowsiness (not in deeper sleep)

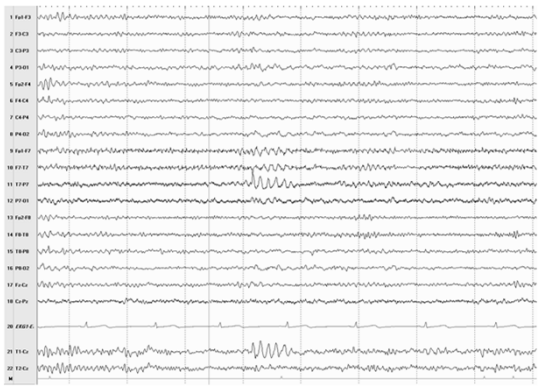
- Should not disrupt the background
  - Have a “smooth” rhythm
  - No associated slow / delta activity

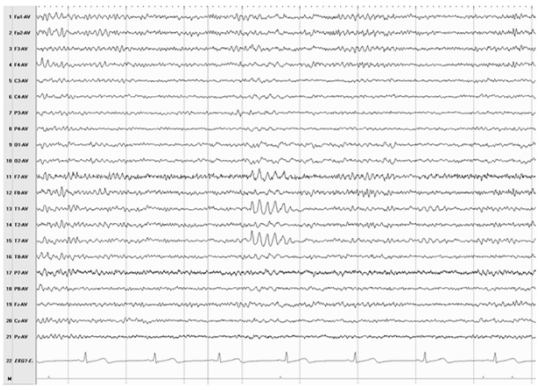
Which of the following normal / benign variants occurs in waking (and not drowsiness)?

A. Wicket waves
B. 14- and 6-Hz positive bursts
C. Small sharp spikes
D. Lambda waves
E. Psychomotor variant

Wickets

- Rhythmic bursts of monophasic 6-11 Hz activity
- Seen bitemporally in drowsiness (not in deep sleep)
- Typically occur in trains or runs
  - don't disrupt background
  - tend to be "isosceles" (no aftergoing slow wave)
  - when seen as single waves – may be overinterpreted
  - surrounded by similar waves (may be lower amplitude)
- On a spectrum with third rhythm





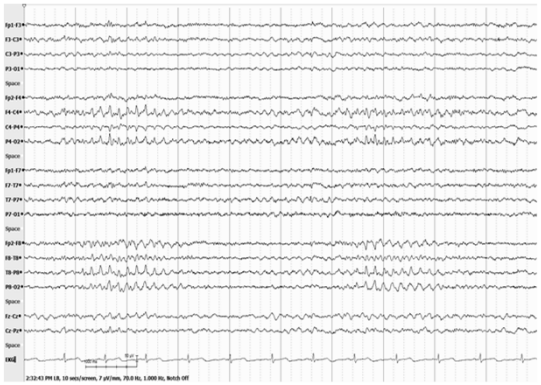
Wickets

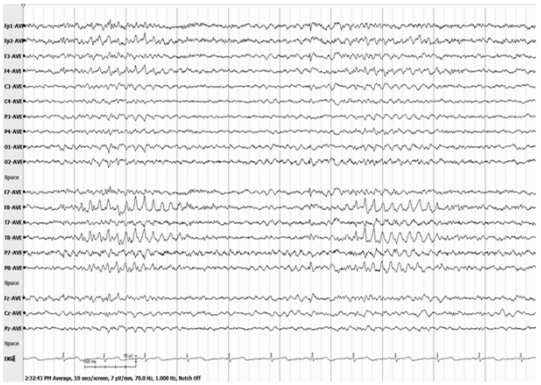
- One of the most commonly over-read benign variants
- One study re-read EEGs of patients referred to an epilepsy center
  - over 50% (25/46) had wicket rhythms misinterpreted as epileptiform
  - these 25 patients had nonepileptic clinical episodes
- Wicket rhythms tend to be more LEFT sided ("classic" teaching is incorrect)

Krauss GL, et al. "Clinical and EEG features of patients with EEG wicket rhythms misdiagnosed with epilepsy." *Neurology* 64.11 (2005): 1879-1883.
Azzam RH, Arain AM, and Azar NJ. "Revisiting the Laterality of Wicket Spikes With Continuous EEG." *Journal of Clinical Neurophysiology* 32.2 (2015): e8-e11.
Vallabhaneni M, et al. "A case–control study of wicket spikes using video-EEG monitoring." *Seizure* 22.1 (2013): 14-19.

Rhythmic Temporal Theta Bursts of Drowsiness (RTTBD)
Rhythmic Midtemporal Theta of Drowsiness (RMTD)
Psychomotor variant

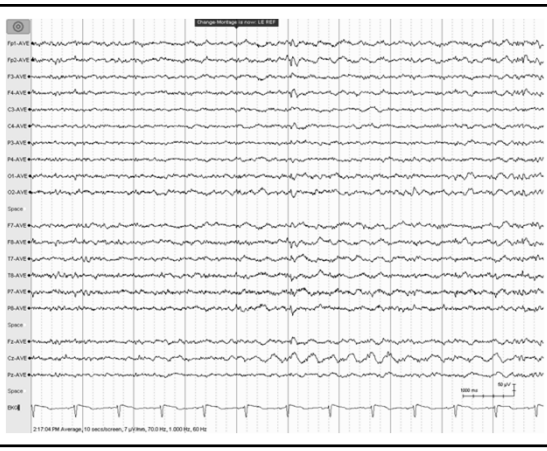
- Bursts of rhythmic, notched 5-7 Hz activity
- Bi-synchronous or bilateral independent in the midtemporal regions
- Seen in drowsiness (disappear in deeper sleep)

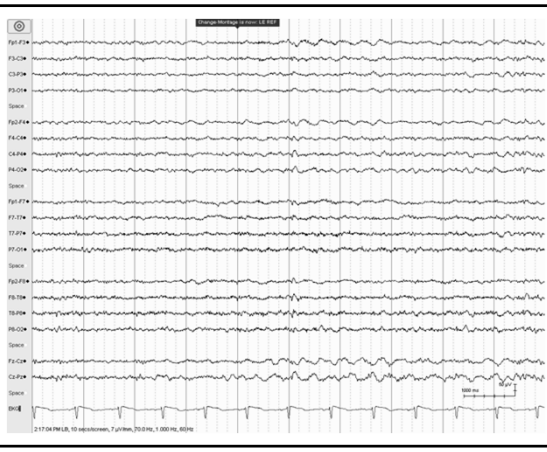


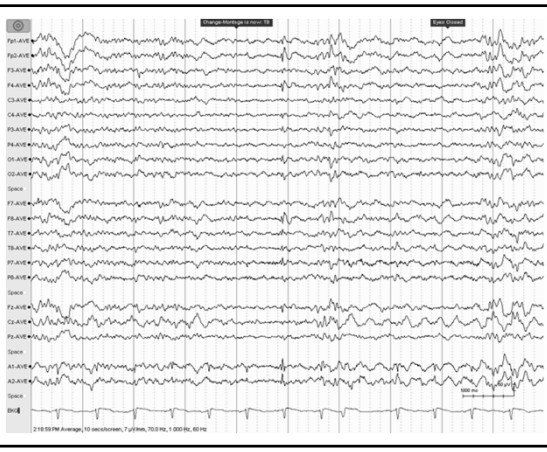


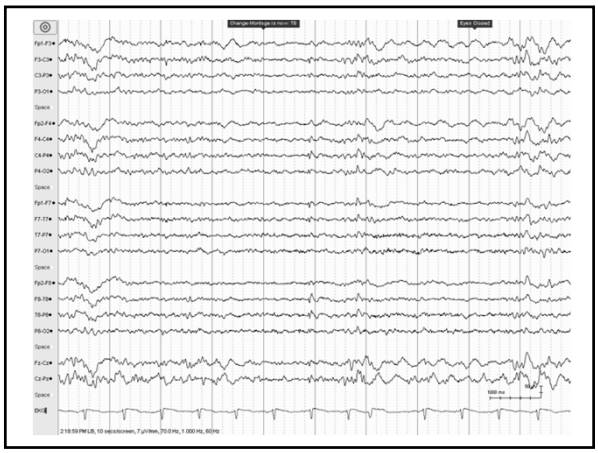
Benign Sporadic Sleep Spikes (BSSS)
Benign Epileptiform Transients of Sleep (BETS)
Small Sharp Spikes (SSS)

- Typically < 50 ms and < 50µV
- May be diphasic (morphology varies)
- May have a transverse dipole
- Usually seen bilaterally independently
- Appear in drowsiness (disappear in deeper sleep)
- Do not distort background; no associated slow activity



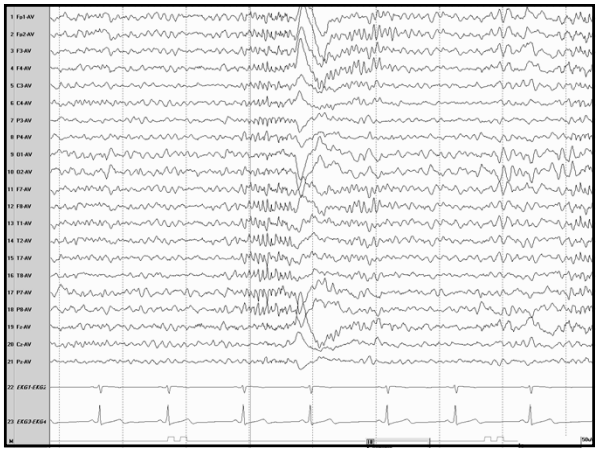


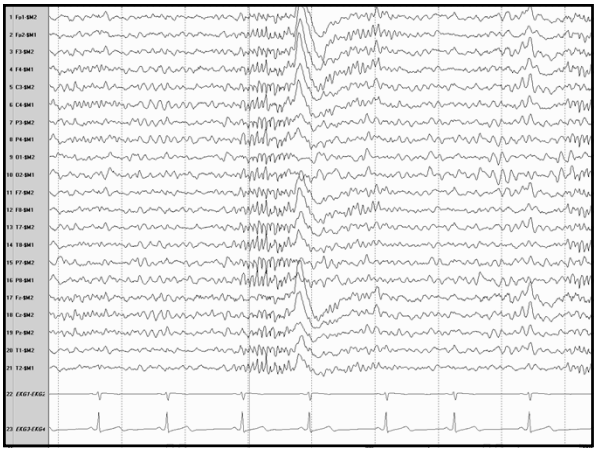


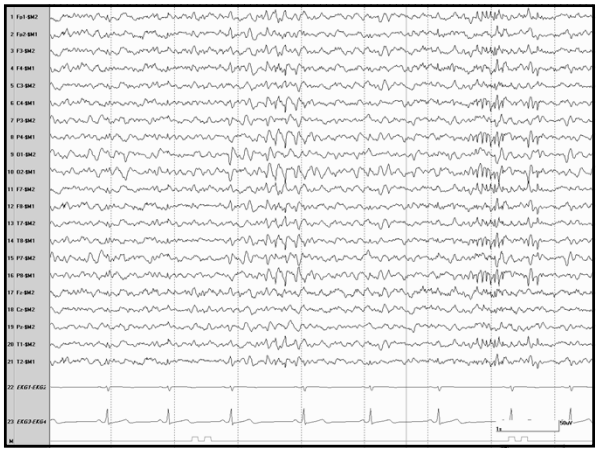


14- and 6-Hz positive bursts (ctenoids)

- Intermixed 14 Hz and 6-7 Hz activity
- Wide field positive polarity (posterior temporal predominance)
- Best confirmed on contralateral ear montage (long distance referential)
- Occur in N1 or N2 sleep
- Seen in normal adolescents but also in hepatic disease (Reye syndrome, hepatic encephalopathy)







6-Hz Phantom Spike-and-Wave

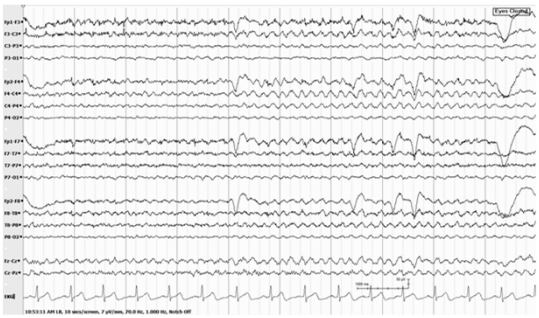
- Spike is often very low voltage (“phantom”)
- Occur in two forms:

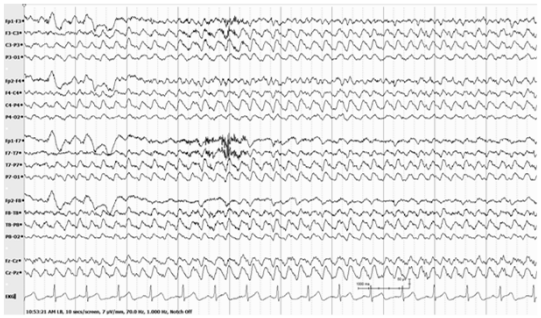
WHAM	FOLD
Waking	Female
High Amplitude	Occipital
Anterior	Low Amplitude
Male	Drowsiness

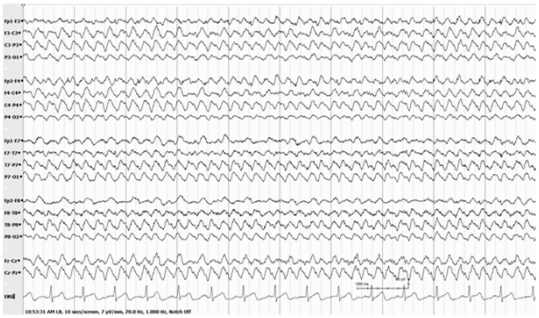
- WHAMs have an association with epilepsy (may actually represent true epileptiform frontally predominant generalized spike-and-wave)

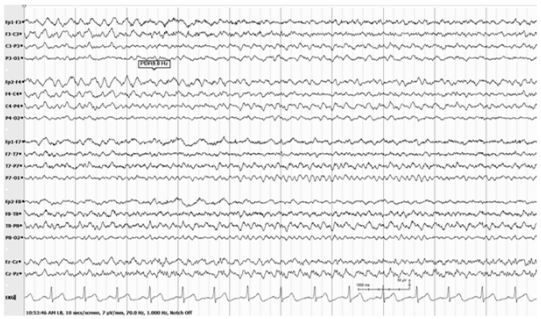
Subclinical Rhythmic Electrographic Discharges in Adults (SREDA)

- Mainly seen in older adults in waking or drowsiness (often during HV)
- Wide field (parietal or posterior temporal predominance)
- Mixed delta-theta rhythmic activity that evolves to faster frequencies over 20-80 seconds
- Has been described as 'seizure' in reverse
- Must be <u>without</u> clinical signs









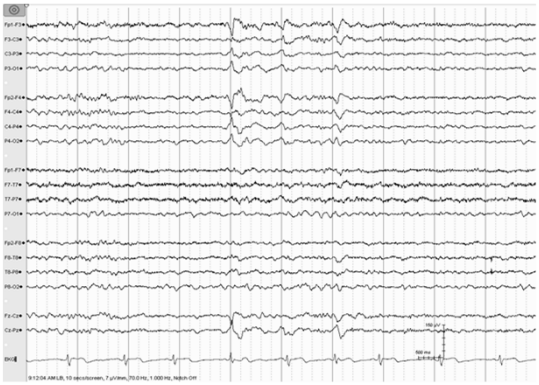
Sleep EEG

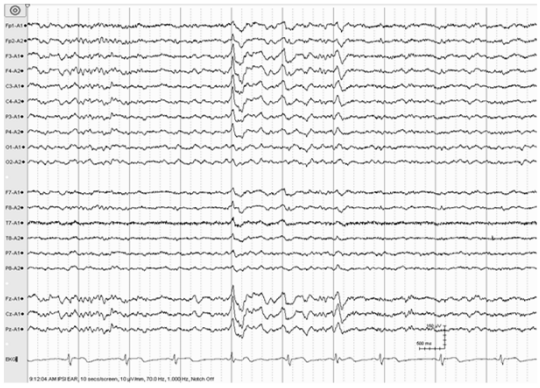
- Stage N1 - drowsiness
- Stage N2 - specific architecture
- Stage N3 - slow wave sleep
- REM - rapid eye movement

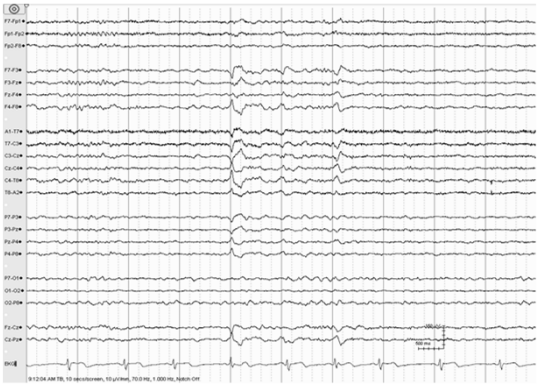
Patterns in Stage N2 Sleep*

- Sleep spindles
- K complexes
- Vertex waves (can also be in stage 1)
- POSTS

* all are normal, though some appear “sharp”

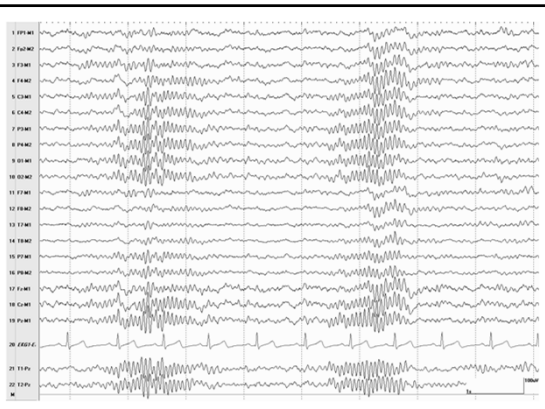






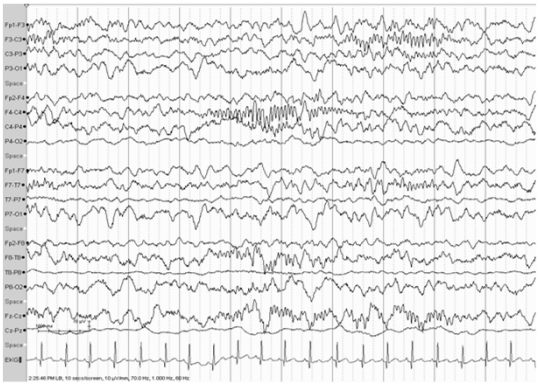
Vertex Waves

- High voltage, sharp looking, surface negative waves
- Originate at Cz (the vertex)
- Thought to be generated by the thalamus



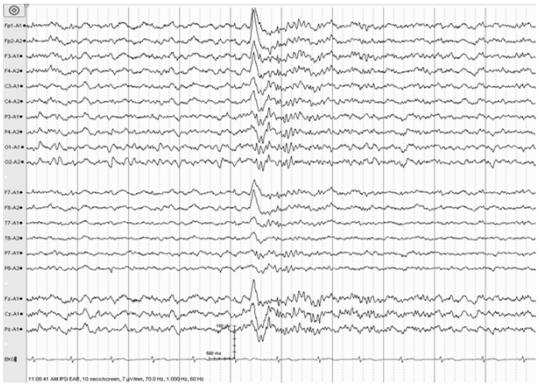
Sleep spindles

- Bursts of beta activity (12-16 Hz)
  - symmetric and synchronous (age > 2 yrs)
  - fronto-central head region
  - last 1-1.5 seconds
- Thought to be generated by the thalamus



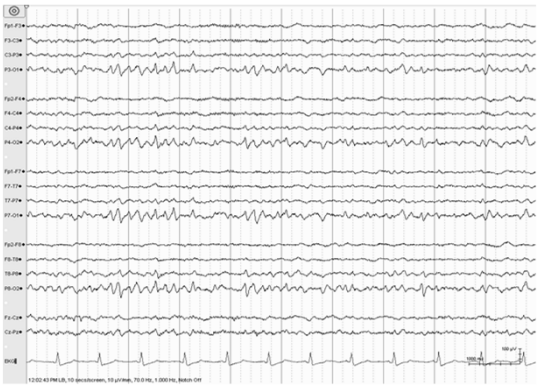
By what age should sleep spindles become synchronous?

A. 2 months
B. 6 months
C. 12 months
D. 2 years
E. 6 years



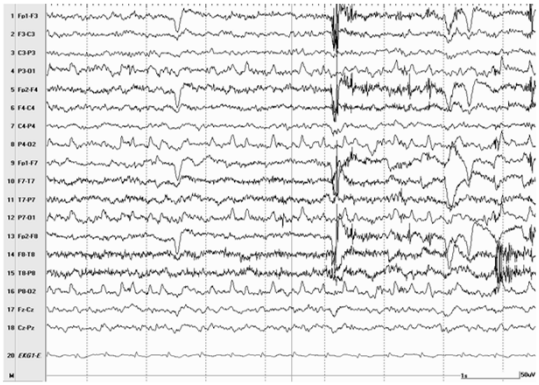
K complexes

- Broad 0.5-2 second long wave
- Fronto-central predominance
- Might be followed by a sleep spindle
- related to arousal (noise, clapping, knock)



POSTS

- Positive Occipital Sharp Transients of Sleep
- That's exactly what they are.
- Should be symmetric and synchronous.



Lambda Waves

- A sharp looking wave that has a positive polarity in the occipital regions
- looks like the letter "λ"
- synchronous and symmetric
- Occurs when scanning lines or looking at an picture (visual activity)

Summary

- Awake EEG includes PDR, Mu, and third rhythm
- Benign variants do not disrupt the background, do not persist into deep sleep, and must not be over-interpreted
- Normal N2 sleep structures include K complexes, vertex waves, sleep spindles, and POSTS

Interictal Epileptiform Patterns

Mohamad Z. Koubeissi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

INTERICTAL EPILEPTIFORM PATTERNS

Mohamad Z. Koubeissi, MD
Professor of Neurology
Director, Epilepsy Center
The George Washington University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Interictal Epileptiform Discharges

- Distinctive waveforms or complexes resembling those recorded in a proportion of human subjects suffering from epileptic disorders and in animals rendered epileptic experimentally".
  - *The International Federation of Societies for Electroencephalography and Clinical Neurophysiology (1)*
- EEG abnormalities associated with a predisposition (i.e. association is not absolute) to experiencing or developing epileptic seizures (2).
- Detection of epileptiform abnormalities increases the likelihood of an epileptic seizure disorder.
- Need to be taken together with the clinical history and other diagnostic test results

(1) (1974) A glossary of terms most commonly used by clinical electroencephalographers. Electroencephalogr Clin Neurophysiol 37:538-548. (2) Sam MC, So EL (2001). Epilepsia 42:1273-1278.

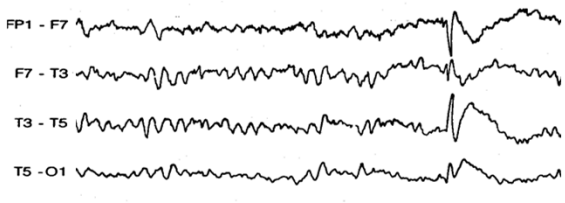
EEG of asymptomatic first-degree relatives of patients with JME, CAE, and rolandic epilepsy

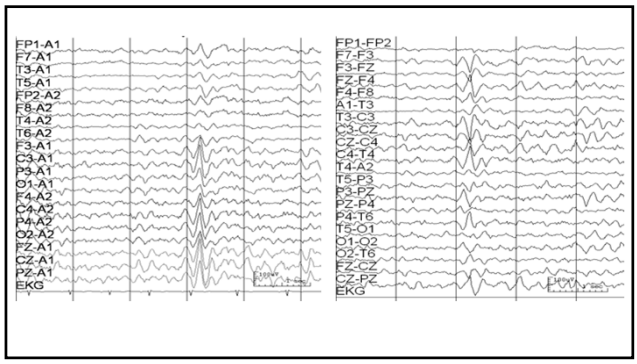
- Possible genetic roles in all three syndromes, yet genes remain unknown
- Metanalysis: 15 studies, a total of 3,858 asymptomatic relatives.
- Prevalence of 'abnormal' EEG waves :
  - 42% for CAE
  - 33% for RE
  - 21% for JME
- Close to what would be expected based on Mendelian inheritance
- However, EEG signature traits were as low as 5%

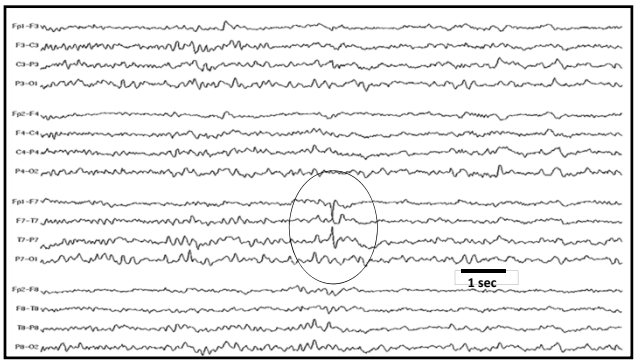
Tashkandi et al. (2019) Epileptic Disord 21(1):30-41

Spikes/Sharp Waves

- Have pointed peaks when recorded at 30 mm per second.
  - Spike duration = 20 to 70 msec
  - Sharp wave duration = 70 to 200 msec
- Both types of waves often occur in the same clinical disorder or the same patient.
- Distinct from the background
- Disrupt the background
- Polyphasic
- Main component is surface negative
- Often followed by a slow wave with variable amplitude
- Have a field
- Asymmetrical slopes





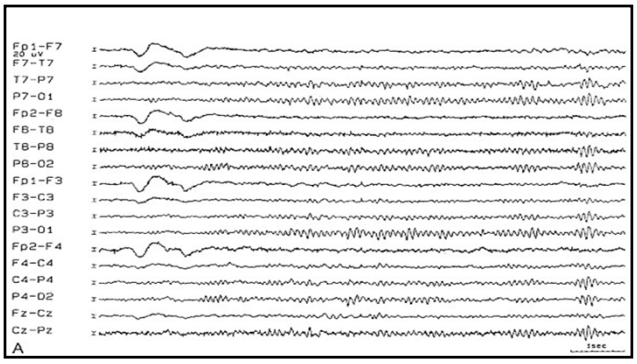


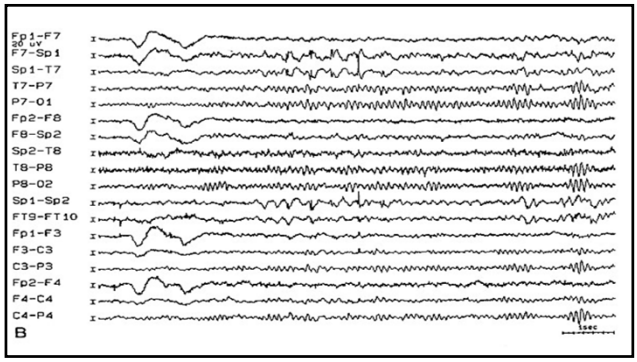
Spike/Sharp Wave Locations

- Temporal > Frontal > Centrotemporal > Parietal > Occipital > Central /paracentral.
- Association with epilepsy is better for temporal than rolandic or occipital spikes (1)

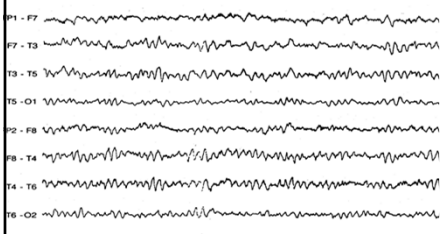
Anterior Temporal Spikes →	90% Epilepsy
Rolandic Spikes →	38% Epilepsy

(1) Fois A et al. (1988) Epilepsia 29:620-623

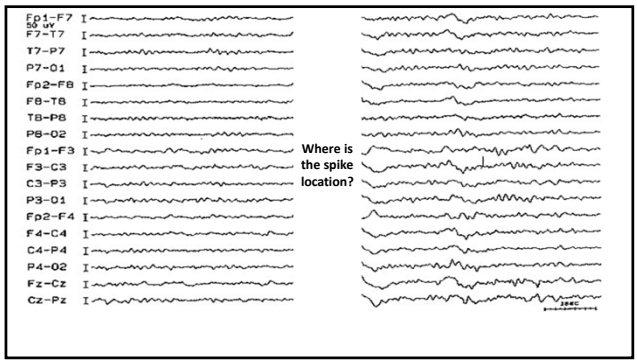




Hyperventilation in a 63 year old woman



There is a spike hidden under this panel. Can you guess its location?



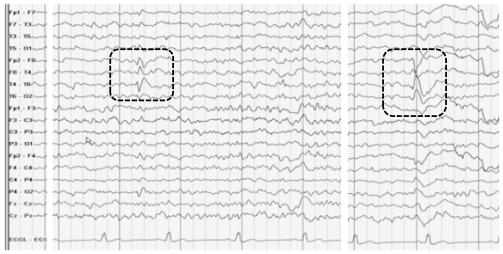
Spike/Sharp Wave Locations

- Occipital IED are encountered in migraine (1)
- About 60% of children with occipital spikes do not have epilepsy.
- Occipital "Needle spikes" are seen in the EEG of children with congenital blindness, but no seizures (2).

(1) Slatter KH (1968). Brain 91:85-98. (2) Kellaway P (1955) Electroencephalogr Clin Neurophysiol Suppl Suppl. 4:212-213.

Focal Spikes

- Scalp surface-positive IED can be seen
  - After brain surgery
  - In newborns with periventricular hemorrhage or leukomalacia
  - In young children with multifocal IED and global encephalopathy



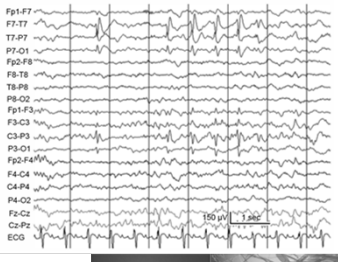
*

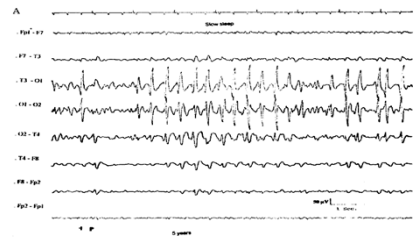
Focal Spikes

- Spikes have typical features in
  - Benign Epilepsy with Centrotemporal Spikes
    - Negative over T and C
    - Positive end of the dipole over frontal regions
  - Benign Childhood Epilepsy with Occipital Paroxysms
  - Early-onset Childhood Seizures with Occipital Spikes (Panayiotopoulos syndrome) (1)

(1) Caraballo R et al (2000) Neurology 55:1096-1100.

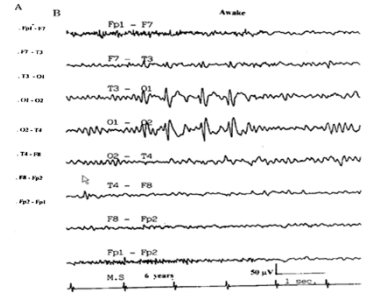
BECTS





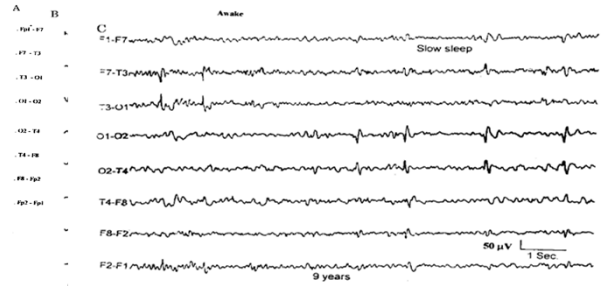
(A) Occipital paroxysms during sleep in a 5-year-old girl.

(1) Caraballo R et al (2000) Neurology 55:1096-1100.



(B) Occipital paroxysms in a 6-year-old child in alert stages

(1) Caraballo R et al (2000) Neurology 55:1096-1100.



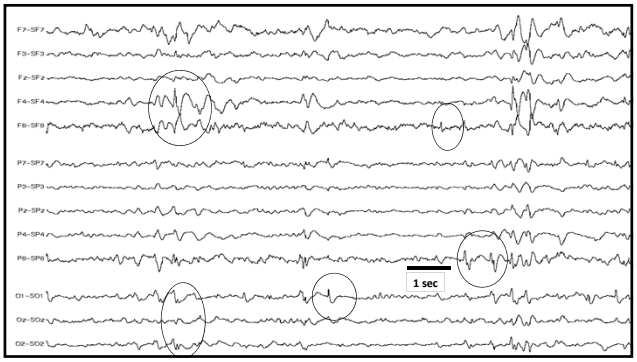
(C) Occipital and centrotemporal spikes of a 9-year-old child during sleep.

(1) Caraballo R et al (2000) Neurology 55:1096-1100.

Multifocal Spikes

- Multiple independent foci of IEDs affecting both hemispheres.
- Most frequently seen in children 4-7 years old (1)
- Background EEG slowing is present is nearly all (97%) of the patients.
- 94% of patients have seizures
- Generalized motor seizures are the most common seizure-type (76% of patients)
- Seizure frequency is high, 50% have daily seizures.
- Concomitant neurological abnormalities are very frequent

(1) Noriega-Sanchez A, Markand ON (1976) Neurology 26:667-672.



Lateralized Periodic Discharges (LPDs)*(PLEDS)*

- Epileptiform discharges that recur at regular periodicity in one hemisphere
- Monophasic or polyphasic
- May or may not be associated with slow waves
- May affect a whole hemisphere
- Recur every 0.3 to 4 seconds
- Highly associated with acute cerebral disorders, especially structural lesions such as stroke, brain trauma, herpes encephalitis, tumor, and abscess.
- Rare causes are metabolic encephalopathy, Creutzfeldt-Jakob disease, migraine, and toxic encephalopathy (e.g. aminophylline or alcohol).

Lateralized Periodic Discharges (LPDs) *(PLEDS)*

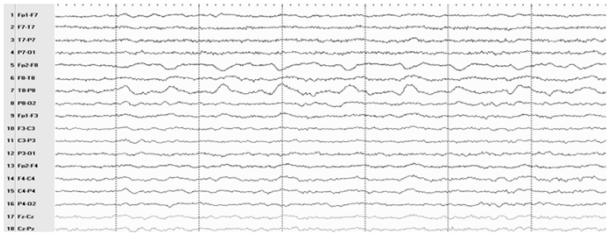
- Fifty percent of patients with LPDs develop seizures.
- Seizures are most often focal
- The interval between LPDs lengthens over days-weeks
- LPD Plus = when low amplitude rhythmic discharges are present – Higher association with seizures (within 30 min)
- BiLPDs are PLEDS that occur independently over both hemispheres
- Seen in patients with severe hypoxic encephalopathy or bilateral hemisphere destructive lesions.
- BIPLEDS are associated with poor prognosis for survival and or recovery of neurological functions.

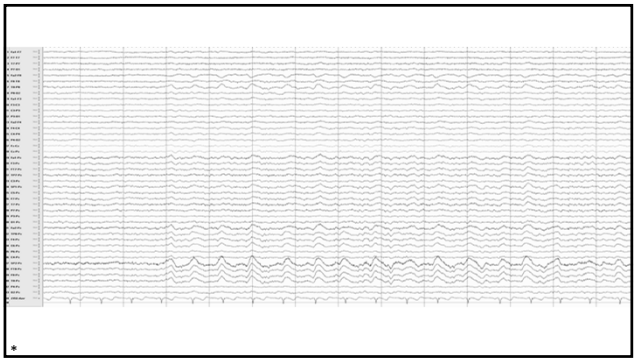
Lateralized Periodic Discharges (LPDs)*(PLEDS)*

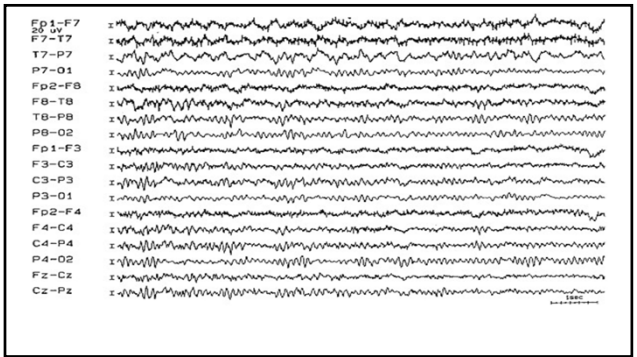
- Multifocal LPDs consist of at least three foci of PLEDS involving both hemispheres
- Seen in patients with severe diffuse dysfunction or multifocal lesions
  - strokes, infection, state of seizure exacerbation, and toxic/metabolic encephalopathy.
- 90% of patients have seizures.
- Prognosis depends on underlying etiology
  - Acute cerebral lesions or infections have higher mortality than those whose underlying neurological condition such as a state of seizure exacerbation.

Temporal Intermittent Rhythmic Delta Activity (TIRDA)

- Intermittent sinusoidal trains of rhythmic 1 to 4 Hz waves at the temporal lobe, lasting for about 5 seconds
- Most commonly 2 to 3 Hz
- Appears either during wake or drowsiness and sleep.
- Highly correlated with temporal lobe seizures
- Temporal depth electrode recording during TIRDA showed active spiking activity in mesial temporal structures
- Two-thirds of the patients had a pathological lesion at the temporal lobe.

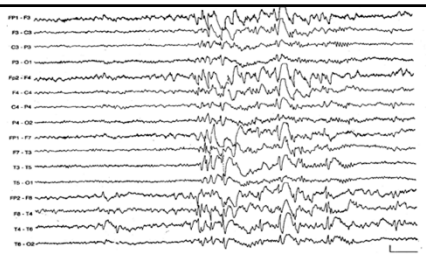






Secondary Bilateral Synchrony

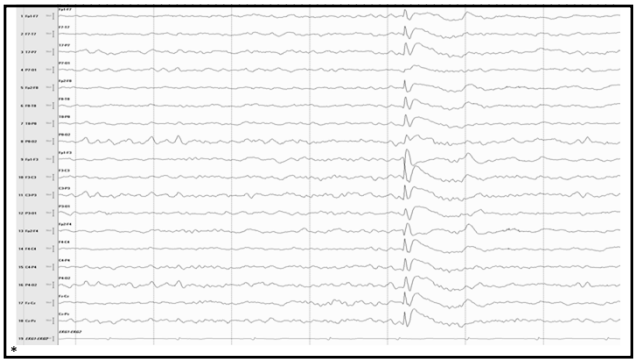
- Focal or regional spikes leading directly to bisynchronous spikes and/or spike-waves.
- Focal interparoxysmal abnormality in same region.



Secondary bilateral synchrony. 33 years. Sequential 3 Hz theta with intermingled electropositive spikes at F8-T4 lead into irregular spike-wave discharges whose durations occasionally extend to 500 msec. These are followed by regional theta and right hemisphere-accentuated spikes. All of these features are characteristic of secondary bisynchrony and satisfy the definition of "a bilaterally synchronous discharge which can be shown to arise from a unilateral cortical focus." Calibration signal 1 sec, 70uV.

Generalized IEDs.

- 3-Hz spike-and-wave discharges
- Bursts last 1-3 seconds, but can be longer
- Activated by hyperventilation or drowsiness
- Synchronous in timing and symmetric in amplitude
- Shifting asymmetries may be seen - usually no more than 20 milliseconds difference
- Maximum over midline frontal region.
- EEG signature of absence epilepsy
- Can interfere with mental functions in a subtle manner



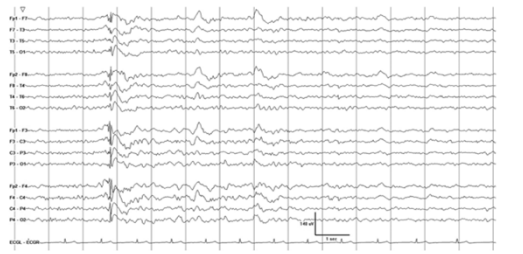
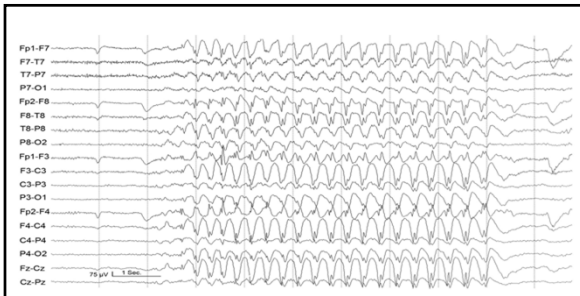
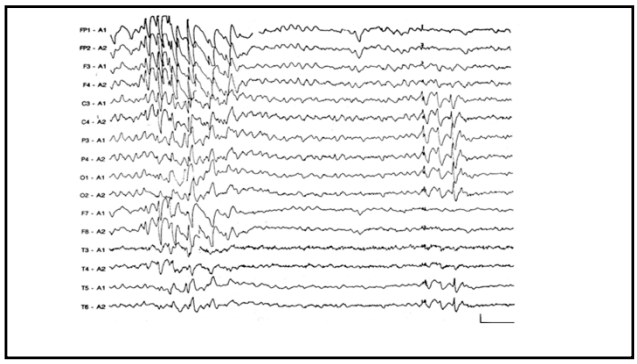


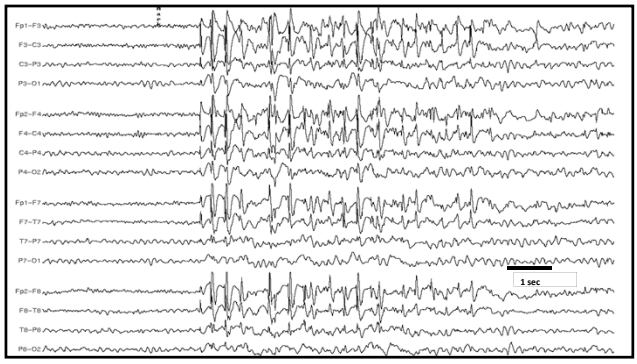
FIGURE 7-8
EEG of a 43-year-old man with myoclonic seizures showing diffuse spike discharges. Diffuse spike-and-wave discharges were noted in EEG recordings.





Generalized IEDs.

- Generalized Atypical Spike-and-Slow-Waves
- Resemble 3 Hz spike-and-wave discharges, but have variable rates
- Complexes vary in amplitude and morphology
- Enhanced by drowsiness and non-REM sleep
- Correlate with primary generalized epilepsies
- In generalized epilepsies, focal spikes of low amplitude may appear during drowsiness

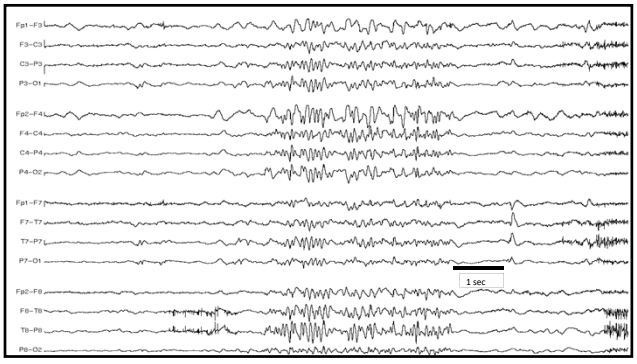


Generalized IEDs.

- Slow Spike-and-Waves
- Frequency is around 1.0 to 2.5 Hz
- Not as rhythmic in repetition
- Mostly sharp waves: wide duration and blunt peaks
- Fluctuating asymmetry of amplitude is common
- Drowsiness or Non-REM sleep may activate trains → ESES?
- May be enhanced by hyperventilation, but not photic stimulation
- Seen in Lennox-Gastaut syndrome

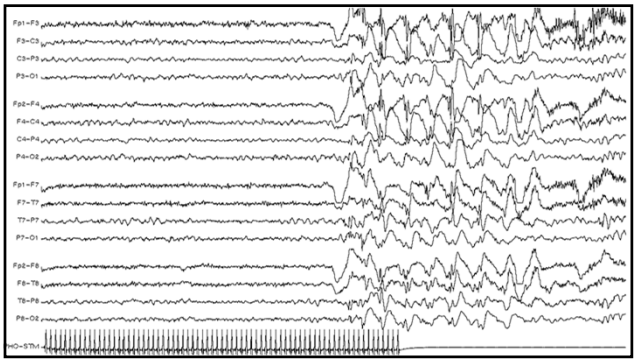
Generalized IEDs.

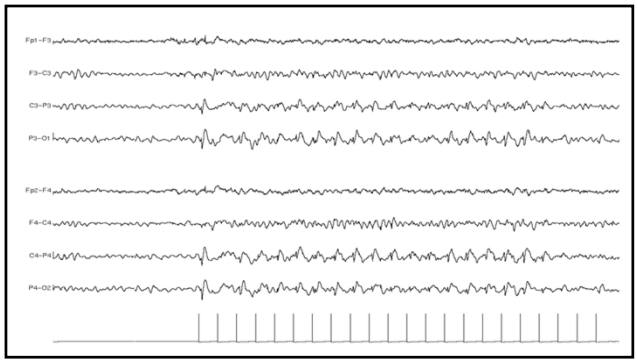
- Generalized Repetitive Fast Discharge (GRFD)
- Also known as paroxysmal fast rhythm, generalized paroxysmal fast activity, or "runs of rapid spikes"
- Alpha or beta frequency range
- Last typically less than 10 seconds
- Electrodecrement consists of very fast and very low amplitude activity
- GRFD may be preceded or followed by generalized slow spike-and-wave discharge
- Often associated with Lennox-Gastaut syndrome
- Most GRFD occur during sleep
- May be an ictal rhythm - could be accompanied by tonic seizures



Generalized IEDs.

- Photo-epileptiform discharges
- IEDs elicited by intermittent photic stimulation
- Can be self-limited or self-sustaining
- Four types
  - (1) generalized (most common)
  - (2) bilateral posterior dominant
  - (3) bilateral occipital
  - (4) focal unilateral discharge (least common)
- 70 to 77% of generalized photo-epileptiform discharges have seizure disorders, but bilateral occipital photo-epileptiform discharges are less commonly associated with epilepsy.





Ictal Patterns

Mohamad Z. Koubeissi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

ICTAL PATTERNS

Mohamad Z. Koubeissi, MD
Professor of Neurology
Director, Epilepsy Center
The George Washington University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Importance of Ictal Recordings

- Evaluation of paroxysmal episodes
- Epileptic vs. nonepileptic spells
- Characterizing and quantifying each seizure type
- Syndromic classification
- Indispensable for presurgical evaluation

(1) Koubeissi, M. and E. So (2013). Interictal and Ictal EEG. EEG in Clinical Practice. J. a. P. Ebersole, T.

Ictal Discharges – General Considerations

- Seizure patterns can be isomorphic or metamorphic
- An electrographic deviation from the baseline
  - Frequency - Field
  - Morphology - Amplitude
- The most recognizable EEG seizure pattern consists of rhythmic, organized discharge that may or may not have apiculate waveforms.

(1) Koubeissi, M. and E. So (2013). Interictal and Ictal EEG. EEG in Clinical Practice. J. a. P. Ebersole, T.

Focal Aware Seizures

- These can occur without a clear ictal correlate on the EEG
- 10 cm^2 rule
- 21% of seizures are associated with EEG ictal discharge (1)
  - 33% with motor manifestations
  - 15% with no motor manifestations
- Seizures may be motor, sensory, autonomic, or psychic
- Semiology is an important indicator of the area of seizure onset
- When recorded, seizure discharges are not different from focal impaired awareness seizures
- May be focal fast frequency discharge, rhythmic slowing, or repetitive spike discharge. Irregular non-rhythmic delta or theta frequency discharge is less frequent.

(1) Devinsky, et al NEUROLOGY 1988;381347-1352

Focal Impaired Awareness Seizures

- EEG changes occur almost always – Exceptions: some frontal or parietal lobe seizures
- Mesial temporal: Often theta-range temporal ictal discharge
- Closer to ictal onset zone → higher frequency
- Deep or far generators → slower frequency
- Common evolving discharge is that of rhythmic discharge, then developing into higher voltage and slower frequency discharge, then regular slow waves increasing in frequency

Focal Impaired Awareness Seizures

- Postictal EEG changes include generalized or focal slowing, amplitude attenuation or increase the focal spike frequency
- When present, focal postictal slowing has lateralizing or sometimes localizing value for the ictal onset zone
- The latency between the first clinical sign of a seizure and the ictal EEG onset should always be assessed

Ictal Patterns in Focal Impaired Awareness Seizures

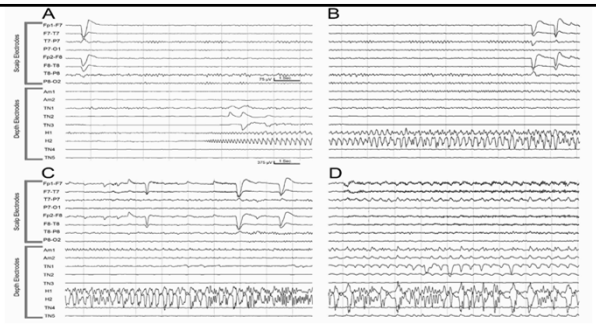
– Rhythmic fast (alpha, beta)
– Rhythmic slow (delta, theta)
– Periodic sharp waves or spikes
– Electrodecrement

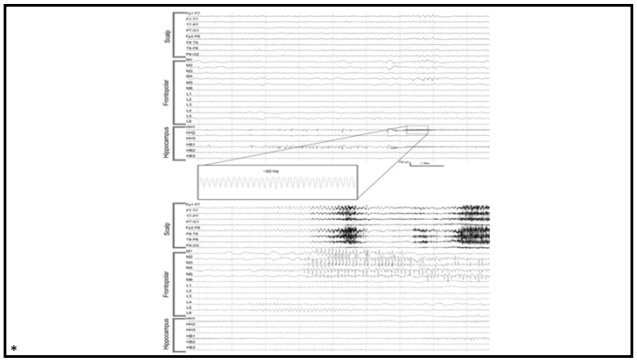
Ictal Patterns in Focal Impaired Awareness Seizures

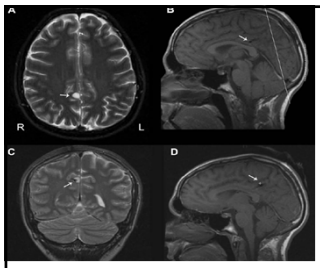
- Whatever the pattern, all focal seizures have one important characteristic, which helps identify it as a seizure:
- The pattern should **EVOLVE** in
  - Frequency
  - Amplitude
  - Morphology
  - Field (propagation)
- Post-ictally focal abnormalities usually appear in the region of maximum seizure intensity which is usually the area of onset
  - Attenuation
  - Delta
  - Increased spike activity

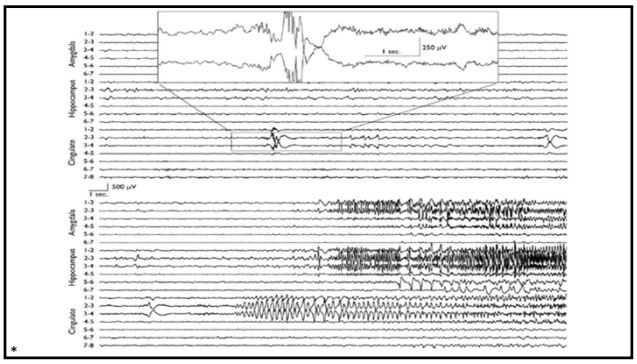
Temporal Lobe Seizures

- Most common focal epilepsy
- Originate from the hippocampus or other mesial temporal structures and propagate to involve the basal and lateral temporal lobe cortices, as well as frontal lobe regions.
- If limited to the hippocampus, non scalp discharge
- Workup of non-lesional cases
- Extratemporal may look temporal
- Temporal may look extratemporal



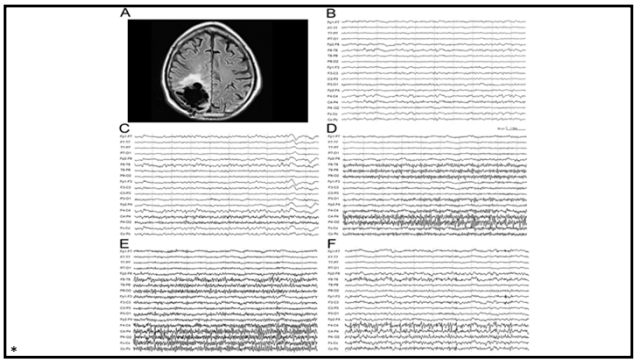


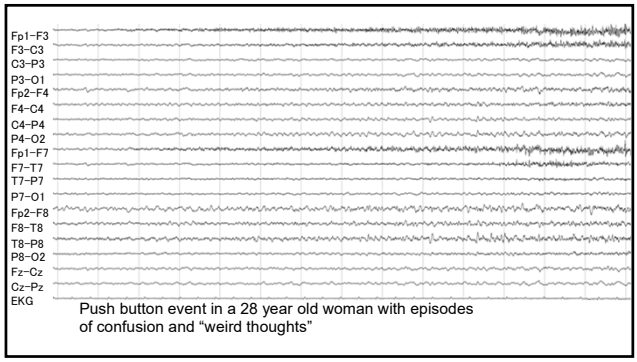




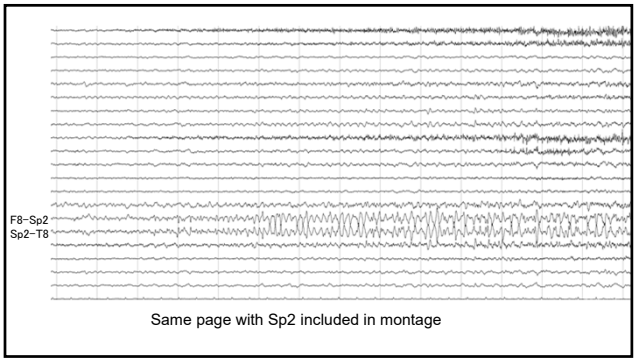
EEG in Extratemporal Epilepsy

- In general, ETLE is less commonly associated with ictal discharges
- A fast, beta-range ictal discharge may be more common
- FLE tend to have abrupt hypermotor activity and rapid propagation
- Only about half of FLE will have localizing EEG pattern
- In 25% of FLE, ictal beta discharge is present: 90% of the patients becoming seizure-free
- EEG of parietal lobe seizures often do not show localizing findings
- Occipital lobe seizures may propagate to ipsilateral or contralateral temporal lobe

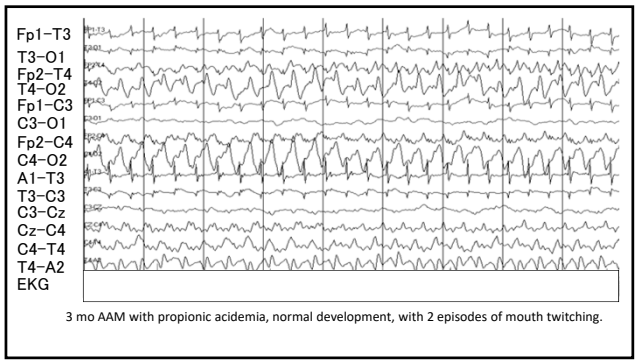




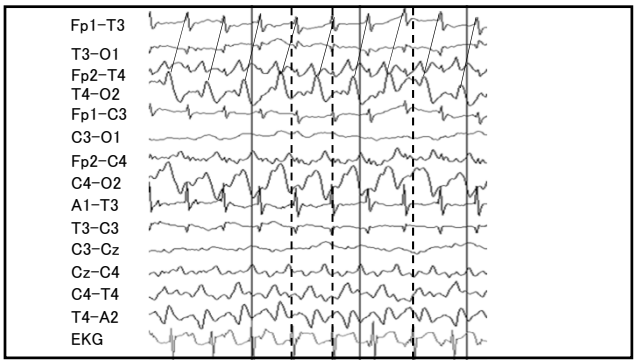
Push button event in a 28 year old woman with episodes of confusion and "weird thoughts"

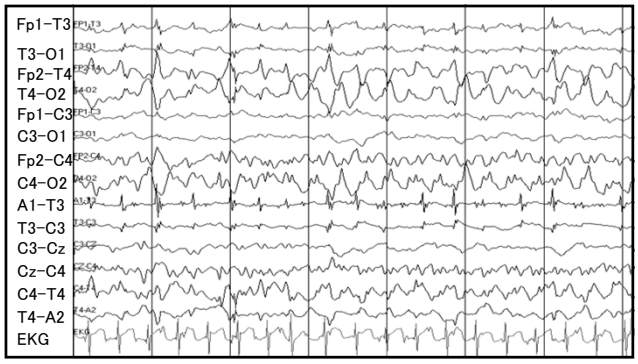


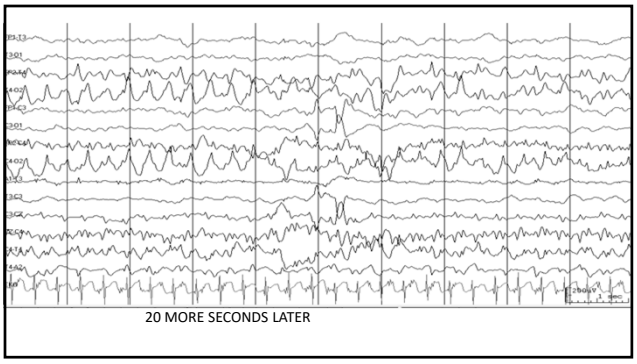
Same page with Sp2 included in montage

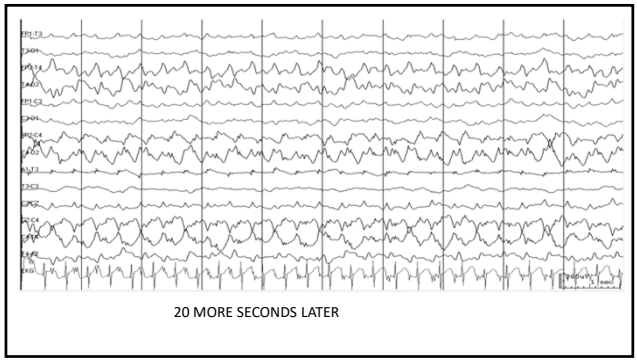


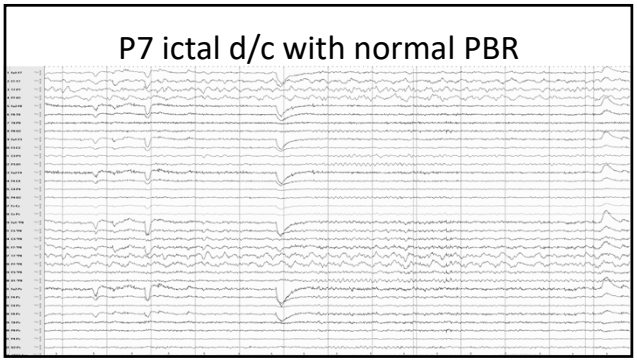
3 mo AAM with propionic acidemia, normal development, with 2 episodes of mouth twitching.



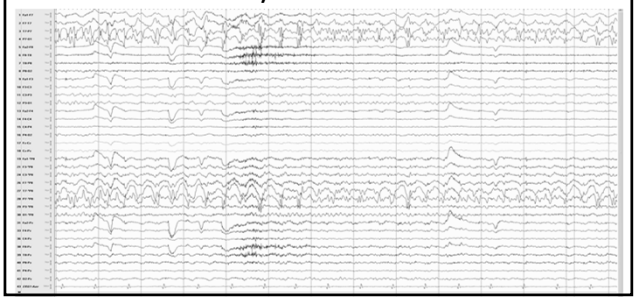



20 MORE SECONDS LATER

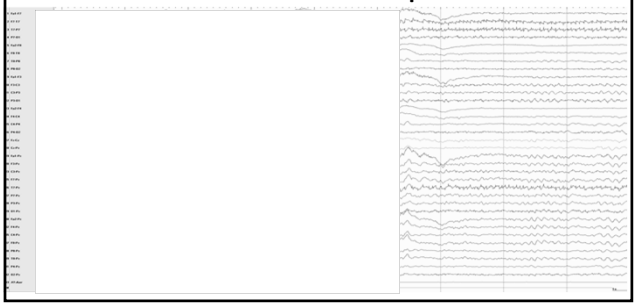

20 MORE SECONDS LATER



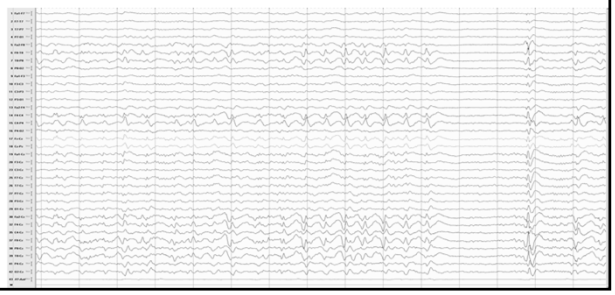
P7 ictal d/c with normal PBR

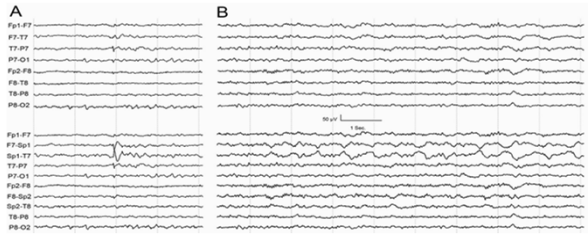


What's under the panel?

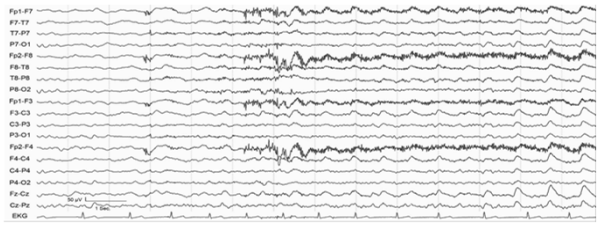


RH Seizure after Stroke

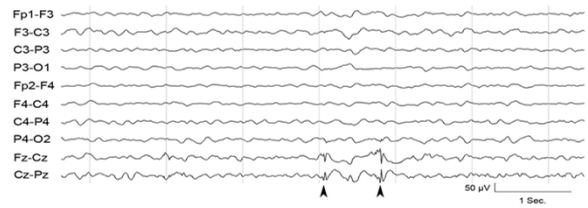




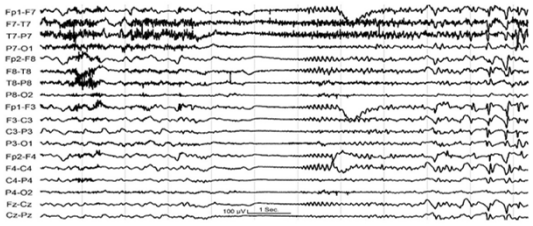
The patient is a 36 year-old woman: low voltage, poorly defined L T spikes. A sphenoidal electrode allowed better definition of these spikes. (A) interictal EEG without (upper) and with (lower) the left sphenoidal electrode. (B) typical cephalic aura



The patient is a 38 year-old man with episodes of "smelling sweet smells". This is a nocturnal seizure with right hand and mouth automatisms, facial grimacing, and smiling. Awareness and language appeared to be preserved in the immediate postictal period.



The patient is a 58 year-old man with h/o respiratory failure and anoxic brain injury. The spikes correspond to intermittent left sided jerking.c



A 7 year-old with LGS and many seizure types. This EEG shows his ictal discharge during an atonic seizure that is characterized by a head drop. Note the sudden electrodecrement with superimposed fast activity that evolves within 2 seconds into a generalized, frontal-maximum, alpha-range activity. This is followed by re-emergence of the interictal pattern that consists of high-voltage generalized slowing and slow spike and wave activity.

Generalized Seizures

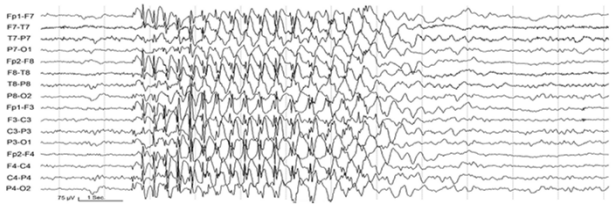
- Generalized seizures consist of bilaterally synchronous sequential SWC, spikes, or rhythmic waves
- Higher frequency phenomena (fast rhythmic activity, polyspikes) usually appear earlier in the seizure that lower frequency ones (SWC, rhythmic delta)
- Usually an abrupt non-focal onset and offset

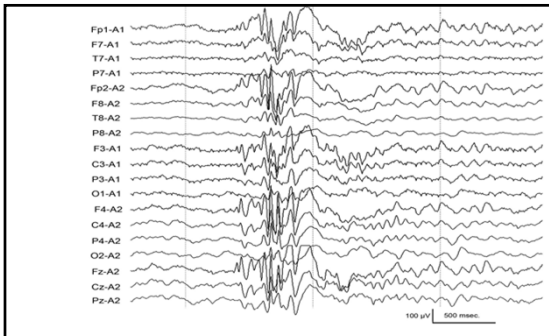
Generalized Epilepsy

- Absence epilepsy:
  - Discharges that last longer than 3 seconds will often have clinical correlates
  - Abrupt onset and offset, with no postictal slowing
  - Average frequency of 3 Hz, starting at approximately 3.5 Hz, and slowing down to 2.5 Hz
  - Some ictal discharges may include polyspike components.
  - Occasionally, the spikes may be more posteriorly prominent

Generalized Epilepsy

- Juvenile myoclonic epilepsy (JME):
  - Bursts of bilateral frontal-maximum polyspike-and-slow-wave discharge
  - Discharges may have irregular morphology and frequency
  - Shortly after arousal or during photic stimulation
  - One third of the patients will have a generalized photo-epileptiform discharges
  - During myoclonic seizures, 10-16 Hz spike discharge
  - Some absence seizures seen in JME have an ictal 3-Hz discharge





Encephalopathic Patterns and ICU EEG

Hai Chen, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

ENCEPHALOPATHIC PATTERNS AND ICU EEG

Hai Chen, MD, PhD
Assistant Professor of Neurology
The George Washington University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Outline

- Slow frequency
  - Generalized theta slowing
  - Generalized polymorphic delta
  - Rhythmic delta
- Specific EEG pattern in coma
  - Alpha coma
  - Beta coma
  - Spindle coma
- Burst suppression
- ECI (brain death)

- Periodic discharges (PDs)
  - ACNS terminology
  - LPD and GPD
  - Triphasic discharges
  - CJD and SSPE
- Cardiac arrest EEG patterns

Outline

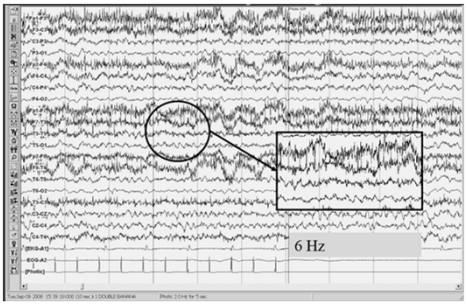
- Slow frequency
  - Generalized theta slowing
  - Generalized delta slowing
  - Rhythmic delta
- Specific EEG pattern in coma
  - Alpha coma
  - Beta coma
  - Spindle coma
- Burst suppression
- ECI (brain death)

- Periodic discharges (PDs)
  - ACNS terminology
  - LPD and GPD
  - Triphasic discharges
  - CJD and SSPE
- Common cardiac arrest patterns

Diffuse theta slowing

- Diffuse theta activity
- May admixed with delta activity or alpha activity
- Often reactive to stimulation
- Often indicate mild diffuse encephalopathy of non-specific etiology
  - toxic, metabolic derangement, medical condition among others

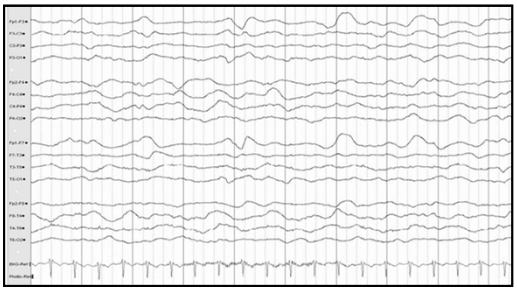
Theta slowing



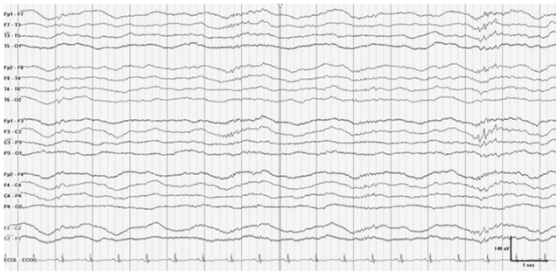
Generalized Delta Slowing

- Typically continuous high voltage polymorphic delta slowing in patients with AMS
- May reactive to afferent stimuli or mixed with theta activity at early stage.
- Further worsening of mental status, more prominent delta activity.

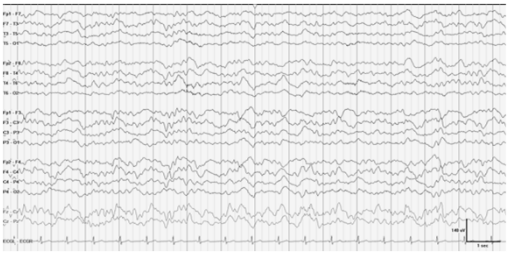
Polymorphic delta slowing



Diffuse delta activity

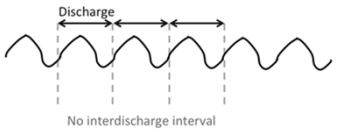


Diffuse delta with admixed theta



Rhythmic delta activity (RDA)

- Repetition of delta activities
  Relatively uniform morphology, without intervals



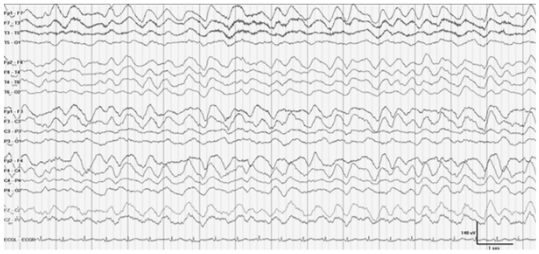
Rhythmic delta activity (RDA)

- Usually symmetric and synchronous. Rarely, unilateral RDA (LRDA)
- Intermittent RDA usually frontal dominant (FIRDA) in adults, In children it is usually occipital (OIRDA).
- Nonspecific in terms of pathology
- The prognosis of RDA depends on the underlying etiology.

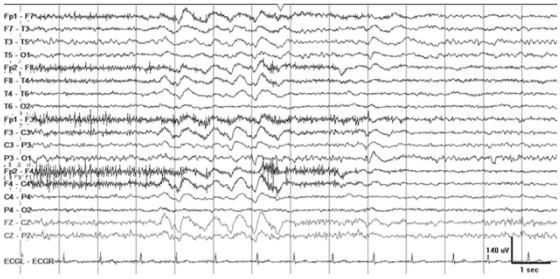
- ACNS standard terminology:
- Prevalence: Continuous (> 90%) of record, abundant (50-89%), 10-49% (frequent), 1-9% (occasional), < 1% (rare)
- Duration: Very long (> 1 hour), long (5-59 min), Intermediate duration (1-4.9 minutes), Brief (10-59 sec), Very brief (10 seconds)

Hirsch et al., 2013

GRDA (Generalized RDA)

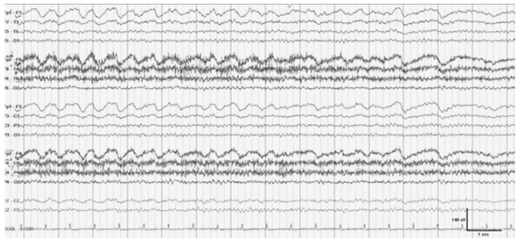


FIRDA (very brief frontally predominant GRDA)

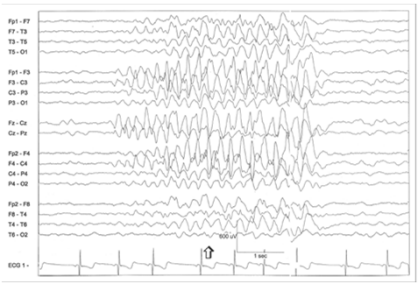


84 y/o woman AMS, electrolyte imbalance

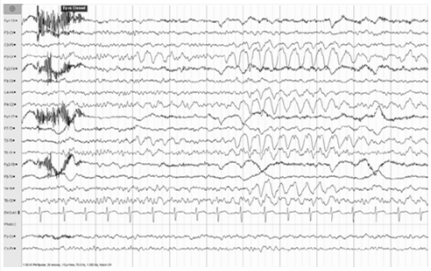
Eye fluttering



Normal variant: hypnagogic hypersynchrony



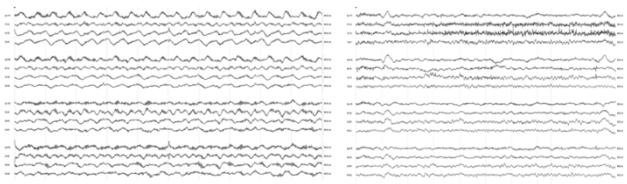
OIRDA



Mostly in children

More likely associated with generalized epilepsy (such as absence epilepsy) than encephalopathy

Extreme Delta Brush: NMDA encephalitis



23 serology confirmed NMDA encephalitis
> 30% delta brush
Prolonged hospital stay and EEG monitoring.

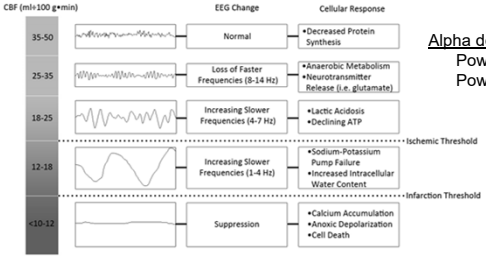
Schmitt et al., 2012

TABLE 2. Qualitative Classification of EEG Alteration

Score	Description
0: Normal EEG	Well-structured EEG with stable and symmetrical posterior basic rhythm > 8 Hz and < 13 Hz dominant in the posterior regions. Such activity has medium amplitude (30–50 μV) and is reactive to eye opening. No slow activities or irritative signs are present.
1: Normal-limit EEG	Unstable or suppressed alpha rhythm frequently replaced by high prevalence of diffuse beta rhythm (corresponding to grade A of Parsons-Smith's classification)
2: Mild signs of encephalopathy	Low frequency alpha rhythm (8 Hz) disturbed by random waves in the theta range over both hemispheres. (corresponding to grade B of Parsons-Smith et al.'s classification).
3: Distinctive features of encephalopathy	Background activity in the theta range, diffuse over both hemispheres. Random appearance of high waves in the delta range (roughly corresponding to grade C of Parsons-Smith et al.'s classification).
4: Signs of severe encephalopathy	Severe disorganization of EEG activity without any normal elements. Diffuse asynchronous theta and delta waves over both hemispheres with or without triphasic waves (roughly corresponding to grade D–E of Parsons-Smith et al.'s classification).

Kaplan 2004

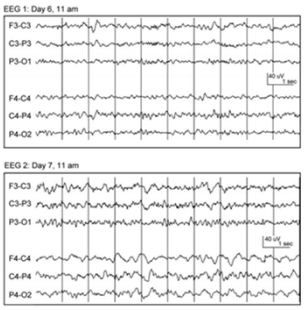
Cerebral perfusion and EEG monitoring



Alpha delta ratio (ADR)
Power of alpha activity
Power of delta activity

Foreman et al., 2012

ADR in delayed cerebral ischemia (DCI) after SAH



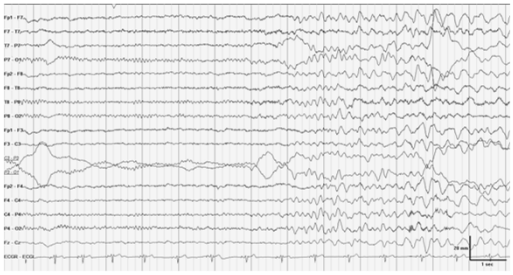
9/34 patients (26%) developed DCI after SAH.

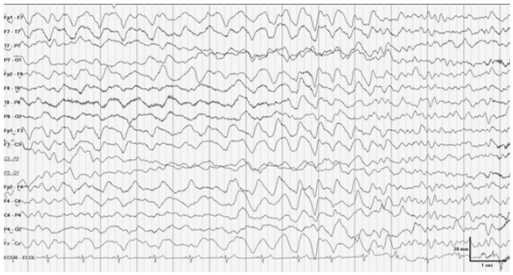
	With DCI	Without DCI
ADR	- 24%	+ 3%

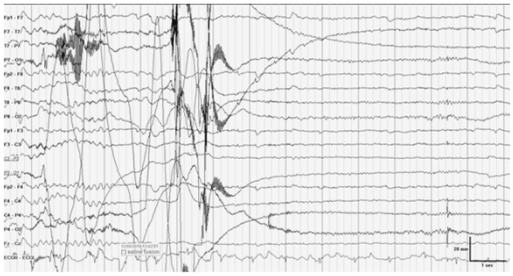
A decrease in the ADR may be a sensitive method of detecting DCI, with reasonable specificity.

Wickering et al., 2016

Cerebral hypoperfusion







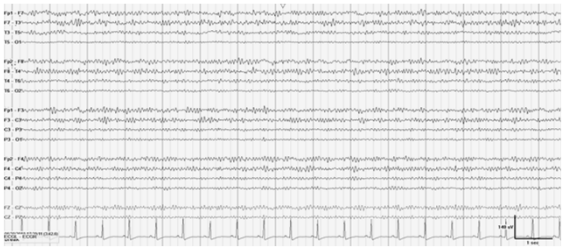
Outline

- Slow frequency
  - Generalized theta slowing
  - Generalized polymorphic delta
  - Rhythmic delta
- Specific EEG patterns in coma
  - Alpha coma
  - Beta coma
  - Spindle coma
- Burst suppression
- ECI (brain death)
- Periodic discharges (PDs)
  - ACNS terminology
  - LPD and GPD
  - Triphasic discharges
  - CJD and SSPE
- Common cardiac arrest patterns

Alpha Coma

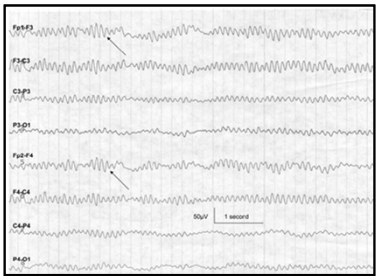
- First described by Loeb and Poggio (1954) in a patient with brainstem hemorrhage. Also seen in other conditions.
- Consists of alpha frequency activities
- Unlike awake alpha rhythm
  - Diffusely distributed
  - Often anterior dominant
  - Often invariable and non-reactive

Alpha coma



58 year old woman cardiac arrest, patient is comatose

Alpha Coma



Prognosis of alpha coma

Overall high mortality 256/335 (76%). The cause of alpha coma largely predicts outcome

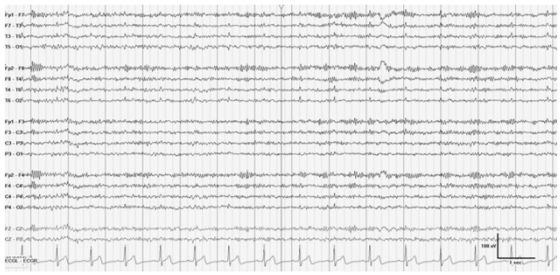
- Anoxia brain injury (90%)
- Brain stem infarct (90%)
- Hypoxia without cardiac arrest (60%)
- Drug-induced alpha coma (8%)

Kaplan et al., 1999

Excessive beta activity

- Generalized 12 to 16 Hz activity, with a frontal predominance
- Reactivity to sensory stimulation is usually preserved in lighter coma; but lost in deeper coma
- Seen with overdose of sedative-hypnotics (BZD and barbiturates)
- Prognosis is usually favorable

Excessive beta



29 y/o man had a breakthrough seizure. Received multiple doses of lorazepam

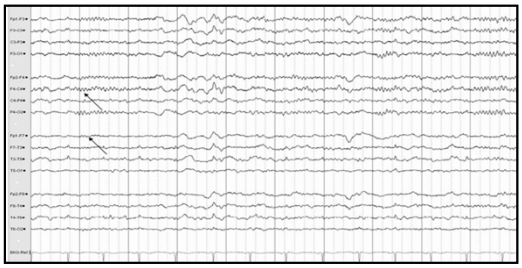
Spindle Coma

- First described (1953) in a patient midbrain tumor.

- EEG features
- Diffuse slowing background,
- Large amount of spindles; may have others (vertex waves).

- Possible mechanism
- Dysfunction of ascending reticular activating system (RAS) at midbrain level (arousal impairment); However sparing thalamocortical pathway (mediates sleep).
- Also in diffuse brain involvement (toxic, metabolic, etc), ? presumably impairment of reticulothalamocortical pathways

Spindle Coma



Spindle coma

- Prognosis mainly depending on etiology
- Total mortality 56/242 (23%)
- Structural/brainstem pathway dysfunction 73%
- Hypoxia 33%
- Trauma 15%
- Drug/toxic/encephalopathy 0

Kaplan et al., 2000

Outline

- Slow frequency
- Generalized theta slowing
- Generalized polymorphic delta
- Rhythmic delta
- Specific EEG pattern in coma
- Alpha coma
- Beta coma
- Spindle coma
- Burst suppression
- ECI (brain death)

- Periodic discharges (PDs)
- ACNS terminology
- LPD and GPD
- Triphasic discharges
- CJD and SSPE

- Common cardiac arrest patterns

BURST SUPPRESSION

- Bursts of high-voltage, mixed-frequency activity (often sharply contoured)
- Alternating with periods of suppression

- ACNS nomenclature
- Suppression: < 10 μV
- Attenuation: > 10 μV however < 50% of baseline voltage

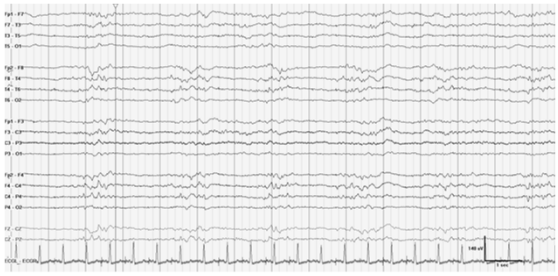
- Discontinuous background: 10-49% recording suppression/attenuation
- Burst suppression/attenuation: > 50% recording suppression/attenuation

Burst-suppression

- Variable severity
  Coma worsens; the duration of the bursts decrease and periods of suppression increases.

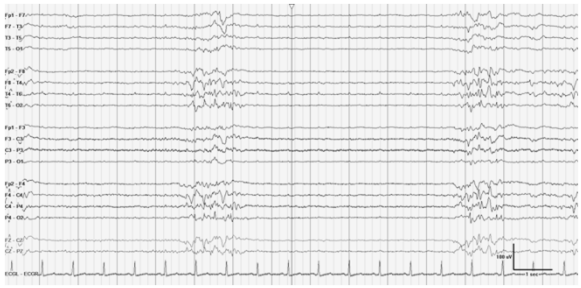
- Common etiologies:
  Anoxic encephalopathy; Intoxication with sedative drugs; Anesthetic use

Burst-suppression

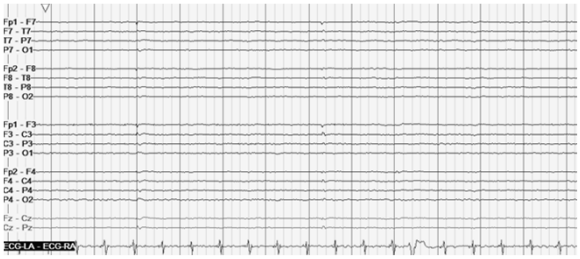


67 year old woman on porpofol for status epilepticus

More suppression



Nearly complete suppression



ECI (Electrocerebral inactivity)

- ECI:
  - Absence of brain-generated EEG activity
  - Many types of artifacts can be seen: EKG, respiration, IV drips

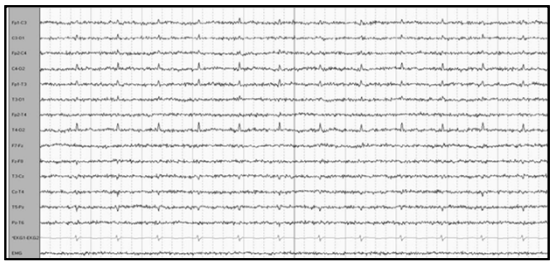
- Need the minimum technical requirements proposed by ACNS

- ECI is the most severe abnormality, as it represents an irreversible coma, with all patients either dying or continuing in a persistent vegetative state

Criteria for Recording in Suspected ECI

- **Must be recorded according to strict ACNS guidelines: specify recording time, double interelectrode distances, testing reactivity, and the integrity of the system.**
- Minimum of 8 scalp electrodes/full set electrode (ensure ECI is not focal pathology)
- 100 Ω < electrode Impedance < 10,000 Ω
- Interelectrode distance > 10 cm (double distance)
- Sensitivity 2 μV/mm
- Filter high-frequency not below 30 Hz, low-frequency not above 1 Hz.
- Integrity of the whole system should be tested
- Monitoring techniques (EKG, Vent, etc) to detect possible artifact if necessary.
- Check reactivity to external stimulation (not reactive)
- At least 30 min

ECI (Electrocerebral inactivity)



2 μV/mm

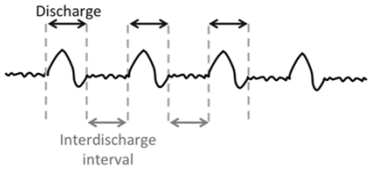
Outline

- Slow frequency
  - Generalized theta slowing
  - Generalized polymorphic delta
  - Rhythmic delta
- Specific EEG pattern in coma
  - Alpha coma
  - Beta coma
  - Spindle coma
- Burst suppression
- ECI (brain death)

- Periodic discharges (PDs)
  - ACNS terminology
  - LPD and GPD
  - Triphasic discharges
  - CJD and SSPE
- Common cardiac arrest patterns

Periodic discharges (PD)

- Repetition of discharges
  - Relatively uniform morphology
- Nearly regular intervals between discharges.



Periodic discharges (PD)

- Generalized: bilateral, bisynchronous and symmetric pattern, even if it has a restricted field.
- Lateralized: unilateral or bilateral synchronous but asymmetric

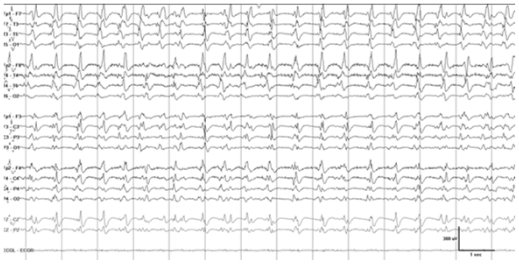
- Generalized periodic discharges GPDs
- Lateralized periodic discharges LPDs

Hirsch et al., 2013

GPDs

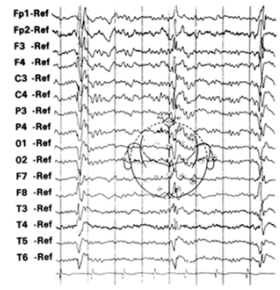
- Generalized, symmetric, and synchronous
- Acute cerebral anoxia
- Severe metabolic disease
- Toxic, overdose (lithium and baclofen etc)
- Neurodegenerative diseases
- CJD
- SSPE

GPDs



64 y/o woman cardiac arrest

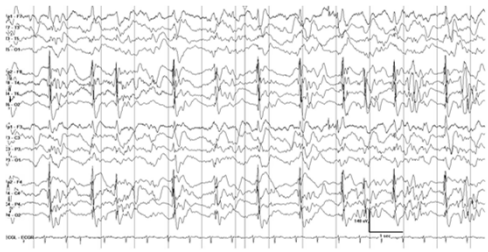
GPDs



Overdose baclofen

Fachourly et al., 1998

LPDs



63 year old woman with history of focal epilepsy from R ICH.

Triphasic Waves, GPD with triphasic morphology

- Morphology: three phases.
  - Large amplitude positive phase in the middle
  - Preceded & followed by lower voltage negative phases.
- Amplitude: Moderate- to high (100 to 300 μV)
- Duration of triphasic waves 150-500 msec. Often 1.5-2.5 Hz

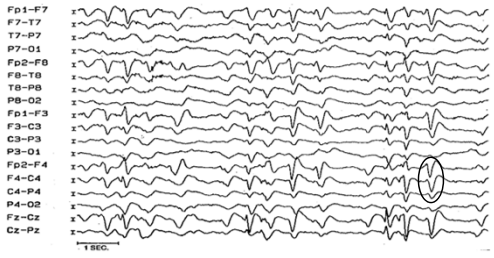
- Distribution
  - Symmetrical bilaterally synchronous, sometimes shifting asymmetry.
  - Usually maximal frontally.
  - Anterior-posterior lag seen typically

Triphasic Waves

- Encephalopathy of various etiology

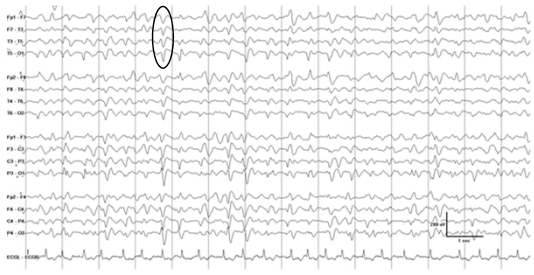
- Background delta/theta slowing

Triphasic discharges



63-year-old woman with cirrhosis, awaiting liver transplant, became obtunded.

Triphasic waves.



Triphasic discharges: epileptiform discharges or encephalopathy

- Retrospectively analysis EEG with TWs.
- Triphasic discharges in encephalopathy vs NCSE
  - Amplitude predominance of phase two (40.8% vs 0)
  - Longer duration of phase one (p=0.001)
  - Less extra-spikes components (0 vs 69%)
  - Less in frequency (1.8Hz vs 2.4 Hz)
  - Phase lag (41% vs 0).
- Background: Background slowing (91% vs 15%)
- Reactivity: NCSE less activity to auditory/noxious stimulation.

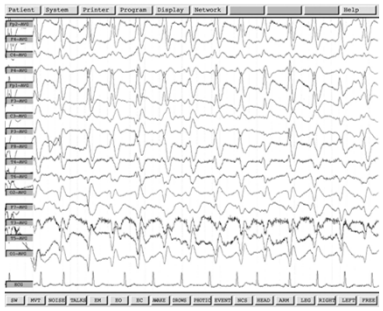
Boulanger JM et al., 2006

Neurodegenerative disorder: CJD

- Creutzfeldt-Jakob disease (CJD)
- Rapid progressive dementia
- Myoclonus
- Ataxia
- Motor system: Pyramidal and extrapyramidal signs

CJD EEG findings

- Background: (Progressively decline)
  Loss of normal activity, increasing slow activity, and then decline in amplitude, eventually with a featureless appearance between complexes.
- Periodic discharges:
- Mostly 0.5-2 Hz; 100-500 ms in duration
- Mostly diffuse, can be lateralized or focal
- May or may not associated with myoclonus



~ 1 Hz periodic discharges

Low amplitude featureless background between discharges

Smith 2005

CJD, EEG features

- In autopsy confirmed (n=150) or excluded (n=56) CJD

EEG sensitivity 64%; Specificity 91%.

Falsely positive in 9% (n=5) of other dementias. Alzheimer's disease (n=4) and vascular dementia (n=1)

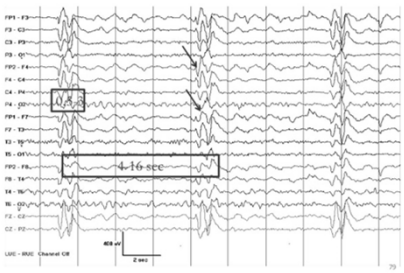
Steinhoff BJ 2004

Neurogenerative disorder: SSPE

Subacute sclerosing panencephalitis (SSPE)
- Measles infection; Prolonged and variable latency
- Intellectual deterioration
- Motor system: Myoclonus, Ataxia, rigidity

EEG: Generalized periodic discharges
- Periodic high-voltage discharges, long in duration
- Low in frequency; ~ 4-15 sec

EEG OF SSPE



High amplitude discharges

long in duration 0.5-2 sec

Periodic high-voltage complexes, recurring every 4-15 sec.

CJD vs SSPE

Period	Classically 1 sec	4-14 sec
Complex Morphology	Di- or Triphasic sharp waves	Slow waves or groups of slow waves; may have sharp component
Distribution	Generalized, but may lateralize or begin focally	Generalized, maximal in frontocentral leads
Background Activity	Diffusely slow when complexes first appear	May be normal when complexes first appear

Outline

- Slow frequency
  - Generalized theta slowing
  - Generalized polymorphic delta
  - Rhythmic delta
- Specific EEG pattern in coma
  - Alpha coma
  - Beta coma
  - Spindle coma
- Burst suppression
- Low voltage background
- ECI (brain death)

- Periodic discharges (PDs)
  - ACNS terminology
  - LPD and GPD
  - Triphasic discharges
  - CJD and SSPE
- Common cardiac arrest patterns

EEG monitoring after cardiac arrest

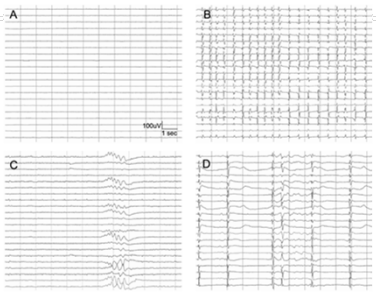
- Comatose patients after cardiac arrest:
  - Prevalence of epileptiform discharges 12% to 22%.
  - NCSE may be a reason that patients are not awakening from coma
  - Prolonged epileptiform discharges associated with secondary brain injury

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Circulation 2015

Cardiac arrest EEG features

- After rewarming EEGs were classified into:
- Highly malignant
  - Suppression
  - Burst-suppression
  - Suppression with periodic discharges
- Malignant
  - Abundant periodic discharges, electrographic seizures
  - Discontinuous
  - Low voltage
  - Nonreactive background
- Absence of those features above.

Westhall et al., 2016



(A) Suppressed background
(B) Suppressed background with superimposed continuous PDs.
(C) Burst-suppression
(D) Burst-suppression with superimposed discharges

Predict poor prognosis

Highly malignant EEG: specificity 100%, sensitivity 50%.

One malignant EEG feature: low specificity to predict poor prognosis (48%)

Two malignant EEG features: high specificity to predict poor prognosis (96%)

Westhall et al., 2016

Status Epilepticus and Hypsarrythmia

Archana Pasupuleti, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

Status Epilepticus & Hypsarrhythmia

Archana Pasupuleti, MD
Children's National Hospital
George Washington School of Medicine

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Objectives

- Define of Status Epilepticus (SE), Refractory SE, Non Convulsive SE
- Review classification of Status Epilepticus
- Review of Status Epilepticus EEG patterns
- Identification and treatment of Electrographic Status Epilepticus in Sleep (ESES)
- Review of hypsarrythmia, BASED criteria, and treatment of infantile spasms

Time is Brain: Status Epilepticus

- Status epilepticus is considered the most common neurological emergency around the world, often requiring intensive care.
- Estimated incidence of 15 to 20 cases per 100,000 people
- On average, 20% of cases are fatal; reported long-term mortality rates as high as 22% in children and 57% in adults.

Time is Brain: Status Epilepticus

- Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures.
- This definition has two important time factors:

  Time point 1 (t1): the length of the seizure and the time point (t1) beyond which the seizure should be regarded as "continuous seizure activity."

  Time point 2 (t2): The second time point is the time of ongoing seizure activity after which there is a risk of long-term consequences.

Trinka E, et al. A definition and classification of SE – Report of the ILAE Task Force on Classification of SE. Epilepsia 56(10): 1515-23, 2015

Time is Brain: Status Epilepticus

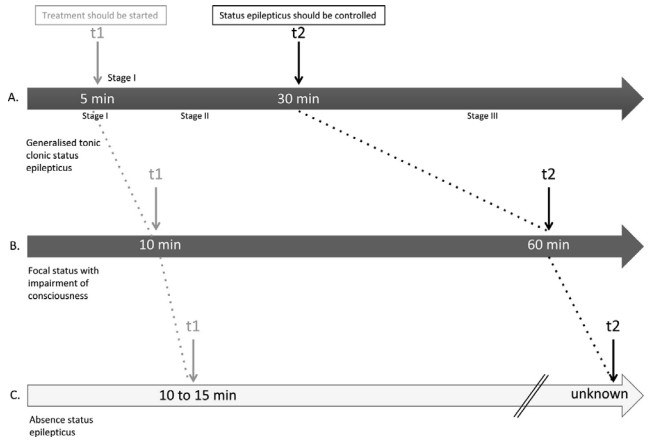
E. Trinka et al.

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

Trinka E, et al. A definition and classification of SE – Report of the ILAE Task Force on Classification of SE. Epilepsia 56(10): 1515-23, 2015



Trinka E, et al. A definition and classification of SE – Report of the ILAE Task Force on Classification of SE. Epilepsia 56(10): 1515-23, 2015

Classification of Status Epilepticus

4 axis proposed classification categories

1. Semiology (+/- motor symptoms, +/- impaired consciousness)
2. Etiology (symptomatic, cryptogenic)
3. EEG correlates (terminology - location, name of pattern, morphology, time-related features, modulation, effect of intervention on EEG)
4. Age (neonatal, infancy, childhood, adolescence and adulthood, elderly)

Classification of Status Epilepticus

- Convulsive SE
  - Simple partial:
    - Motor (EPC)
  - Secondarily Generalized
  - Generalized
    - Atonic
    - Myoclonic
    - Tonic
  - Clonic
- Non-convulsive SE
  - Partial:
    - Simple partial (aphasic, sensory, autonomic or psychic symptoms).
    - Complex partial
  - Generalized:
    - Absence – typical or atypical absence
  - Subtle:
    - NCSE after generalized convulsive SE

Classification of Status Epilepticus

Table 2. Axis I: Classification of status epilepticus (SE)

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
A.1.a. Generalized convulsive
A.1.b. Focal onset evolving into bilateral convulsive SE
A.1.c. Unknown whether focal or generalized
A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
A.2.a. With coma
A.2.b. Without coma
A.3 Focal motor
A.3.a. Repeated focal motor seizures (Jacksonian)
A.3.b. Epilepsia partialis continua (EPC)
A.3.c. Adversive status
A.3.d. Oculoclonic status
A.3.e. Ictal paresis (i.e., focal inhibitory SE)
A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
B.2.a. Generalized
B.2.a.a Typical absence status
B.2.a.b Atypical absence status
B.2.a.c Myoclonic absence status
B.2.b. Focal
B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
B.2.b.b Aphasic status
B.2.b.c With impaired consciousness
B.2.c Unknown whether focal or generalized
B.2.c.a Autonomic SE

Table 3. Currently indeterminate conditions (or "boundary syndromes")

Epileptic encephalopathies
Coma with non evolving epileptiform EEG pattern[a]
Behavioral disturbance (e.g., psychosis) in patients with epilepsy
Acute confusional states, (e.g., delirium) with epileptiform EEG patterns

[a]Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.[24,27]

Table 4. Etiology of status epilepticus

Known (i.e., symptomatic)
Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)
SE in defined electroclinical syndromes
Unknown (i.e., cryptogenic)

Classification of Status Epilepticus

Table 5. SE in selected electroclinical syndromes according to age

SE occurring in neonatal and infantile-onset epilepsy syndromes
Tonic status (e.g., in Ohtahara syndrome or West syndrome)
Myoclonic status in Dravet syndrome
Focal status
Febrile SE
SE occurring mainly in childhood and adolescence
Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies; see Appendices 1–3)
Tonic status in Lennox-Gastaut syndrome
Myoclonic status in progressive myoclonus epilepsies
Electrical status epilepticus in slow wave sleep (ESES)
Aphasic status in Landau-Kleffner syndrome
SE occurring mainly in adolescence and adulthood
Myoclonic status in juvenile myoclonic epilepsy
Absence status in juvenile absence epilepsy
Myoclonic status in Down syndrome
SE occurring mainly in the elderly
Myoclonic status in Alzheimer's disease
Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease
De novo (or relapsing) absence status of later life

These forms of SE may be encountered prevalently in some age groups, but not exclusively.

Epilepsia, 56(10):1515–1523, 2015
doi: 10.1111/epi.13121

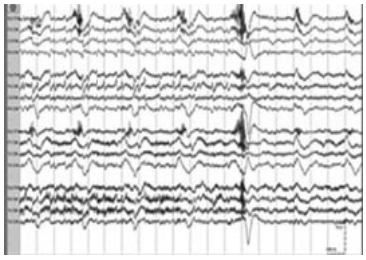
Five sequential electrographic patterns

1. Discrete seizures
2. Merging seizures with waxing and waning amplitude and frequency
3. Continuous ictal activity
4. Continuous ictal activity punctuated by low voltage "flat periods"
5. Periodic epileptiform discharges on a flat background

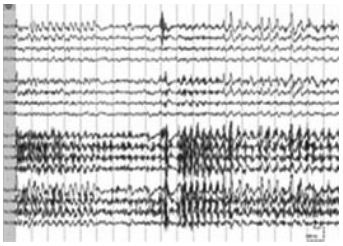
(Treiman DM, et al. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus Epilepsy Res. 1990;5(1):49-60)

Stages of Status Epilepticus: Patterns

Discrete seizures



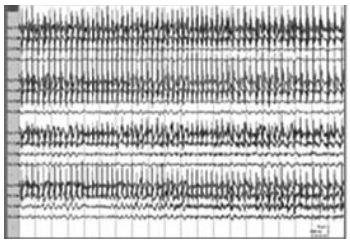
Merging seizures



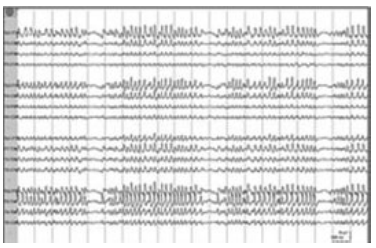
Pender RA and Losey TE. A rapid course through the five electrographic stages of status eplepticus. Epilepsia 2012;53(11):e193-e195.

Stages of Status Epilepticus: Patterns

Continuous ictal activity

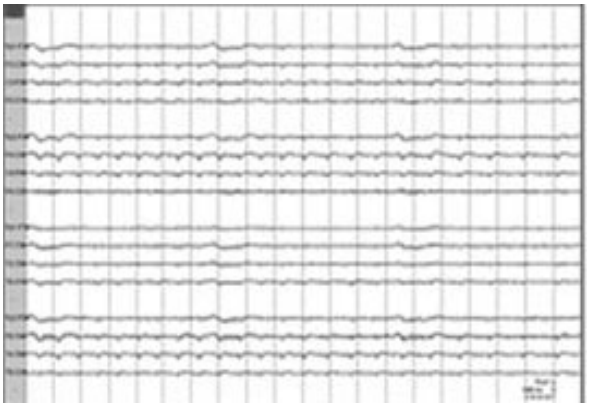


Continuous ictal activity punctuated by flat periods



*

Stages of Status Epilepticus: Patterns



*

Periodic epileptiform dicharges on flat background

Convulsive Status Epilepticus

Partial status epilepticus:

- Simple partial status epilepticus:
  Epilepsia partialis continua (EPC): EEG may or may not show ictal changes
- Secondarily generalized SE:
  focal interictal discharges may suggest the diagnosis

Generalized convulsive status epilepticus:

- Atonic SE: bilateral synchronous spike and slow waves
- Myoclonic SE: bilateral synchronous polyspikes
- Clonic SE: bilateral synchronous spikes
- Tonic SE: low voltage fast activity

Kaplan PW. The EEG of status epilepticus. J Clin Neurophysiol 2006;23:221-229

Non-convulsive Status Epilepticus(NCSE)

Definition: Alteration of consciousness or behavior from baseline state for at least 30 minutes without convulsive movements, and the presence of one or more of the following epileptiform patterns:

Repetitive focal or generalized discharges or rhythmic activity at >2/second

EEG pattern as in 1 at <1/second, but with improvement of epileptic activity and clinical state following benzodiazepine

Evolution of epileptiform or rhythmic activity at >1/second

Kaplan PW. The EEG of status epilepticus. J clin Neurophysiol 2006;23:221-229.

NCSE

For patients with preexisting learning, cognitive and behavioral problems:

Change in behavior from baseline functioning and/or neuropsychologic evaluation which persists for >30 minutes associated with continuous or near continuous paroxysmal electrographic activity in the absence of tonic, clonic or tonic-clonic movements.

Walker M, et al. Nonconvulsive status epilepticus: Epilepsy research foundation workshop report. Epileptic Disord 2005;7(3):253-96.

Salzburg Criteria

Table 4
The modified Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus (mSCNC), which is suggested for all patients with qualitative or quantitative disturbance of consciousness and suspicion of NCSE. The diagnosis of NCSE is the result of combining EEG and clinical data. Clinical symptoms/signs raising suspicion of NCSE have to last at least 10 min [14,15].

EEG data:
EEG changes fulfilling the criteria have to be continuously present for ≥10 s. Criteria not applicable to physiological graphoelements.
A: Patients without known epileptic encephalopathy (at least ONE of the criteria 1–3 should be fulfilled for diagnosis of NCSE)
1. EDs > 2.5 Hz (i.e., >25 EDs in "worst" 10-second epoch)
2. Typical ictal spatiotemporal evolution* of:
–(2a) EDs OR
–(2b) Rhythmic activity** (>0.5 Hz)
3. Subtle ictal clinical phenomena*** with:
–(3a) EDs OR
–(3b) Rhythmic activity** (>0.5 Hz)
4. If criteria 1–3 are not fulfilled, but one of the following patterns is present, apply appropriate AED(s) after careful consideration of clinical situation and document response****:
–(4a) EDs ≤ 2.5 Hz with fluctuation***** OR
–(4b) Rhythmic activity** (>0.5 Hz) with fluctuation***** OR
–(4c) Rhythmic activity** (>0.5 Hz) without fluctuation*****
B: Patients with known epileptic encephalopathy
In addition to the criteria above (A), these patients have to fulfill one of the following:
–Increase in prominence or frequency when compared to baseline with observable change in clinical state
–Improvement of clinical and EEG features with IV AEDs (see A.4.)
Clinical data:
Add clinical information for establishing the diagnosis of NCSE:
–Transition from premorbid to current ill state within minutes to hours
–Patient did not improve significantly in last minutes to hours, apart from waxing and waning.
–No information from brain imaging sufficiently explaining EEG pattern (e.g., brain stem hemorrhage)
–No metabolic/toxicological derangement sufficiently explaining EEG pattern (e.g., acute renal or liver failure)

Martin H. Krogstad,* Hans Høgenhaven,* Christoph P. Beier,*† and Thomas Krøig°ard*† Nonconvulsive Status Epilepticus: Validating the Salzburg CriteriaAgainst an Expert EEG Examiner Journal of Clinical Neurophysiology Volume 36, Number 2, March 2019

Salzburg Criteria

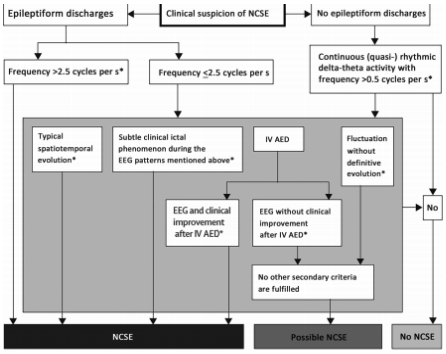


FIGURE 1 Salzburg electroencephalographic (EEG) criteria for the diagnosis of nonconvulsive status epilepticus (NCSE). To qualify for a diagnosis of NCSE, the whole EEG recording should be abnormal, and EEG criteria have to be continuously present for at least 10 seconds. If criteria are not fulfilled at any stage, EEG recording will not qualify for a diagnosis of NCSE or possible NCSE. AED, antiepileptic drug; IV, intravenous. *Patients with known epileptic encephalopathy should fulfil one of the additional secondary criteria: increase in prominence or frequency of the features above when compared to baseline, and observable change in clinical state; or improvement of clinical and EEG features with IVAEDs. (With permission from The Lance Neurology)

Refractory Status Epilepticus

- New-onset refractory status epilepticus (NORSE) is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause
- Febrile infection-related epilepsy syndrome is a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus.

Hirsch LJ, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018; 59(4):739-744

Refractory Status Epilepticus

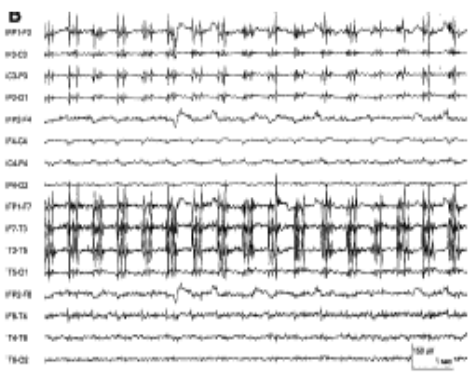
- Refractory SE (RSE): SE persisting despite administration of at least 2 appropriately selected and dosed parenteral medications including a benzodiazepine. There is no specific seizure duration required.
- Super-Refractory SE (SRSE): SE persisting at least 24 hours after onset of anesthesia, either without interruption despite appropriate treatment with anesthesia; recurring while on appropriate anesthetic treatment; or recurring after withdrawal of anesthesia and requiring anesthetic reintroduction.

**"Anesthesia" includes commonly used agents such as midazolam, propofol, pentobarbital, thiopental, ketamine, and others, so long as they are used at anesthetic doses.

Refractory Status Epilepticus

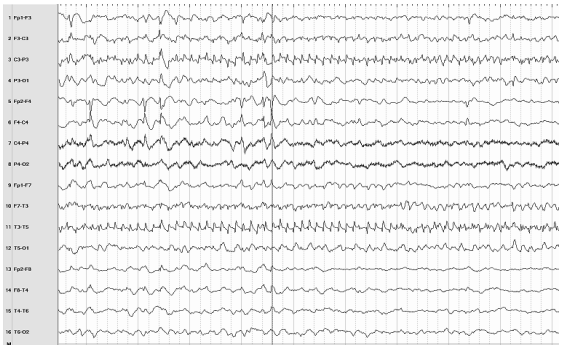
- Prolonged RSE (PRSE): RSE that persists for at least 7 days despite appropriate management, but without use of anesthetics.
- Prolonged SRSE (PSRSE) : SRSE that persists for at least 7 days, including ongoing need for anesthetics.

Left facial motor seizure

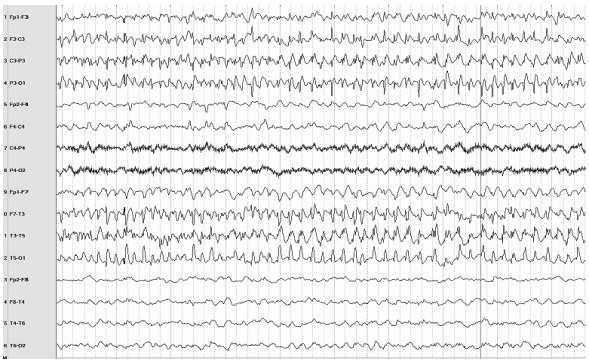


Brewer RP. EEG in convulsive and non-convulsive status epilepticus. J Clin Neurophysiol 2004;21:319-331.

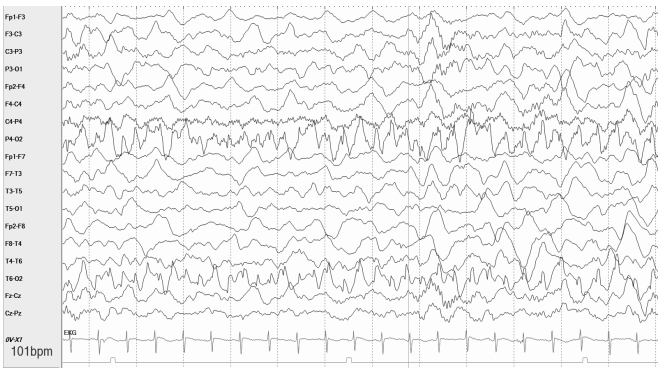
Focal motor seizure leading to Status Epilepticus



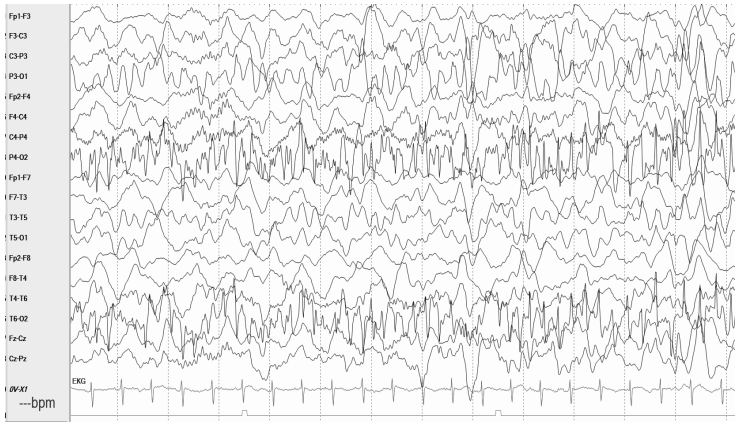
Focal motor seizure continued



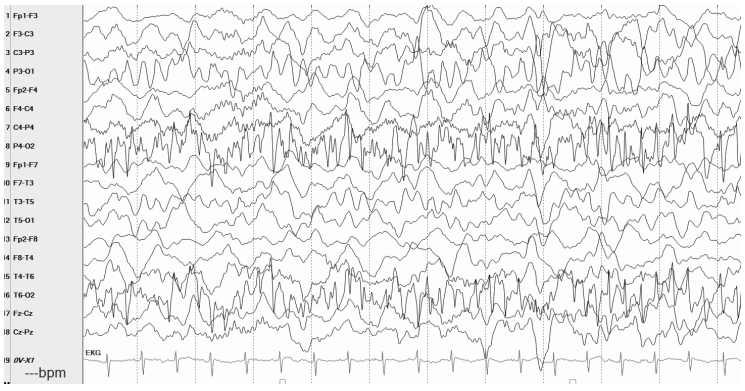
Focal Status Epilepticus



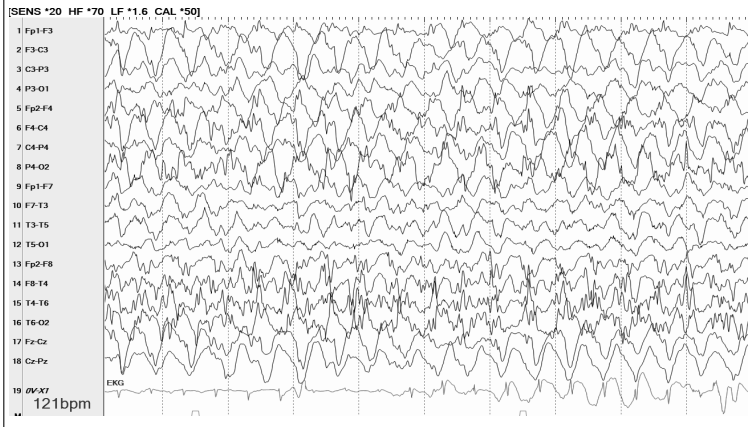
Focal Status Epilepticus



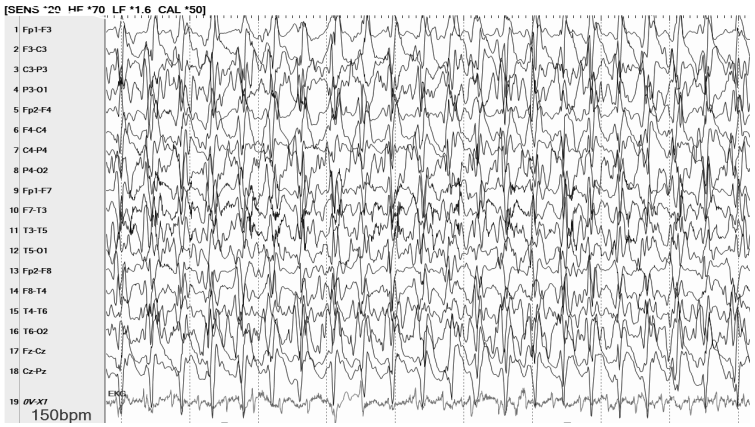
Focal Status Epilepticus



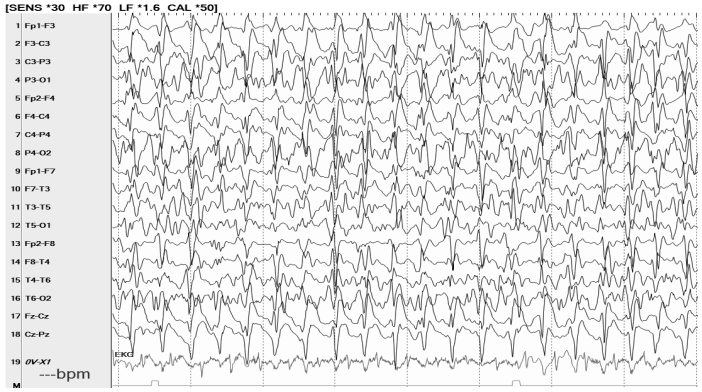
Focal Status Epilepticus



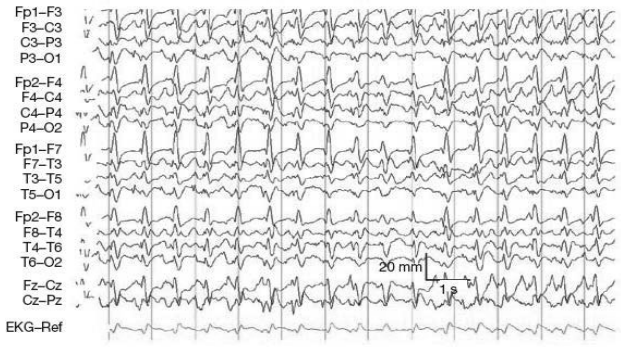
Focal Status Epilepticus



Focal Status Epilepticus



Absence SE



Korff CM, Nordli DR. Diagnosis and management of nonconvulsive status epilepticus in children. Nat Clin Pract Neurol 2007;3(9):505-16.

Ictal-Interictal continuum
Periodic discharges (PDs)

- Periodic - repetition of a waveform with relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals.
- Discharges are defined as waveforms with no more than 3 phases (i.e. crosses the baseline no more than twice) or any waveform lasting 0.5 seconds or less, regardless of number of phases.

Hirsh LJ, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013;30: 1–27

Ictal-Interictal continuum

- **Periodic discharges (PDs):**
  - **LPDs/PLEDs:** repetitive periodic, focal or hemispheric epileptiform discharges. Indicate structural lesion (eg. stoke, infection, tumor)
  - **LPDs+/PLEDs+**: PDs with intervening rhythmic discharges and superimposed faster frequencies, highly associated with seizures
  - **BIPDs/BIPLEDs**: bilateral and asynchronous PLEDs
  - **GPDs/GPEDs**: bilateral synchronous rhythmic epileptiform discharges
- **Triphasic waves** (GPDs with triphasic morphology)
  - Moderate to high amplitude 1.5-2.5 Hz activity
  - Often frontal predominant; fronto-occipital lag

Ictal-Interictal continuum

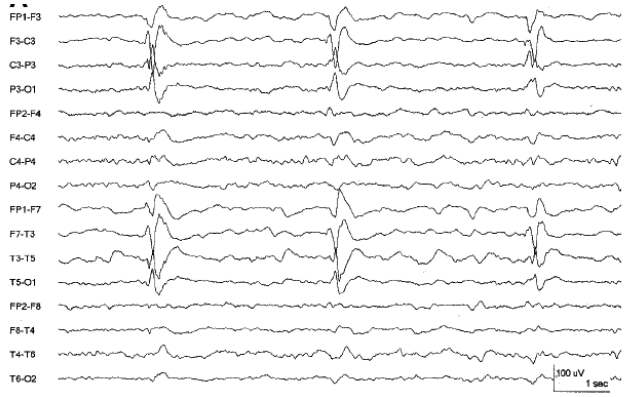
TABLE 1. New Terms for Older Terms

OLD Term		NEW Term
Triphasic waves, most of record	=	continuous 2/s GPDs (with triphasic morphology)
PLEDs	=	LPDs
BIPLEDs	=	BIPDs
GPEDs/PEDs	=	GPDs
FIRDA	=	Occasional frontally predominant brief 2/s GRDA (if 1-10% of record)
PLEDS+	=	LPDs+
SIRPIDs* w/ focal evolving RDA	=	SI-Evolving LRDA
Lateralized seizure, delta frequency	=	Evolving LRDA
Semirhythmic delta	=	Quasi-RDA

*SIRPIDs = stimulus-induced rhythmic, periodic or ictal discharges.

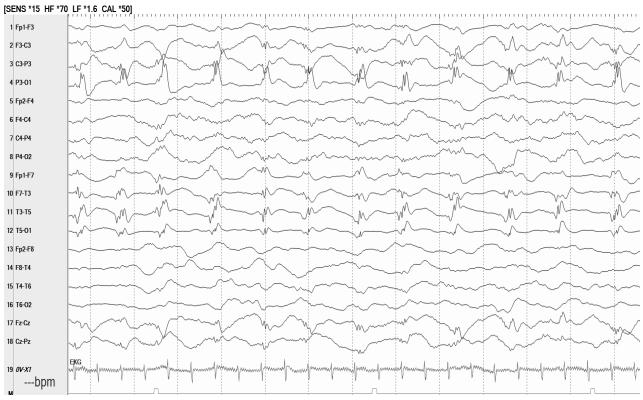
Hirsh LJ, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013;30: 1–27

LPDs/PLEDs

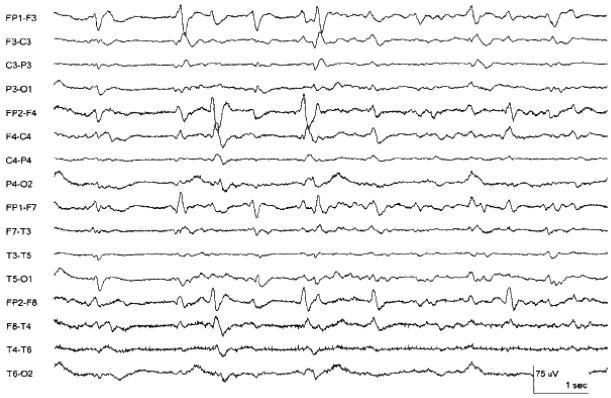


Brenner RP. EEG in convulsive and non-convulsive status epilepticus. J Clin Neurophysiol 2004;21:319-331.)

LPD

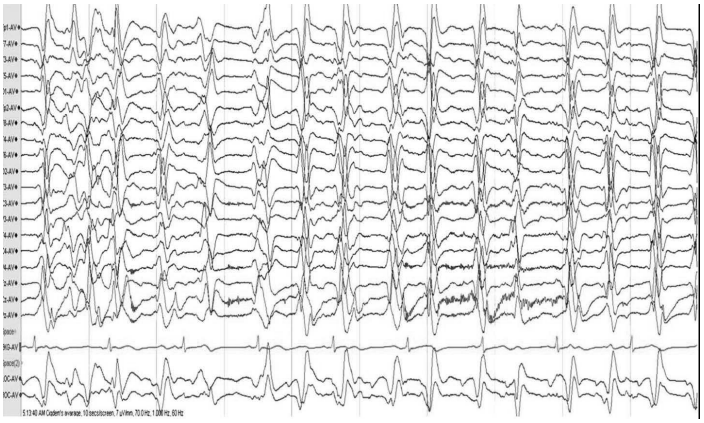


BIPDs/BIPLEDs



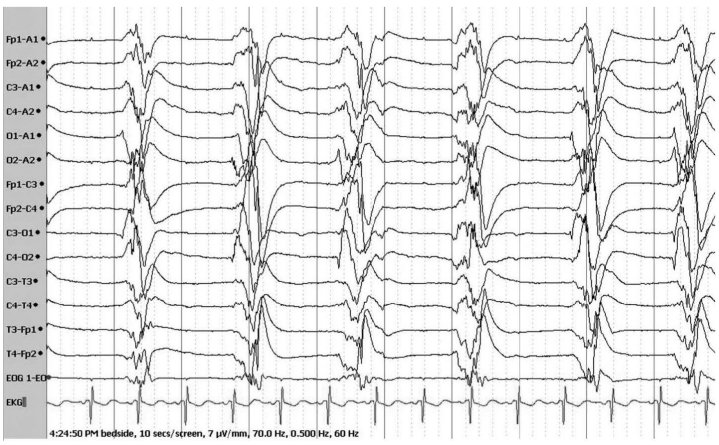
Brenner RP. EEG in convulsive and non-convulsive status epilepticus. J Clin Neurophysiol 2004;21:319-331.

GPDs/GPEDs



Akman and Riviello, 2011

GPDs/GPEDs



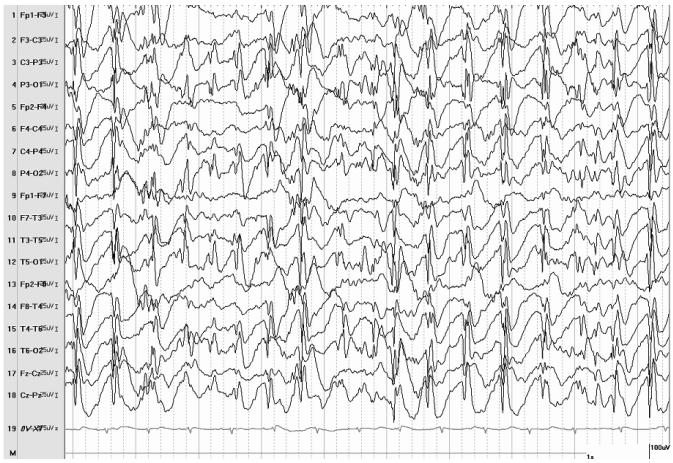
PART TWO:
ELECTROGRAPHIC STATUS EPILEPTICUS IN SLEEP

Electrical Status Epilepticus in Sleep (ESES)

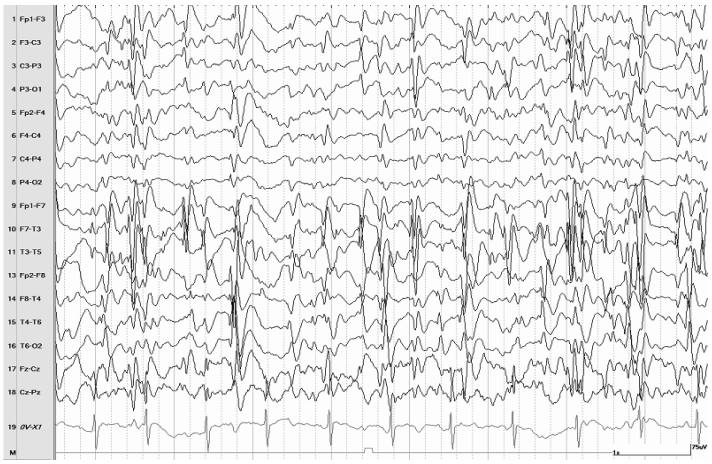
- ESES is characterized by near-continuous slow spikes and waves in NREM sleep.
  - Bilateral or lateralized (occasionally)
  - Defined as epileptiform activity occupying >85% of NREM sleep [variable spike wave index (SWI) cut-off reported in the literature].

- Syndromes with ESES:
  - Landau-Kleffner Syndrome (LKS)
  - Continuous spike and wave during sleep (CSWS)
  - Atypical benign epilepsy with centro-temporal spikes (BECTS)

ESES



ESES



Treatment of ESES

First line treatments:
- high-dose benzodiazepines (47%)*
- valproate (26%)**
- a corticosteroids (15%)

Second line treatments:
- valproate (26%)
- high-dose benzodiazepines (24%)
- corticosteroids (23%)

*the preferred one was diazepam 1 mg/kg for one night followed by 0.5mg/kg/day.
**The preferred dose of valproate was 30–49 mg/kg/day.

Fernandez, et al. Treatment for continuous spikes and waves during sleep (CSWS): Survey on treatment choices in North America. Epilepsia. Vol 55, Issue 7, July 2014. Pages 1099-1108.

Treatment Algorithm ESES

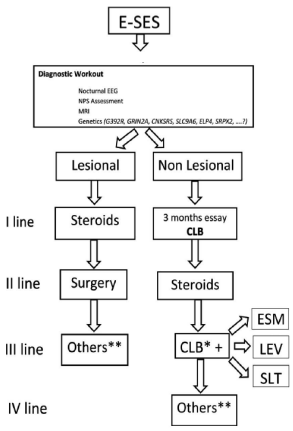


FIG. 1. The flowchart shows our diagnostic and therapeutic suggested management. It is divided into two sections: (1) lesional that means structural epilepsy and (2) nonlesional that means idiopathic epilepsy/unknown origin. CLB, clobazam; ESM, ethosuximide; LEV, levetiracetam; SLT, sulthiame. *Clobazam or the antiepileptic drug prescribed to patient previously the diagnosis of E-SES. **Ketogenic diet or acetazolamide.

Veggiotti, et al, 2016

Part Three: Infantile Spasms

Case 1

- 9 month old male
- Clusters of forward body and limb flexion for 3 weeks
- Hypoplastic left heart syndrome
- Post-operative watershed infarcts and status epilepticus at 2 months
- No fever or other infectious symptoms; stable cardiac function
- Global developmental delay; no regression in association with onset of movements
- On Keppra; weaning gabapentin
- No family history of seizures or consanguinity
- Microcephalic infant with moderate to severe hypotonia; G-tube

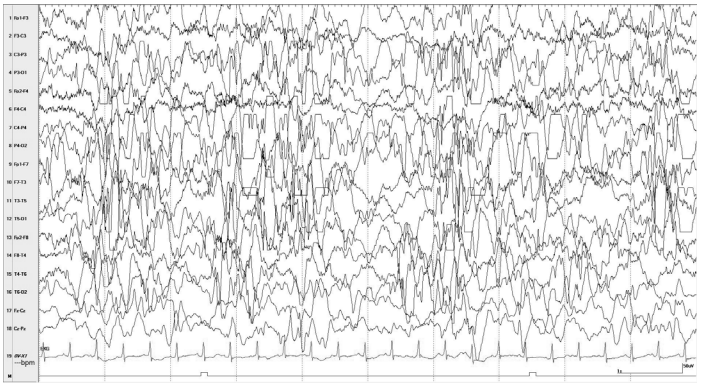
Which of the following do this patient's abnormal movements most likely represent?

A. Reflux
B. Irritability due to weaning of gabapentin
C. Exaggerated startle response
D. Myoclonic-astatic seizures
E. Infantile spasms

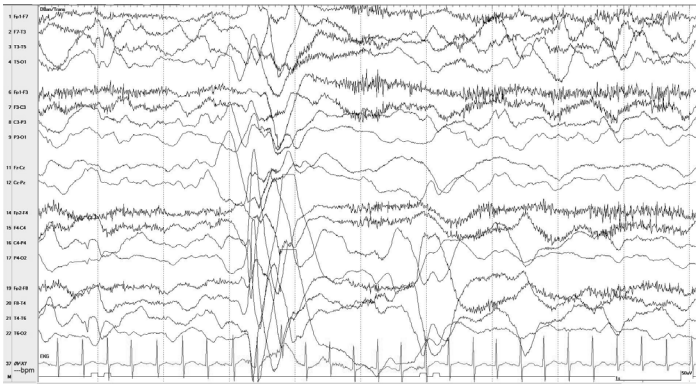
Which of the following EEG patterns is most likely to be seen in association with patient's abnormal movements?

A. Slow spike wave
B. Generalized slow-wave transient followed by an abrupt attenuation of background activity
C. Movement artifact with no ictal correlate
D. Polyspikes
E. 3 Hz generalized spike wave

Hypsarrythmia



Electroclinical Spasms



Interrater reliability

- 6 blinded pediatric electroencephalographers from 4 centers reviewed 22 EEG samples from patients with IS.
- Inter-rater reliability assessed.
- **Results:**
  - K 0.89 in determining whether a study was normal or abnormal
  - K 0.40 for identification of hypsarrhythmia; 0.47 for modified hypsarrhythmia
  - Despite generally unsatisfactory interrater agreement, raters consistently reported high confidence in assessments.

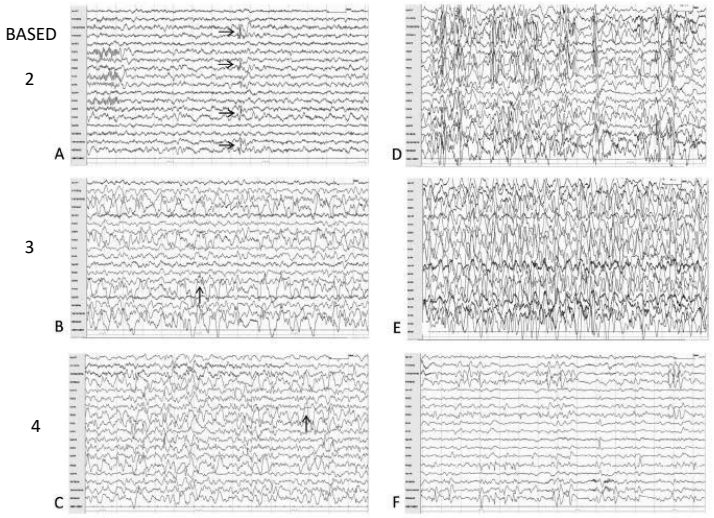
Hussain SA, et al. Hypsarrhythmia assessment exhibits poor interrater reliability: A threat to clinical trial validity. Epilepsia, 56(1):77–81, 2015

BASED SCORE

- BASED (Burden of Amplitudes and Epileptiform Discharges) score
  - ≤2: <3 spike foci AND no common background slow waves ≥200uV
  - 3: Multifocal spikes <50% of one second bins and no common background slow waves ≥200uV OR no multifocal spikes but common background slow waves ≥200uV
  - 4*: Multifocal spikes <50% of one second bins AND common background slow waves ≥200uV
  - 5*: Multifocal spikes ≥50% of one second bins OR common background slow waves ≥300uV in two or more bilateral head regions

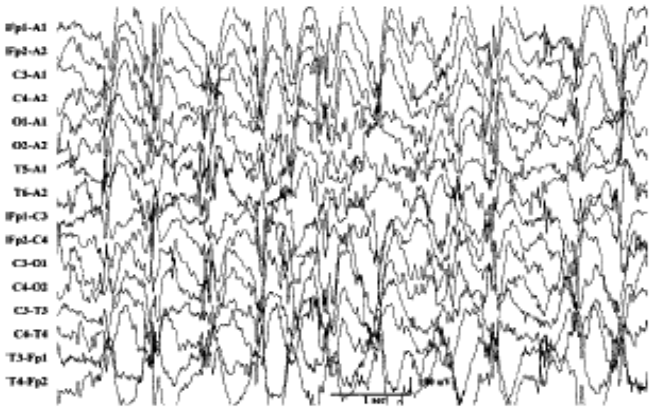
*hypsarrhythmia

Mytinger et al. Epilepsy Research 2015; 116: 93-98



Mytinger JR, et al

Hypsarrhythmia with increased interhemispheric synchronization



Interrater reliability BASED SCORE

- Twenty patients with infantile spasms were prospectively evaluated
- Forty EEG clips (20 pre-treatment and 20 post-treatment), representing the most severely abnormal five minute sleep epoch of each study, were assessed by three reviewers blinded to treatment and clinical outcome.
- Fleiss' kappa (K) was used to assess the inter-rater agreement in the interpretation of hypsarrhythmia when using the BASED score compared to the traditional method of EEG analysis.

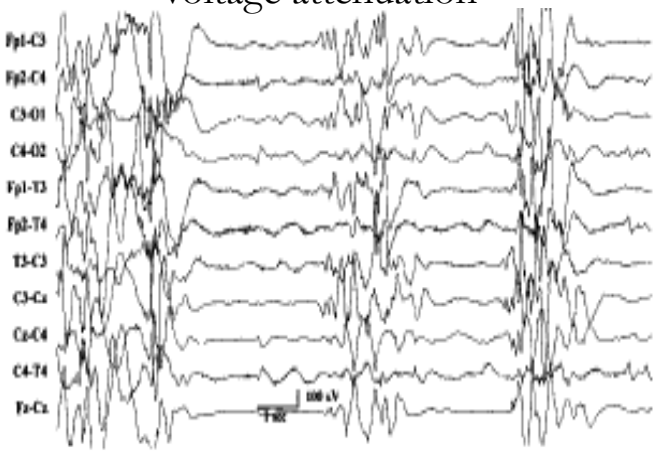
Mytinger JR, et al Improving the inter-rater agreement of hypsarrhythmia using a simplified EEG grading scale for children with infantile spasms. Epilepsy Res. 2015 Oct;116:93-8

Interrater Reliability

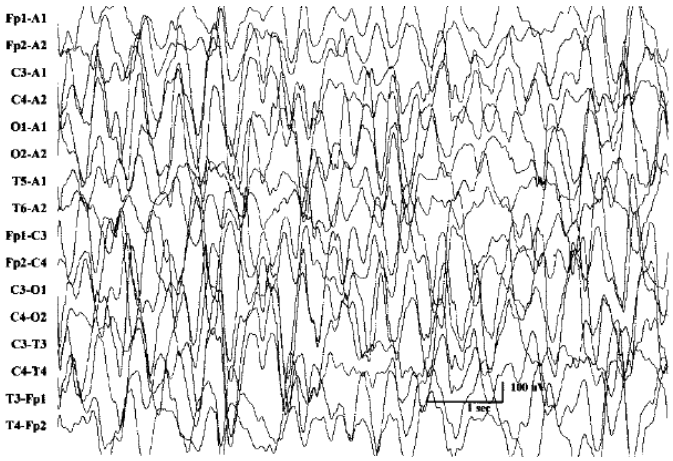
Results: Reviewers had favorable inter-rater agreement using the BASED score in interpreting hypsarrhythmia (K: 0.87) compared to when using the traditional method of EEG analysis to interpret hypsarrhythmia (K: 0.09). The three reviewers all agreed on the presence or absence of hypsarrhythmia in 37/40 (93%) epochs using the BASED score but in only 15/40 (38%) epochs using the traditional method of EEG analysis, p <0.001.

Mytinger JR, et al. Epilepsy Res. 2015 Oct;116:93-8

Hypsarrhythmia with episodes of voltage attenuation



Hypsarrhythmia with little spike and sharp activity



Infantile Spasms Triad

- West syndrome
  - Peak onset 4-6 months of age
  - Infantile spasms
    - Brief, bilateral symmetric contraction of the muscles of the neck, trunk, and extremities
    - Mixed>flexor>extensor
    - Tend to cluster, most commonly after arousal from sleep
  - Hypsarrythmia
    - Gibbs and Gibbs: random high voltage slow waves and spikes that vary from moment to moment both in duration and in location
    - Most pronounced in slow wave sleep
  - Developmental regression

Treatment

- ILAE summary of recommendations for the management of infantile seizures:
  - ACTH preferable in the short-term control of spasms (level B)
  - Oral steroids probably effective in the short-term control of spasms (level C)
  - Data insufficient to comment on the optimal preparation, dosage, and duration of treatment with steroids (level U)
  - Low-dose ACTH may be considered as an alternative to high-dose ACTH for treatment of epileptic spasms (level B)
  - Vigabatrin possibly effective in the short-term control of spasms (level C), especially in the case of tuberous sclerosis complex (level C)
  - Treatment with ACTH/oral steroids may result in a better long-term neurodevelopmental outcome than treatment with vigabatrin in children with epileptic spasms due to unknown etiologies (level C)
  - A shorter interval from the onset of spasms to treatment initiation may improve the long-term neurodevelopmental outcome, especially in cases where there is no identified etiology (level C)

Better with earlier treatment?

Table 1. Unadjusted VABS scores at the 4-year assessment in each category of lead time for all infants and by etiology

	All infants		Proven etiology		No identified etiology	
Lead time to treatment	VABS mean (SD)	Number	VABS mean (SD)	Number	VABS mean (SD)	Number
<8 d	76.2 (28.4)	11	55.6 (12.9)	5	93.3 (26.4)	6
8–14 d	62.8 (26.4)	17	49.7 (12.9)	10	84.7 (29.6)	6
15 d to 1 m	65.4 (29.8)	8	51.0 (13.9)	3	74 (34.7)	5
1–2 m	65.3 (25.0)	15	60.3 (26.9)	8	71 (23.3)	7
>2 m	55.5 (24.3)	21	43.8 (9.4)	10	66.2 (28.9)	11
Not known		5		3		2
Total number		77		39		37

d, days; m, months.

Decrease by 3.9 as go from one lead time category to another

O'Callaghan Epilepsia 2011

Outcomes Infantile Spasms

- Developmental delay, persistent neurologic deficits, ongoing seizures, persistent EEG abnormalities common
- Favorable outcome: normal neuroimaging, normal development before onset of spasms, absence of associated etiologic factors, sustained response to therapy, absence of other seizure types
- 50-60% have epilepsy, most commonly develop LGS
- 70-80% with intellectual disability

Summary

Classification of Status Epilepticus: Semiology, Etiology, EEG correlates, Age

Stages of Status Epilepticus: EEG Patterns

Refractory SE (RSE): SE persisting despite administration of at least 2 appropriately selected and dosed medications

Treatment of ESES

Identification of Hypsarrhythmia- BASED criteria

Treatment of Infantile Spasms

.

History, Examination, and Semiology/ Chemical and Metabolic Screening

Amar B. Bhatt, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

History, Examination, Semiology/Chemical and Metabolic Screening

Amar B. Bhatt, MD
Assistant Professor of Neurology, Epilepsy Section
Rush University Medical Center
Program Director, Neurology Residency

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Overview

- History
- Semiology
- Physical Examination
- Laboratory Evaluation

History

- History is crucial, even in a busy clinic
- Initial EEG positive in 40-50% of epilepsy patients
- Interictal epileptiform discharges are NOT diagnostic
  - 0.5-1% prevalence in healthy adults
  - may be over-read
  - generalized spike-and-wave *trait* can be seen in family members of patients with generalized epilepsy

History

- True onset of events (seizures vs. epilepsy)
- Seizure Triggers and Provoking Factors
- Epilepsy Risk Factors
- Event types

True onset of events

- From first event or birth → onward
- From most recent → backward
- First recognized event may not be first true seizure
- Some may be provoked / triggered (but not all)

Triggered vs. Provoked

Triggered (Epilepsy)

- Sleep deprivation
- Fever/illness
- Stress
- Reflex seizures
- Missed AEDs

Provoked (not Epilepsy)

- Medications/Drugs
- Medication or Alcohol Withdrawal
- ↑Na, ↓Na, ↑Ca, ↓Mg
- Renal or Hepatic Failure
- Acute CNS insult (stroke, trauma)

Which of the following medications is LEAST likely to lower seizure threshold?

A. Quetiapine
B. Varenicline
C. Amitriptyline
D. Bupropion
E. Citalopram

Common Seizure-Provoking Meds

- Tramadol
- Bupropion
- Fluoroquinolones
- Carbapenems
- Cefepime
- Varenicline (a.k.a. Chantix)
- 4-aminopyridine and dalfampridine
- Atypical (not typical) antipsychotics*
- Tricyclic antidepressants*
- Lithium*
- Baclofen (toxicity and withdrawal)*
- Stimulants*
- Diphenhydramine*

*personal opinion: still may be used cautiously in epilepsy patients

Epilepsy Risk Factors

- Family history*
- Febrile seizures*
- Birth and prenatal/pregnancy history
- Developmental history
- CNS injury or instrumentation
- Head trauma (penetrating, LOC/amnesia > 30 min)
- Age

*include FH of febrile seizures; focus on first degree relatives

Highest epilepsy incidence in elderly

Hauser et al. Epilepsia. 1993

A healthy 31-year-old man presents with his first generalized convulsion. He returns to baseline by the time he arrives in the emergency room, and his vital signs, general examination, and neurological examination are normal. Head CT is normal. He has no epilepsy risk factors. He is discharged from the emergency room and follows up in the neurology clinic, at which time routine EEG and brain MRI are normal. He has had no further convulsions. He denies any history of staring events or myoclonus. What is his approximate seizure recurrence risk in the next 2 years?

A. 5%
B. 20%
C. 40%
D. 60%
E. 80%

Two-Year Seizure Recurrence Risk

- First unprovoked seizure: ~40%
  + normal EEG and MRI: ~25%
  + epileptiform EEG, prior brain injury, or significant MRI finding: ~60%*
- Second unprovoked seizure: ~60%*

*meets ILAE definition for epilepsy

Krumholtz et al, Neurology, 2015

Event types

- Avoid conclusive language, esp. when used by patients ("grand mal"; "seizure")
- Use patient's language for each event type
- Establish a relationship between event types, including progressive semiology/symptoms
- Note frequency of each event type

Event types – use simple language

- Aura
  - warning just prior (or without an actual seizure)
- Absence or complex partial seizures (CPS)
  - staring / spacing out
  - lost time / memory lapses
- Myoclonic jerks
  - Quick jerks lasting < 1 sec
  - What happens when we get startled or are nodding off
  - Dropping cup or brush in the morning

ABSENCE	***COMPLEX PARTIAL***
No aura	Maybe aura
Abrupt onset	Gradual or abrupt
<15 sec	>30 sec
Abrupt end	Usually gradual
Immediate return to baseline	Post-ictal lethargy or confusion
Occur daily	Occur weekly or monthly
Triggered by hyperventilation	–

Semiology

- "the study of signs"
- (Video) analysis of signs/symptoms to:
  - Localize (lobe/region)
  - Lateralize (hemisphere)
- No sign has perfect predictive value
  - May reflect spread and not onset
  - Accuracy increases when used in combination
  - Very helpful when EEG non-localizing / misleading

Semiology

- Most retrospective / descriptive studies report sensitivity and specificity in a specific population (e.g., temporal lobe epilepsy)
- What we really want – positive and negative predictive value in all patients (epileptic and non-epileptic combined, temporal and extratemporal combined)

What we really want

- How often is déjà vu really predictive of mesial TLE?
- How certain are we that ictal speech is non-dominant hemisphere?
- How certain are we of autonomic symptoms being mesial temporal? Or insular?
- How certain are we of fear being amygdala? Or cingulate? Or even temporal?

Temporal Lobe Seizures

- Mesial Auras
  - epigastric rising, fear, anxiety, déjà vu, jamais vu
  - autonomic (palpitations, unilateral goosebumps)
  - olfactory/gustatory not common (often reported in PNES)
- Lateral (Neocortical) Auras
  - auditory auras, vertigo
- Other symptoms (usually awareness is altered by now)
  - memory loss
  - behavioral/speech arrest
  - oroalimentary or limb automatisms

Abou-Khalil et al, Neurology in Clinical Practice, 2012

Utility of Hand/Limb movements

- Ipsilateral
  - Distal, manipulative, semi-purposeful automatisms
  - But may also be bimanual…
  - Post-ictal nose wiping (with the mobile arm)
- Contralateral
  - Rhythmic ictal non-clonic hand movements (RINCH)
  - Non-manipulative proximal automatisms
  - Dystonic /tonic posturing and limb immobility

Abou-Khalil et al, Neurology in Clinical Practice, 2012
Lee et al, Epilepsia, 2006
So, J Clin Neurophysiol, 2006

A 29-year-old right handed man has seizures consisting of sudden onset right > left arm stiffening (left arm flexion, right arm extension) with preserved consciousness. The seizures are very brief and painful. The most likely localization/lateralization for this seizure is:

A. Left temporal
B. Right temporal
C. Left frontal
D. Right frontal
E. Left insular

Extratemporal Seizures – Frontal

- Very bizarre, often out of sleep
- Hypermotor, frantic movements and odd vocalizations (even swearing)
- Brief seizures often without post-ictal confusion
- Partial tonic seizures have preserved consciousness (unlike generalized)

Abou-Khalil et al, Neurology in Clinical Practice, 2012

Extratemporal Seizures – Frontal

Semiology	**Localization/Lateralization**
Focal Clonic	Contralateral Motor Strip
Tonic (Y sign) With Fencer posturing	Supplementary motor area Contralateral to extended arm
Unilateral tonic posturing	Mesial frontal
Turning prone (along body axis)	Mesial frontal

Abou-Khalil et al, Neurology in Clinical Practice, 2012

A 16-year-old left handed boy has seizures consisting of staring, confusion, and memory loss for 1-2 minutes, followed by 3-5 minutes of lethargy. He reports that his typical warning consists of laryngeal constriction followed by drooling. The most likely localization for this seizure is:

A. Occipital
B. Parietal
C. Temporal
D. Insular
E. Frontal

Extratemporal Seizures – Other

Semiology	Localization/Lateralization
Paresthesiae Numbness Pain	Contralateral Sensory Strip*
Non-formed or simple visual hallucinations	Occipital Cortex
Laryngeal, chest, abd discomfort Dyspnea, dysarthria, dysphonia Hypersalivation	Insular

Abou-Khalil et al, Neurology in Clinical Practice, 2012

*supplementary sensory area may cause ipsilateral or bilateral symptoms

	TEMPORAL	*FRONTAL*
Onset	Slow	Abrupt
Progression	Slow	Rapid
Motor activity	Motionless	Hypermotor or Tonic
Complex Postures	Less frequent Less prominent Later (sGTCS)	More frequent More prominent Early
Vocalization	Formed speech if non-dominant	Not formed speech
Automatisms	More common More upper extremities	Less common More lower extremities
Duration	Long	Brief
Post-ictal confusion	Long	Brief or absent

So, J Clin Neurophysiol, 2006

Lateralizing motor signs

Sign	Hemisphere of Seizure Onset
Positive motor signs	
Early nonforced head turn ☆	Ipsilateral
Late contraversive forced head turn	Contralateral ☆
Late ipsiversive forced head turn	Ipsilateral
Eye deviation	Contralateral ☆
Focal clonic	Contralateral
Asymmetric clonic ending ☆	Ipsilateral
Dystonic limb	Contralateral ☆
Tonic limb	Contralateral
Complex postures	
M2E and fencing	Contralateral
"Figure 4" sign	Contralateral to extended limb
Negative motor signs	
Ictal paresis or immobile limb	Contralateral
Todd paresis	Contralateral ☆

So, J Clin Neurophysiol, 2006

Other useful semiology

Semiology	Localization/Lateralization
Ictal laughing (gelastic)	Hypothalamic Hamartoma, Mesial Temporal, or Cingulate
Ictal urinary urge	Right temporal
Ictal emesis	Right temporal Occipital in children
Ictal speech arrest	Dominant hemisphere (67% PPV)
Ictal speech (in TLE)	Non-dominant hemisphere (83% PPV)
Post-ictal aphasia (esp > 1 min)	Dominant hemisphere (90% PPV)
Post-ictal cough	Right temporal

So, J Clin Neurophysiol, 2006

Physical Examination

- Skin
  - Neurocutaneous syndromes / genetic conditions
- Cardiovascular
  - Stroke / vasculopaths
  - Orthostatic vital signs
- Neurological
  - Upper motor neuron signs
- AED toxicity (skin, eyes, teeth, cerebellar, neuropathy)

Laboratory Evaluation

- Glucose, electrolytes, renal function, tox screen are often performed in ER
- In clinic, these tests are probably unnecessary
- Lumbar puncture only if suspicious for meningitis, encephalitis, or subarachnoid hemorrhage
- Overall no systematic studies for lab tests

Gavvala and Schuele, JAMA, 2016

Neuroimaging and EEG

- Type and timing of neuroimaging is still uncertain
  - CT usually done in ER
  - MRI (epilepsy protocol) should be considered
- EEG is abnormal in 29%, and more likely to be abnormal within 24-48 hours after seizure
- EEG and MRI can be done as an outpatient if no concern for a structural lesion

Gavvala and Schuele, JAMA, 2016

Prolactin

- Specific for GTCS/CPS when compared to PNES
- Usu. normal in frontal CPS
- Cannot differentiate syncope from GTCS
- Ideally need to compare to baseline prolactin
- Not sensitive; if normal, no specific diagnosis can be reliably reached

If level ≥2x upper limit of normal within 20 minutes, the event was not psychogenic

Chen et al, Neurology, 2005

References

Abou-Khalil BW, Gallagher MJ, Macdonald RL. Ch. 101: Epilepsies. Bradley's Neurology in Clinical Practice, 7th ed. Elsevier, 2016. 1563-1614.

Chen DK, So YT, Fisher RS; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Use of serum prolactin in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005 Sep 13;65(5):668-75. Review. PubMed PMID: 16157897.

Gavvala JR, Schuele SU. New-Onset Seizure in Adults and Adolescents: A Review. JAMA. 2016 Dec 27;316(24):2657-68.

Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993 May-Jun;34(3):453-68. PubMed PMID: 8504780.

Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2015 Oct 27;85(17):1526-7. doi: 10.1212/01.wnl.0000473351.32413.7c. PubMed PMID: 26503589.

Lee GR, Arain A, Lim N, Lagrange A, Singh P, Abou-Khalil B. Rhythmic ictal nonclonic hand (RINCH) motions: a distinct contralateral sign in temporal lobe epilepsy. Epilepsia. 2006 Dec;47(12):2189-92. PubMed PMID: 17201723.

So EL. Value and limitations of seizure semiology in localizing seizure onset. J Clin Neurophysiol. 2006 Aug;23(4):353-7. Review. PubMed PMID: 16885709.

Syed TU, LaFrance WC Jr, Kahriman ES, Hasan SN, Rajasekaran V, Gulati D, Borad S, Shahid A, Fernandez-Baca G, Garcia N, Pawlowski M, Loddenkemper T, Amina S, Koubeissi MZ. Can semiology predict psychogenic nonepileptic seizures? A prospective study. Ann Neurol. 2011 Jun;69(6):997-1004. doi: 10.1002/ana.22345. Epub 2011 Mar 17. PubMed PMID: 21437930.

Ambulatory and Video-EEG

Amar B. Bhatt, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

AMBULATORY AND VIDEO-EEG

Amar B. Bhatt, MD
Assistant Professor of Neurology, Epilepsy Section
Rush University Medical Center
Program Director, Neurology Residency

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Objectives

- Uses of video-EEG monitoring
- Options for EEG monitoring
- Yield of EEG monitoring
- Activation procedures used to increase yield
- Comparison of different types of EEG monitoring

Uses of Video-EEG monitoring

- Diagnosis (epileptic vs. non-epileptic)
- Interictal Epileptiform Discharges
- Classification and Localization
- Medication Adjustment
- Seizure / Discharge Quantification
- Surgical Candidacy Evaluation

Options for EEG monitoring

- Short-term – inpatient or outpatient
  - Routine video-EEG (20-60 min)
  - Prolonged/Extended video-EEG (1-4 hours)
- Long-term – outpatient
  - Ambulatory EEG
  - Home video-EEG – a growing trend
- Long-term – inpatient
  - Portable continuous video-EEG (usu. ICU) – a.k.a. cEEG*
  - Hard-wired continuous video-EEG (usu. Epilepsy Monitoring Unit) – a.k.a. EMU*

*some ICUs are hard-wired, some EMUs are portable

Methods of increasing EEG Yield

- Single routine EEG: 30-50% yield* in epileptic patients
- Repeat and 2-4 hour extended EEGs increase yield* to 80-90%
- Remaining Cases: Long-term monitoring (cEEG, EMU, Ambulatory EEG)

*this yield is not diagnostic of epilepsy (interictal epileptiform discharges)

Diagnostic yield of sequential routine EEG and extended outpatient video-EEG monitoring

- 179 consecutive patients had 20-min video-EEG (REEG) followed by 4h of video-EEG monitoring (EXM)
  - Habitual events captured in 8% of REEG
  - EEGs diagnostic in 50%: LRE 21%; GE 15%; NES 15%
  - REEG alone diagnostic in 27% (49/179): LRE 7%; GE 13%; NES 7%
- After non-diagnostic REEG
  - Habitual events captured in 15% of EXM
  - EXM diagnostic in 32% (41/130): LRE 18%; GE 2%; NES 12%
- EXM relatively more beneficial for LRE / NES (rather than GE)

Modur and Rigdon, Clinical Neurophysiology, 2008

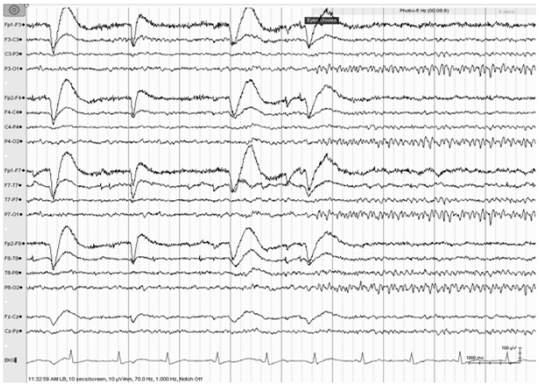
courtesy of Dr. Abou-Khalil

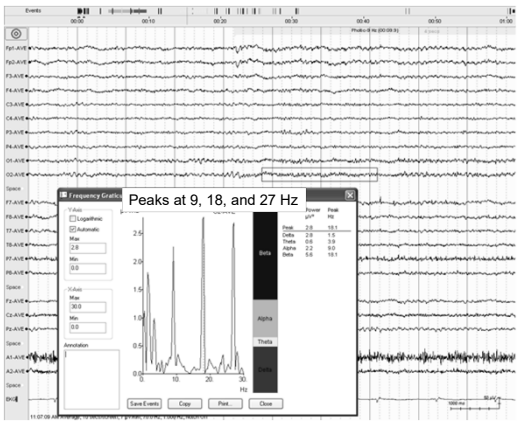
Activating Procedures

- Hyperventilation and Photic Stimulation
  - Mostly for generalized epilepsies
  - Lack of slow activity or driving still normal
- Drowsiness and Sleep

Harmonic driving

- Driving response that is a multiple or factor of the flash frequency
- Can be half, double, triple, etc.
- Can have a “notched” appearance (multiple fused frequencies)





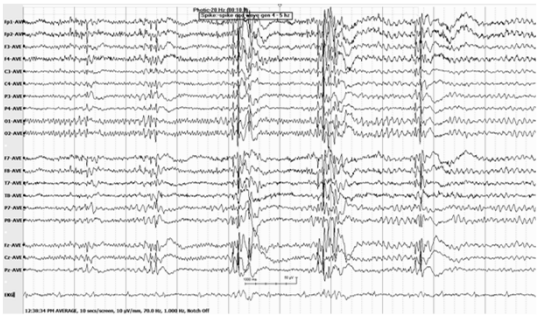
Which of the following responses is abnormal during photic stimulation?

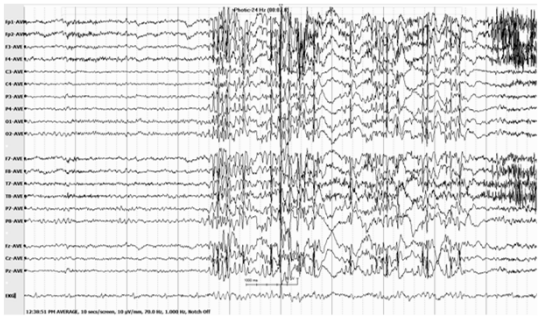
A. Photoconvulsive response
B. Photomyogenic response
C. Photomyoclonic response
D. Photovoltaic response
E. Photocell response

Photoparoxysmal response

- a.k.a. photoconvulsive response*
- Assoc. with generalized epilepsy
  - Usu. generalized / bifrontally predominant
  - May be bioccipitally predominant
  - May have assoc. absence, myoclonic, or generalized tonic clonic (GTC) seizures
- Assoc. with occipital epilepsy if unilateral (rare)

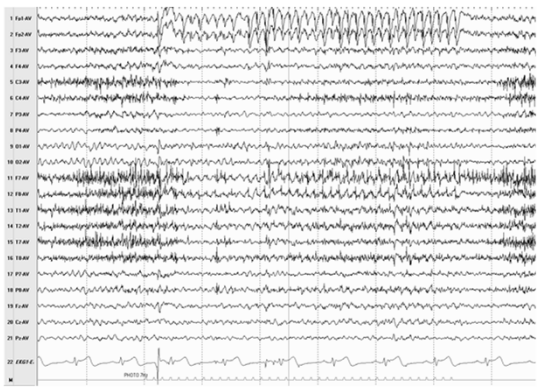
*controversial: some say photoconvulsive implies that discharges outlast the flash





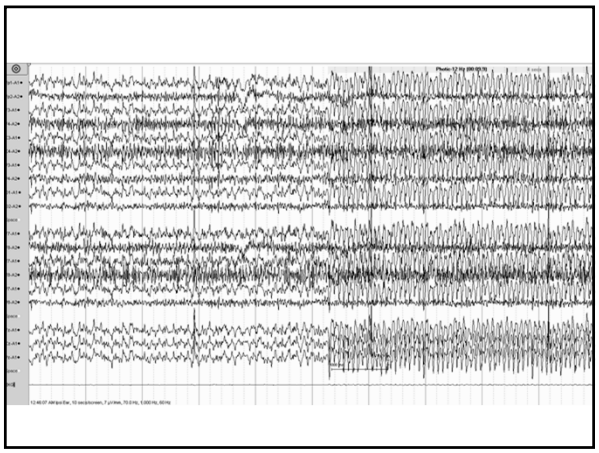
Photomyogenic response

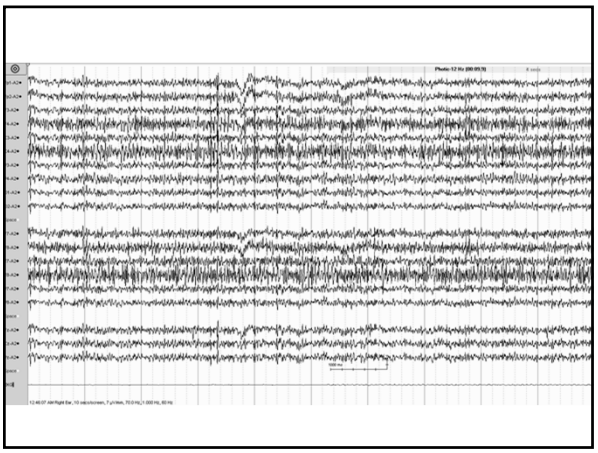
- a.k.a. photomyoclonic response
- this is benign
- don't let "myoclonic" fool you
- EMG potentials (frontal) time-locked to the flash frequency

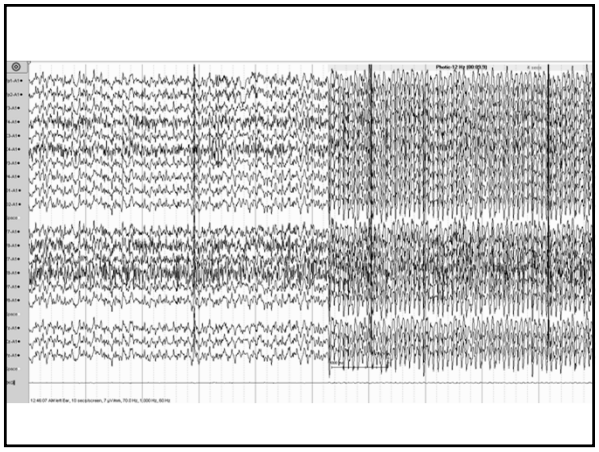


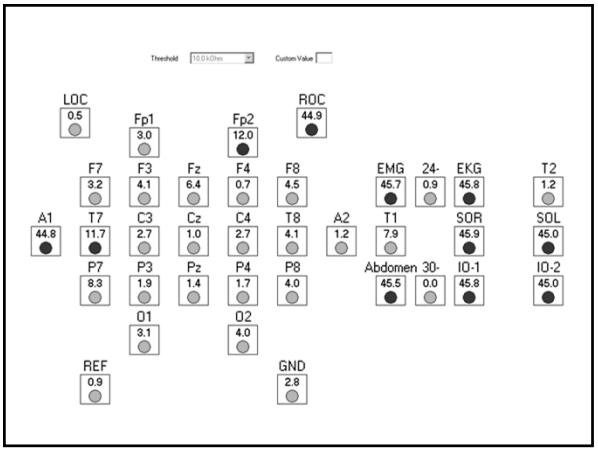
Photovoltaic (photocell) artifact

- high impedance electrode creates a "cell" or "battery" capable of storing charge
- released with each photic flash, resulting in a time locked spiky response on EEG
- only specifically in the electrode with the high impedance.









Ambulatory EEG

- Home-based EEG recording
- Usually have a daily patient visit to fix electrodes and download data
- Patient must push button or record in diary
- Cheaper and more widely available than EMU

Ambulatory EEG – Uses

- Event capture – yield is 40-70%
- Nocturnal disorders (frontal seizures, sleep disorders, ESES/CSWS)
- Quantifying subclinical / subtle clinical seizures
- Determining recurrence risk when considering AED withdrawal

Lawley et al, Epilepsy and Behavior, 2015

Ambulatory EEG

- Advantages
  - minimal interference with patient activities
  - natural environment to trigger events/seizures
- Disadvantages
  - prone to artifacts
  - no video or real-time monitoring (in most cases)
  - cannot examine patient during event
  - cannot safely withdraw medications

Importance of Video

- Semiology analysis
- Correlation to patient / witness history
- Assessment for artifact
- Diagnosis (esp. when EEG is normal)

Long-term video-EEG monitoring

- EMU remains the diagnostic "gold" standard
- Ideally requires:
  - Ictal EEG, video, and exam
  - Interictal EEG recording with AED withdrawal
  - Correlation to history *(confirm all of patient's full blown and typical event types were captured)*

Long-term video-EEG monitoring

- Advantages
  - invasive monitoring
  - ictal functional imaging
  - medication adjustment
- Disadvantages
  - high cost (techs, nursing, physicians, hospital)
  - disrupts patient's normal activities and work/school
  - risk of nosocomial infections
  - risk of physical and psychological harm/injury

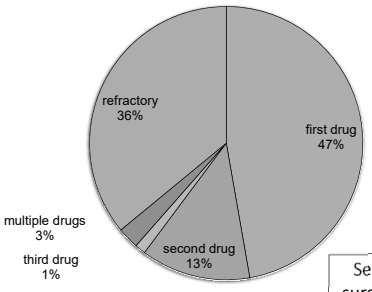
Refer refractory cases!

- Why?
  - To confirm diagnosis of epilepsy
  - For alternative treatment options (surgery, etc.)
  - To avoid inappropriate treatments
- What defines refractory?
  - Lack of seizure control with two properly dosed AEDs
  - NOT failed due to side effects

A 28-year-old man develops new onset partial seizures. Treatment with levetiracetam is initiated, and the dose is titrated up to 1500 mg twice daily without seizure recurrence. However, he does not tolerate this medication due to worsening depression. The medication is tapered off and lamotrigine is titrated upward. What is the patient's chance of seizure freedom with lamotrigine?

A. ~75%
B. ~66%
C. ~50%
D. ~33%
E. ~15%

Chances of Seizure Freedom



Seizure-free with surgery (in the right cases): up to 70%

Kwan and Brodie, NEJM, 2000.
Chen, Brodie, Liew, and Kwan, JAMA Neurology, 2018.

Unnecessary VNS in PNES

- 60 consecutive VNS patients in EMU
- 13 had PNES exclusively (none had prior EMU)
  - all on 2-4 AEDs
  - all discharged off AEDs
  - duration of VNS therapy: 0.5 – 5 yrs
  - mean latency to PNES diagnosis: 2.8 yrs
- Over-interpretation of outpatient EEGs?

Arain et al, Epilepsy and Behavior, 2011

Diagnostic usefulness and duration of the inpatient long-term video-EEG monitoring: findings in patients extensively investigated before the monitoring

- 234 consecutive LTM studies over 2 yrs (221 patients)
- Diagnostically useful in 44% (typical event previously not captured)
  - Not different between age groups
  - Not different between referral groups [diagnostic (41%), classification (41%) and presurgical (55%)]
- Duration of successful LTM significantly longer in the presurgical group (mean: 3.5 days) vs. diagnostic and classification groups (2.4 and 2.3 days, respectively)

Alving and Beniczky, Seizure, 2009

courtesy of Dr. Abou-Khalil

What is the typical diagnostic yield (chance of capturing a patient's typical events) during epilepsy monitoring unit (EMU) admission?

A. 20-25%
B. 40-45%
C. 60-65%
D. 80-85%
E. 90-95%

Non-diagnostic EMU studies

- Diagnostic yield of 1st EMU study: 82-85%
- Diagnostic yield of 2nd EMU study: 42-53%
- Factors associated with non-diagnostic study:
  - younger age (in adults)
  - longer duration of monitoring
  - normal outpatient EEG
  - absence of epilepsy risk factors

Elgavish and Cabaniss, J Clin Neurophysiol, 2011: ~3600 patients
Robinson et al, Epilepsy and Behavior, 2011: ~2400 patients

Co-existent epilepsy and PNES

- Occurrence has "decreased" historically
  - possibly due to wider use of video-EEG monitoring
  - estimated to be 5-15%
- Key factors in successful monitoring
  - duration (5 days suggested as optimal*)
  - AED withdrawal
  - capture of all typical event types

*Foong and Seneviratne, J Clin Neurosci, 2016

Continuous EEG (cEEG) in the ICU

- Non-convulsive seizures / status epilepticus have a typical combined incidence of 20-25%
- May vary (8-48%) depending on the study
- 40-92% of seizures on cEEG are nonconvulsive

NCS/NCSE: When to consider cEEG

- Altered mental status (esp. unexplained)
- History of epilepsy or recent seizures (esp. GTCS)
- Subtle twitching, eye deviation, nystagmus
- Recent CNS procedure, infections, stroke, neoplasms (esp. when pt is worse than expected)
- Chronic focal cortical injury

In critically ill, non-comatose patients undergoing continuous EEG monitoring, what duration of monitoring is recommended to capture a seizure in the majority (95%) of patients who will develop seizures in the ICU?

A. 1 hour
B. 6 hours
C. 12 hours
D. 24 hours
E. 48 hours

Continuous EEG in critically ill patients

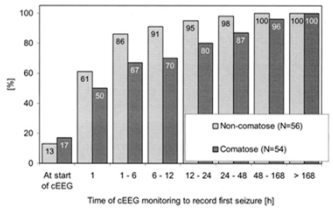


Figure 2. Time to record the first seizure, comparing noncomatose and comatose patients. cEEG = continuous EEG.

570 patients with altered mental status

Longer cEEG duration required in comatose patients

To capture most seizures:
Noncomatose → 24 hrs
Comatose → 48 hrs

Claassen et al., Neurology 2004;62:1743–8.

Is it worth it? Cost effective?

- Review of 100 TBI patients
  - cEEG was 1% of total hospital costs
  - Helped guide decisions in 90% of pts
  - ↓ cost / length of stay compared to historical controls
- Review of ~8,000 ventilated patients
  - cEEG was 5% of total hospital costs
  - cEEG assoc. with significantly lower in hospital mortality, even on multivariate analysis
  - No significant cost difference for patients on continuous vs. routine EEG

Vespa et al., Clin Neurophysiol 1999;16:1–13
Ney et al., Neurology 2013;81(23):2002-8

Value of 30 min study

(if cEEG not available)

- Lack of epileptiform discharges (EDs) may be predictive
- 103/190 lacked EDs
  - 3% had seizures during cEEG
  - these occurred during first 4 hours of recording
- 55/83 lacked EDs
  - 5% had seizures during cEEG
  - 13% developed EDs within 24 hours
- Pre-test probability / etiology still a confounder

Shafi et al, Neurology, 2012
Khan et al, Epileptic Disorders, 2014

	Routine EEG	Extended EEG	Continuous portable EEG	Long-term EEG (EMU)	Ambulatory EEG	Home vEEG
Availability	(+)	(+)	-	(-)	+	--
Duration	--	-	++	++	+	+
Video	+	+	+	+	(-)	+
Ictal EEG	--	-	+	++	+	+
Examination	+	+	-	++	--	--
EEG quality	+	+	+	++	(-)	+
Surgery	-	-	+	++	-	-
Natural environment	-	-	-	-	(+)	+
Acute use	+	+	++	+	--	--
Med change	-	-	+	++	-	-
Hx correlate	-	-	+	++	-	-
Quantify sz	-	+	++	++	+	+
Sleep EEG	-	+	++	++	++	++
HV/Photic	+	+	+	+	-	-
Affordability	++	+	--	(--)	+	-

References

Alving J, Beniczky S. Diagnostic usefulness and duration of the inpatient long-term video-EEG monitoring: findings in patients extensively investigated before the monitoring. Seizure. 2009 Sep;18(7):470-3. doi: 10.1016/j.seizure.2009.04.005. Epub 2009 May 9. PubMed PMID: 19428271

Arain AM, Song Y, Bangalore-Vittal N, Ali S, Jabeen S, Azar NJ. Long term video/EEG prevents unnecessary vagus nerve stimulator implantation in patients with psychogenic nonepileptic seizures. Epilepsy Behav. 2011 Aug;21(4):364-6.

Cascino GD. Video-EEG monitoring in adults. Epilepsia. 2002;43 Suppl 3:80-93. Review. PubMed PMID: 12060010.

Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA neurology. 2018 Mar 1;75(3):279-86.

Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004 May 25;62(10):1743-8. Review. PubMed PMID: 15159471.

Elgavish RA, Cabaniss WW. What is the diagnostic value of repeating a nondiagnostic video-EEG study? J Clin Neurophysiol. 2011 Jun;28(3):311-3. doi: 10.1097/WNP.0b013e31821c3aa9. PubMed PMID: 21633258.

Foong M, Senaviratne U. Optimal duration of video-electroencephalographic monitoring to capture seizures. J Clin Neurosci. 2016 Jun;28:55-60. doi: 10.1016/j.jocn.2015.10.032. Epub 2016 Mar 5. PubMed PMID: 26960265.

Khan OI, Azevedo CJ, Hartshorn AL, Montanye JT, Gonzalez JC, Natola MA, Surgenor SD, Morse RP, Nordgren RE, Bujarski KA, Holmes GL, Jobst BC, Scott RC, Thadani VM. A comparison of continuous video-EEG monitoring and 30-minute EEG in an ICU. Epileptic Disord. 2014 Dec;16(4):439-48. doi: 10.1684/epd.2014.0715. PubMed PMID: 25498516.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9.

Lawley A, Evans S, Manfredonia F, Cavanna AE. The role of outpatient ambulatory electroencephalography in the diagnosis and management of adults with epilepsy or nonepileptic attack disorder: A systematic literature review. Epilepsy Behav. 2015 Dec;53:26-30. doi: 10.1016/j.yebeh.2015.09.032. Epub 2015 Oct 26. Review. PubMed PMID: 26515156.

Modur PN, Rigdon B. Diagnostic yield of sequential routine EEG and extended outpatient video-EEG monitoring. Clin Neurophysiol. 2008 Jan;119(1):190-6. Epub 2007 Nov 26. PubMed PMID: 18042424.

Ney JP, van der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005-2009. Neurology. 2013 Dec 3;81(23):2002-8. doi: 10.1212/01.wnl.0000436948.93399.2a. Epub 2013 Nov 1. PubMed PMID: 24180910; PubMed Central PMCID: PMC3854828.

Robinson AA, Pitiyaruvath N, Abou-Khalil BW, Wang L, Shi Y, Azar NJ. Predictors of a nondiagnostic epilepsy monitoring study and yield of repeat study. Epilepsy Behav. 2011 May;21(1):76-9. doi: 10.1016/j.yebeh.2011.03.014. Epub 2011 Apr 19. PubMed PMID: 21507729.

Shafi MM, Westover MB, Cole AJ, Kilbride RD, Hoch DB, Cash SS. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. Neurology. 2012 Oct 23;79(17):1796-801. doi: 10.1212/WNL.0b013e3182703ftc. Epub 2012 Oct 10. PubMed PMID: 23054233; PubMed Central PMCID: PMC3475619.

Vespa PM, Nenov V, Nuwer MR. Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. J Clin Neurophysiol. 1999 Jan;16(1):1-13. PubMed PMID: 10082088.

Imaging

Taha Gholipour, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

IMAGING

Taha Gholipour, MD
Assistant Professor of Neurology
The George Washington University Epilepsy Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Outlines

- When and what to get for imaging?
  - indications and modalities
- What to look for?
  - common imaging findings
  - What to do when imaging is negative?
- The role of imaging in surgical planning and outcomes

Indications

- ALL patients with new onset seizures
  - Underlying etiology changes immediate course of action
  - Stroke, primary CNS or metastatic neoplasms, infection (e.g. abscess, parasitic,..), hemorrhage to name a few
- Long-standing epilepsy patients who don't have an adequate-quality imaging
  - MRI from 10 years ago is not the same as today
  - Not uncommon to identify surgical candidates 20 years after seizure onset
- Presurgical evaluation of intractable epilepsy
  - Finding lesions, clarifying suspected lesions, not missing dual pathology, and stereotactic/robotic planning
- Post-operative imaging
  - Usually 3-6 month later shows a better view of resection borders
  - Immediate for complications, adequate resection defer to surgeon

ILAE Guidelines for Imaging for Children with Epilepsy (2009)

- When available, MRI is preferred to CT because of its superior resolution, versatility, and lack of radiation
- When focal epilepsy is known or suspected
- When the epilepsy classification is in doubt (e.g. drug-resistant generalized epilepsy)
- When an epilepsy syndrome with remote symptomatic cause is suspected (e.g. perinatal hypoxic-ischemic injury)

Gaillard et al. Epilepsia 2009

ILAE Imaging Task Force Recommendations (2019)

- Perform MRI when possible, CT with contrast when suspecting infection, tumor, vascular lesions
- Use specific epilepsy protocols for identification of subtle structural lesions (use appropriate MRI studies)
- A structural etiology for focal epilepsy refers to abnormalities visible on structural neuroimaging concordant with the electro-clinical assessment and likely cause of the patient's seizures
- The identification of a structural lesion in recent onset epilepsy is a strong indicator of drug resistance

AAN Imaging Guidelines

- Emergency imaging (AAN 2007) :
  - CT "possibly useful" in emergency setting (children and adults)
  - CT "possibly useful" in children <6months, and AIDS + first seizure
- First unprovoked seizure, adults (AAN 2007):
  - MRI or CT "should be considered"
- When possible, MRI preferred over CT

CT imaging in epilepsy

- Excellent for hard tissue (skull defects, bone changes, calcifications)
- Can be high resolution, CTA and CTV highly sensitive
- Low cost, widely available, fast (emergency setting)
- No safety issues in the presence of implanted devices
- Yield is low outside emergent first seizure setting. in focal epilepsies was estimated ~30% (Bronen 1996)
- Other limitations: Radiation, contrast issues, and need for repeat MRI soon after

How good is MRI in finding lesions?

- Depends on reader expertise, and technical considerations such as: field strength, head coils, dedicated protocols
- Few studies comparing the 3T yield vs 1.5T in detection of structural lesions have shown from 5% to 65% increase in detection of lesions
- By using 3T, some lesions are better visualized, more "dual-pathology" or incidental findings are added

MRI yield in focal epilepsy

- A study of 764 patients with new onset seizures (1.5T or 3T MRI)
  - 343 (45%) had a positive finding: an epileptogenic lesion in 23% and a non-epileptogenic abnormality in 22%
- 3T MRI in 161 consecutive cases of focal epilepsy
  - A relevant lesion was identified in 48% of patients
  - Another 12% showed subtle or non-specific lesions in the suspected region
  - Focal cortical dysplasia and vascular lesions were most common, followed by hippocampal sclerosis, tumors, and scars from previous cerebral injuries

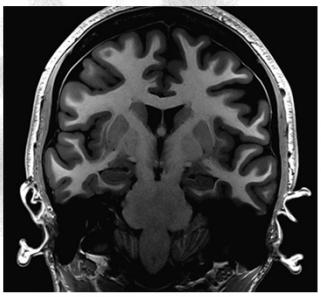
Hakimi et al Neurology, 2013
Toledo et al Clin Neurol & Neurosurg, 2013

Yield depends on MRI acquisition protocol

- **Magnet strength**: 3T significantly outperforms 1.5T MRI in image quality, detection, and characterization of lesions.
  - It provides better signal to noise ratio.
  - 7T does the same compared to 3T.
- **Head coil**: Studies using phased-array head coils at 3T yielded lesions in 65% of patients who had normal 1.5T studies (Knake et al,2005)
- **Sequences and slice thickness**: Using epilepsy protocol for patients with previously "normal" MRI may reveal a lesion in 30%-65% of cases;
- Post- processing of images can increase, sensitivity to as high as 70%

Image Quality in Clinical MRI

- Improvements in MR technology allows us to see more:
  - higher magnetic field – 3T, 7T
  - parallel detection: phased array receivers and transmitters
  - Acquisition processing power, and post-processing power



MGH 3T - 32 channel coil

ILAE Task Force Recommendation for an MRI Epilepsy Protocol

- HARNESS-MRI: Harmonized Neuroimaging of Epilepsy Structural Sequences
  - High-resolution 3D T1-weighted MRI (commonly labeled as MPRAGE or SPGR)
  - High-resolution 3D fluid-attenuated inversion recovery (FLAIR)
  - High in-plane resolution 2D coronal T2-weighted MRI (coronal T2)

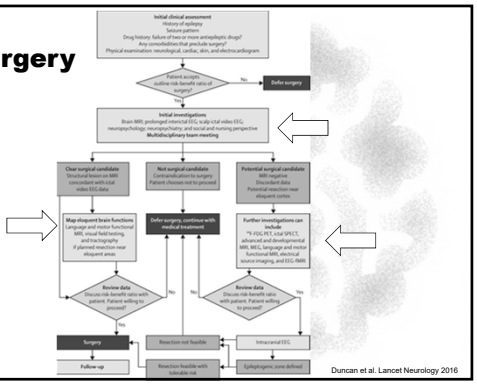
Sequence	T1-weighted	T2-weighted	T2-weighted
Name	MPRAGE	3D FLAIR	2D TSE
Dimension	3D	3D	2D
Orientation	Sagittal	Sagittal	Coronal
Thickness (mm)	1 (no gap)	1.0 (no gap)	2 (no gap)
Voxel size (mm)	1 x 1 x 1	1 x 1 x 1	0.4 x 0.4 x 2.0

Epilepsy Protocol: GWU Epilepsy Center

- Only on 3T; No contrast; <1h duration
- Axial DWI + ADC
- Coronal FLAIR (2mm) angled to the hippocampus
- Coronal T2 (2 mm); angled to the hippocampus
- Axial Susceptibility Weighted Imaging
- 3D Coronal T1 MPRAGE (1x1x1mm)
  - Reconstruct in axial and sagittal planes
- 3D Coronal [T1] Double Inversion Recovery (1x1x1mm)
  - Reconstruct in axial and Sagittal planes*

Path to Surgery

- When imaging makes the calls



Duncan et al. Lancet Neurology 2016

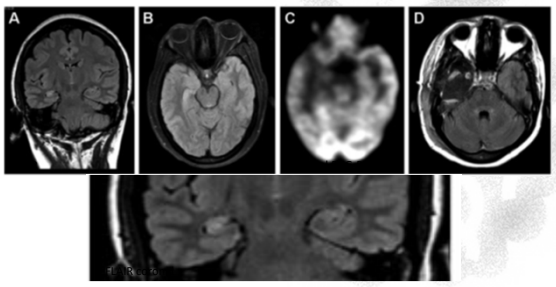
Path to Surgery: Multiple Modalities

Performed invariably	Performed variably	Selective Centers
History and examination	Intracranial grid SEEG	MEG
Scalp EEG	Electrocorticography	**High-Field MRI (7T)**
MRI [Epilepsy Protocol]	**FDG-PET**	**EEG-fMRI**
Video-EEG (scalp)	**Interictal-Ictal SPECT**	**PET receptor studies**
Neuropsychology	Wada test	**SISCOM**
	Functional MRI	**Functional Connectivity MRI**
		MRI volumetry

Modified from Cascino Epi Res 2004

Common Imaging Findings

Hippocampal sclerosis (MTS)



Velez-Ruiz N, Klein JP Seminars in Neurology 2012

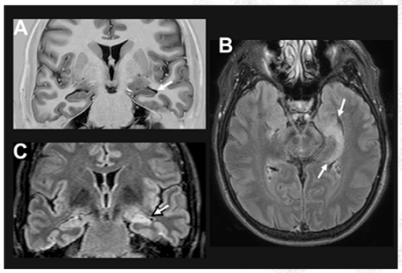
Hippocampal sclerosis (MTS)

- Most common MR finding in temporal lobe epilepsy
- Obtain coronal sections perpendicular to the long axis of hippocampus
- Diagnostic Triad on MRI (needs 2 out of 3):
  - Hippocampal atrophy (coronal T2)
  - High T2/FLAIR signal of hippocampus (coronal FLAIR)
  - loss of internal architecture (interdigitations) of hippocampus (coronal T2)
- Harder to detect when bilateral MTS

Hippocampal sclerosis (MTS)

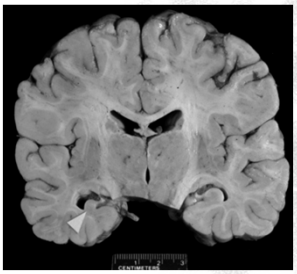
- Long-standing MTS can be associated with volume loss in the amygdala, Papez circuit (parahippocampal gyrus, ipsilateral fornix, mammillary body, anterior thalamic nucleus.
- Enlargement of the temporal horn of the lateral ventricle is sensitive but not a very specific finding
- Dual pathology can occur in an estimated 15% of cases ipsilateral, contralateral, or bilateral to MTS ("MTS+")
- When something is not concordant in clinico-electrographic findings, aim for more non-invasive and if needed invasive evaluation

Hippocampal sclerosis (MTS)



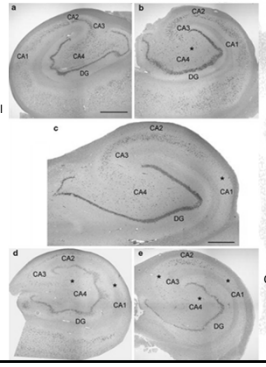
Cendes F, et al. Handb Clin Neurol. 2016

Hippocampal sclerosis (MTS)



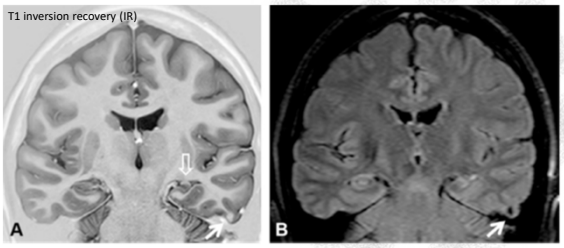
Pathologic Findings in MTS

Current clinical MRI not reliable in predicting specific pathology



Blumcke et al, 2007

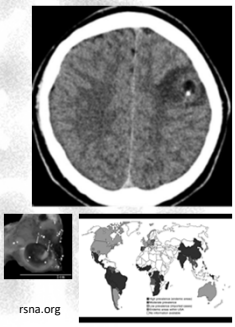
MTS+ neurocysticercosis lesion



Cendes F, et al. Handb Clin Neurol. 2016

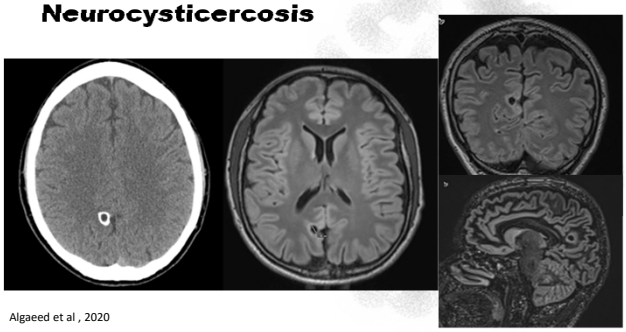
Neurocysticercosis

- A common cause of epilepsy in developing countries, specially in Latin America
- Caused by the encysted larva of the tapeworm *Taenia solium*
- Imaging findings depend on the life cycle stage at presentation, vascular involvement, inflammatory response (edema, gliosis, or arachnoiditis), and, in ventricular forms, degree of obstruction
- An intra-axial cystic lesion with calcification dot (calcified scolex) and surrounding edema suggests a recently evolved neurocysticercosis infection



rsna.org

Neurocysticercosis

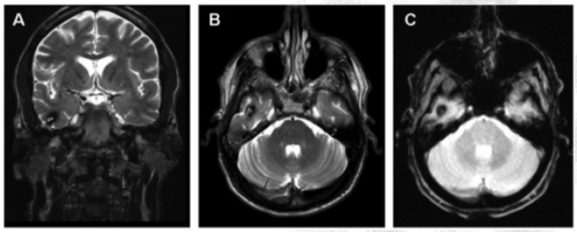


Algaeed et al , 2020

Cavernous angioma

- Intraparenchymal thin and dilated capillaries with a fibrous adventitia and no media, and no communication to normal vessels. The surrounding tissue is gliotic and hemosiderin-laden due to previous hemorrhages, sometime calcified.
- Can be incidental, unrelated to epilepsy. There are familiar forms with innumerable cavernoma.
- T2 image is characteristic (pop-corn appearance), susceptibility imaging/GRE shows hemosiderin surrounding.
- Vascular imaging only useful if a mixed vascular malformation (MVM) is suspected

Cavernous angioma



The lesion appear heterogenous on T2 due to blood products of varying age, and surrounded by a confluent rim of T2 hypointensity due to hemosiderin.

Gradient echo MRI shows susceptibility artifact

Velez-Ruiz N, Klein JP Seminars in Neurology 2012

Malformations of cortical development (MCD): classification

- Malformations due to abnormal neuronal and glial proliferation or apoptosis
  - Decreased proliferation/increased apoptosis: microcephalies
  - Increased proliferation/decreased apoptosis: megalencephalies
  - Abnormal proliferation (abnormal cell types):
    - Non-neoplastic (tuberous sclerosis, **cortical dysplasia with balloon cells**, hemimegalencephaly)
    - Neoplastic (association with disordered cortex): DNET, ganglioglioma, gangliocytoma
- Malformations due to abnormal neuronal migration
  - Lissencephaly/subcortical band heterotopia spectrum
  - Cobblestone complex
  - **Heterotopia** (subependymal, subcortical, marginal glioneuronal)
- Malformations due to abnormal cortical organization
  - **Polymicrogyria** and schizencepahly
  - **Cortical dysplasia without balloon cells**
  - Microdysgenesis
- Malformations of cortical development, not otherwise classified

From Raghavan M, GW Board Review 2018

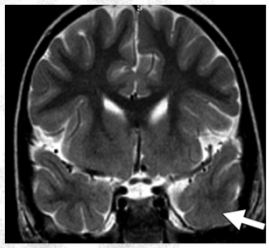
Terminology

- Pachygyria/agyria: Thickened or absent gyri
- Polymicrogyria: Numerous small gyri
- Lissencephaly: Smooth brain with hypoplastic sulci or cobblestone cortical surface
- Schizencephaly: Developmental (Gray-matter lined) cleft in the cerebral hemispheres
- Porencephaly: Acquired (WM lined) cerebral cystic lesion communicating with subarachnoid space/ventricles
- Heterotopias: neuronal clusters in abnormal locations in band or nodular
- Focal cortical dysplasia: Focal disorganization of cortical microstructure, with or without abnormal cell types

From Raghavan M, GW Board Review 2018

Focal cortical dysplasia (FCD)

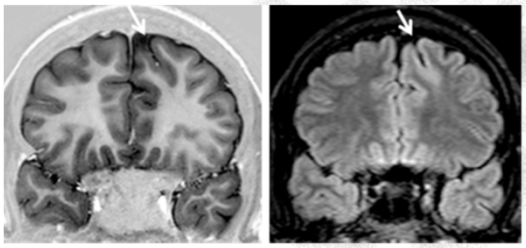
- FCD is a heterogeneous entity, and there are various pathology, genetic underpinning, association with other diseases, and imaging findings.
- FCD often refers to limited cortical dysplasia in the absence of whole brain gyration problems
- The pathology can be co-existent with a number of other lesions
- FCD accounts for 80% of all surgical cases in children, and a large number of adult-onset epilepsy, particularly those with non-visualized lesions
- Imaging hallmarks (frequently missed):
  - gray-white junction blurring
  - cortical signal change (best seen in T1 and T1-double inversion recovery)
  - subcortical T2/FLAIR changes, particularly in type 2.



T2w image- Type I FCD in a 3-year-old boy

Rastogi, Lee, Salamon 2008

Focal cortical dysplasia (FCD)



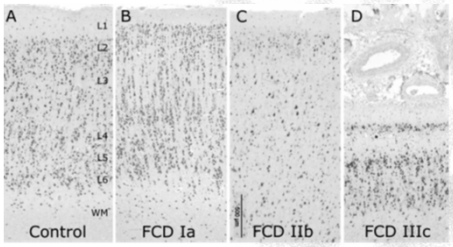
Cendes F, et al. Handb Clin Neurol. 2016

ILAE Classification of FCDs

Type I: focal cortical dysplasia with abnormal cortical lamination
a: radial cortical lamination
b: tangential 6-layer cortical lamination
c: radial and tangential cortical lamination
Type II: focal cortical dysplasia with dysmorphic neuron
a: without balloon cells
b: with balloon cells
Type III: architectural distortion of cortical layer
a: in temporal lobe with hippocampal atrophy
b: adjacent to glial or glioneuronal tumor
c: adjacent to vascular malformation
d: adjacent to other lesions acquired in early childhood

Blumcke et al., Epilepsia 2011

FCD Classification



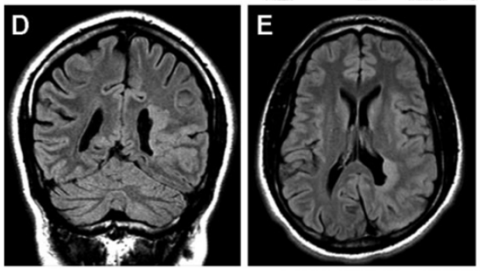
Blumcke et al., Epilepsia 2011

Focal cortical dysplasia

- Neuronal cytomegaly and balloon cells

  FCD - IIB

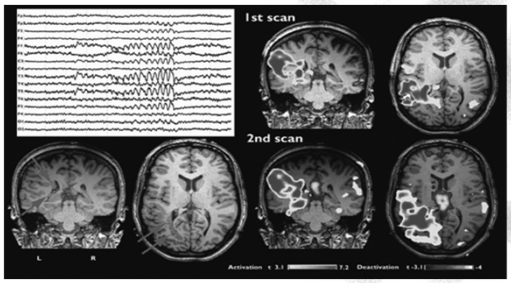
Nodular Heterotopia



Nodular Heterotopia

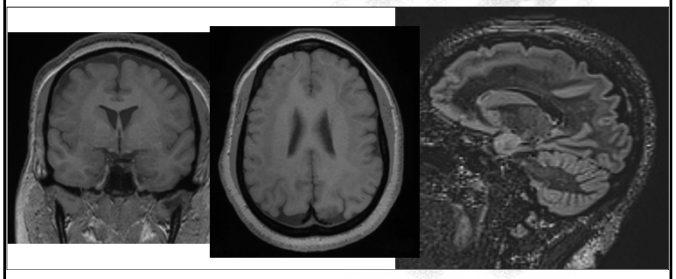
- Abnormal nodules of heterotopic neurons located along the surface of the lateral ventricles, with an apparently normal overlying cerebral cortex
- 15-20% of all MCDs, sometimes "incidental" finding in children with no epilepsy history
- Often temporal or occipital (around trigone)
- Filamin-A (FLNA) mutation associated with diffuse bilateral paravenricular heterotopia, sometimes cardiac/aortic abnormalities
- Patients may have unremarkable development, some with abnormal head size or shape, seizures usually starts around puberty

Nodular Heterotopia

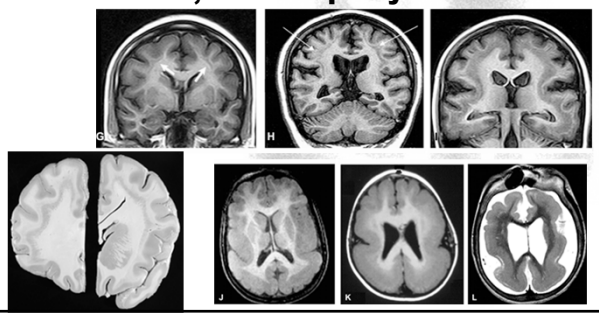


Gholipour et al, 2010

Band Heterotopia



Band heterotopia, double cortex, lissencephaly

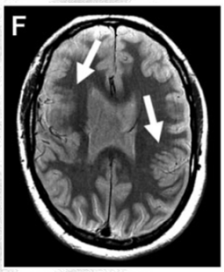


Lissencephaly

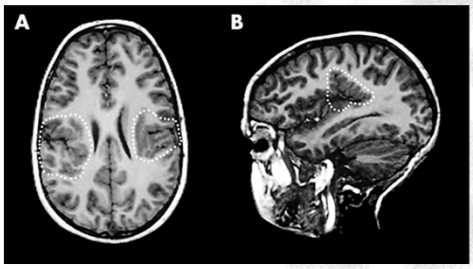
- Lisencephaly type I (classic lissencephaly) or lisencephaly-subcortical band heterotopia spectrum results from neuronal migration
  - Most common genes are Lis1 (autosomal) and DCX (doublecortin X-linked)
  - DCX manifests as infantile spasms and lisencephaly, severe delays in boys, variable, often milder seizures and frontal-dominant band heterotopia
- Lisencephaly type II or Cobblestone lissencephaly-result of neuronal over-migration
  - Cobblestone/pebbly appearance of cortex
  - Congenital muscular dystrophy, FKRP (Fukutin-related prt) gene

Polymicrogyria

- Excessive gyration
- Genetic and intra-uterine insult (ischemia, CMV infection)
- A specific syndrome of bilateral perisylvian polymicrogyria presents with "cerebral palsy" history, bilateral facio-pharyngo-glosso-masticatory paresis, (characteristic), spastic quadriparesis, and intractable seizures.



Bilateral Perisylvian Polymicrogyria



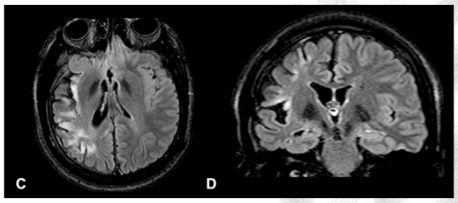
Jansen and Andermann, 2005

Rasmussen's Encephalitis

- Inflammatory disease, onset often around 6-10 years old
- Progressive unilateral atrophy (imaging), seizures with unilateral onset, with evidence of unilateral neurological dysfunction.

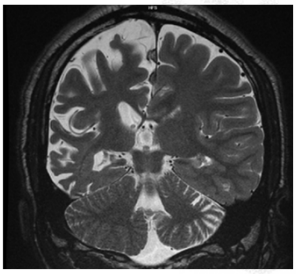
- Focal seizures and refractory *epilepsia partialis continua*
- Other hemisphere is normal, prognosis depends on age of onset
- Treatment with hemispherectomy, anti-inflammatory
- Pathological findings: microglial nodules, perivascular cuffing

Rasmussen's Encephalitis



- A rare, progressive inflammatory hemispheric damage and atrophy.
- Usually initially involves the insular-opercular regions
- Foci of hyperintense FLAIR signal from the initial stages of the disease

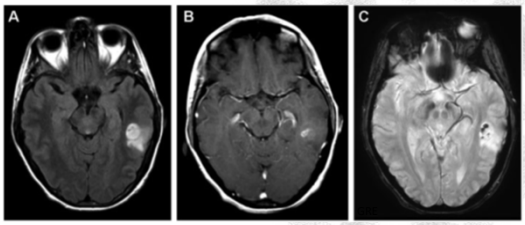
Hemiatrophy (and cerebellar diaschisis)



Low-grade tumors

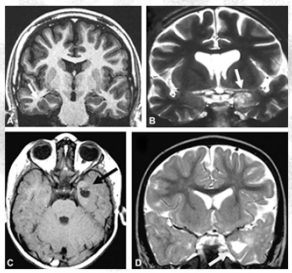
- A cystic and nodular mass with internal calcification in a young person with new-onset seizures:
  - Ganglioglioma
  - Dysembryoplastic neuroepithelial tumor (DNET)
  - Pleomorphic xanthoastrocytoma, and oligodendroglioma
- Although the presence of enhancement could be consistent with a higher-grade lesion, and can be followed closely over time if seizures are controlled
- DNETs are low grade (WHO grade I) tumors arising from cortical or subcortical gray matter. About 60% are temporal, 30% frontal
- DNET pathology has mixed glial-neural neoplasm with multi-nodular architecture, concurrent cortical dysplasia in 80% of cases

Low-grade tumors



Velez-Ruiz N, Klein JP Seminars in Neurology 2012

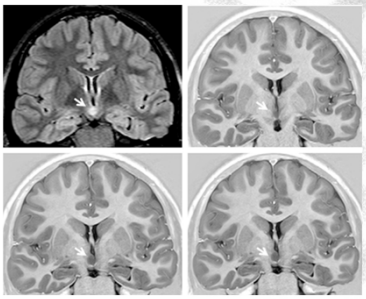
Ganglioglioma



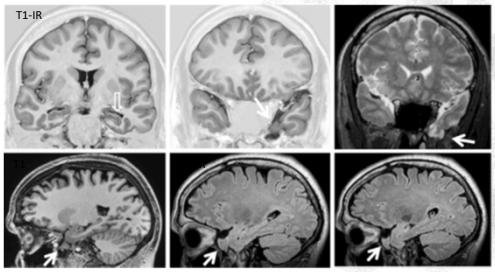
Hypothalamic Hamartoma

- Hamartoma is a mass of disorganized but mature cells indigenous to particular site, e.g. mature neurons, glia, and fiber bundles
- Early onset **gelastic** seizures, or visual field changes, early onset of puberty and behavioral problems
- On MRI has gray matter intensity, no enhancement
- Types: *Sessile* (with no stalk) arising from the mamillary region or ***Pedunculated*** (with a stalk) arising from *tuber cinereum*
- Laser ablation might be best first step and needs good imaging

Hypothalamic hamartoma

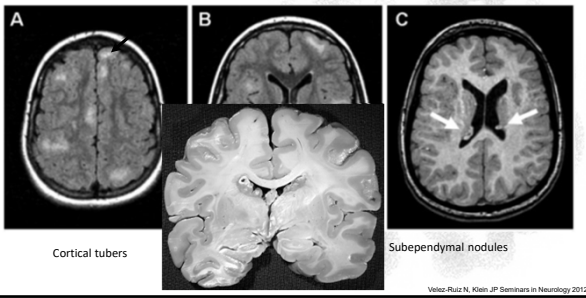


Encephalocele



Cendes F, et al. Handb Clin Neurol. 2016

Tuberous sclerosis complex



Velez-Ruiz N, Klein JP Seminars in Neurology 2012

Tuberous sclerosis complex

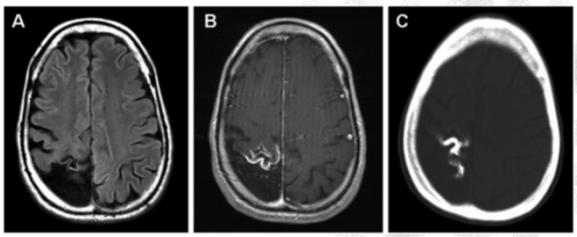
- Multisystem, autosomal dominant disorder. Seizures in 75%.
- Genes: TSC1 (Hamartin, 9q32-34) or TSC2(Tuberin, 16p13.3). TSC2 accounts for most cases. CNS imaging findings :
  - Cortical tubers (high T2 signal, low T1 signal, rarely enhancing)
  - Subependymal nodules/hamartomas (>80% with calcifications in older patients)
  - Subependymal giant cell astrocytomas (SEGAs) **enhance** with contrast
  - Growth on serial imaging is most reliable feature to distinguish SEGAs from subependymal nodules

Sturge-Weber syndrome

- Sporadic, congenital with characteristic port wine stain manifestation, unilateral
- Choroidal or sclerala angiomas, Glaucoma
- Developmental delays in 50%
- CT shows calcification of pial vessels with "tram track" appearance and atrophy
- MRI shows Prominent hemispheric or posterior quadrant leptomenigeal enhancement (pial angiomatosis)

sturge-weber.org

Sturge-Weber syndrome



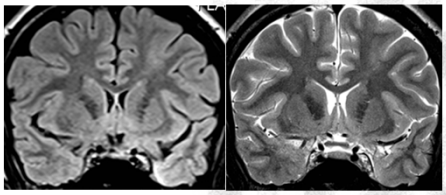
pial angiomatosis

Valaz-Ruiz N, Klein JP Seminars in Neurology 2012

MRI-negative Focal Epilepsy

- 16– 43% of patients referred for presurgical assessment have no identifiable lesion using conventional 1.5 or 3T
- Absence of a structural lesion on MRI still represents a challenge for surgical management: where to start?
- Non-visualized lesions for focal epilepsy are associated with poorer prognosis in both children and adults.

Case 1: "MRI-Negative on 3T"

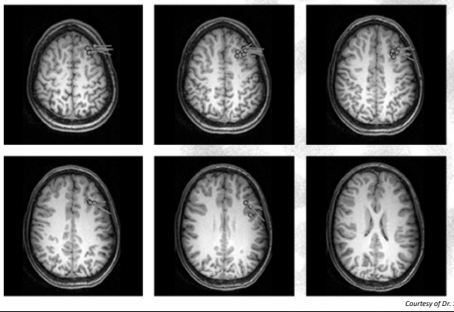


FLAIR **T2**

12 Channel 3T

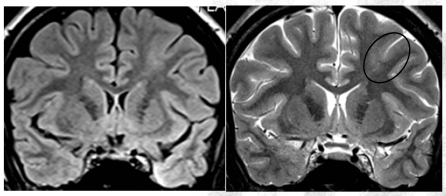
Courtesy of Dr. Steve Stufflebeam, MGH

Case 1: MEG results (ECD)



Courtesy of Dr. Steve Stufflebeam, MGH

Case 1: "MRI-Negative on 3T"

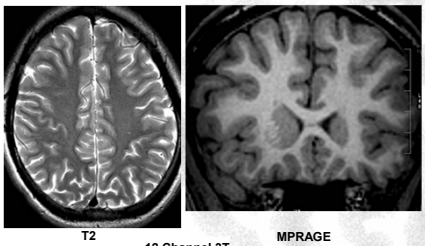


FLAIR **T2**

12 Channel 3T

Courtesy of Dr. Steve Stufflebeam, MGH

Case 2: another "3T MR Negative"

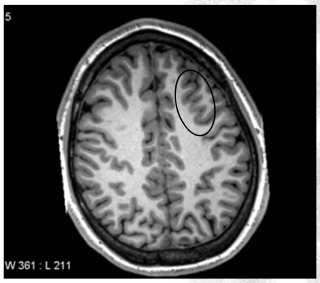


T2 MPRAGE

12 Channel 3T

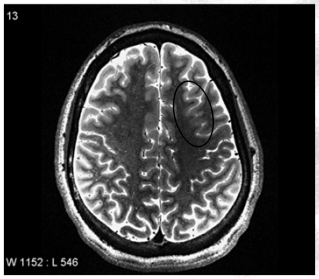
Courtesy of Dr. Steve Stufflebeam, MGH

Case 2: another "3T MR Negative"



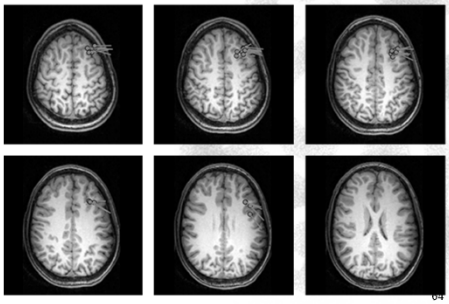
1mm isotropic MPRAGE 32 Channel 3T

Case 2: another "3T MR Negative"



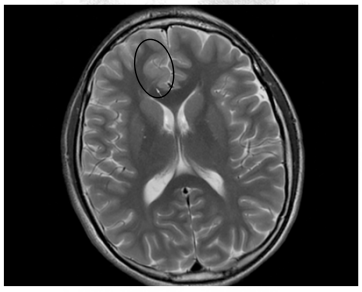
32 channel 7T
FSE T2

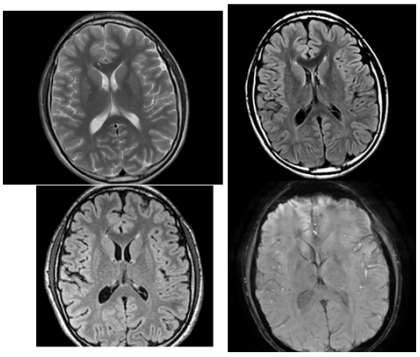
Case 2: MEG results (ECD)



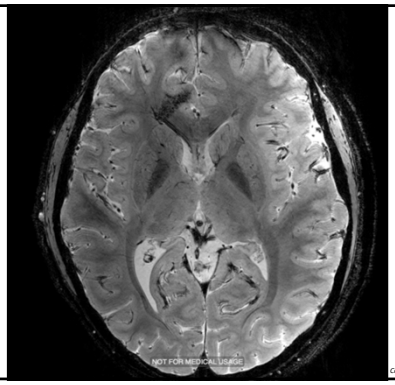
Case 3: 20 year-old male with focal seizures since age 7

- T2-hyperintensity Right Cingulate
- Curvilinear from cortex to frontal horn of right ventricle
- Possible thickening of cingulate cortex
- Possible FCD, however not consistent with clinical left hemispheric onset





32 channel 7T

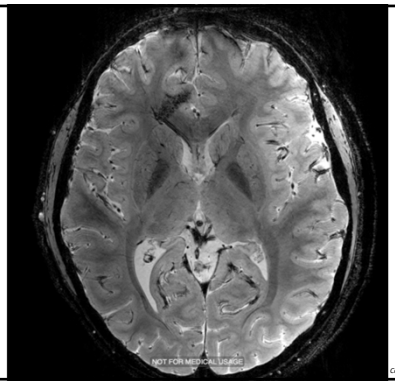


Courtesy of Dr. Steven Stufflebeam, MGH

32 channel 7T

Courtesy of Dr. Steven Stufflebeam, MGH

32 channel 7T

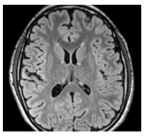


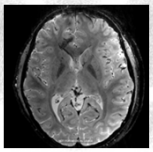
Courtesy of Dr. Steven Stufflebeam, MGH

Capillary Telangectasia

- One of the common benign vascular abnormalities
- Can be epileptogenic, but it is usually not the lesion you are looking for.
- On the spectrum of epileptogenicity

AVM> Cavernous angiomas> Capillary telangiectasia> Venous angiomas



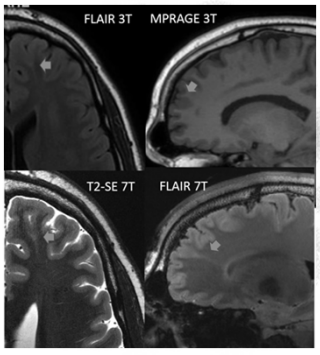


The Added Value of High-Field 7T MRI

- 7T detects new lesions in up to 1/3 of "non-lesional" patients on 3T, affecting the evaluation and treatment plans.
- It also contributes to surgical decision-making in patients by further characterizing suspected or poorly characterized lesions detected on 3T
- In ~30% of non-lesional cases, 7T detected a new structural abnormality concordant with the hypothesized SOZ
- The added value of 7T in detecting structural lesions was achieved using GRE and FLAIR, and high resolution MPRAGE (multi-echo)
- Most lesions detected by 7T were FCD, those missed by 7T were gliosis in subsequent pathology.

De Ciantis et al. Epilepsia 2016
Gholipour et al. submitted.

7T examples



The role of imaging in surgical planning and outcomes

Factors Associated With a Significantly Higher Seizure-Free Outcome Rate

- Positive Association With Seizure Outcome
  - Seizure without loss of consciousness
  - **Complete or extensive resection of lesion**
  - Prolonged febrile seizures
  - Long duration of being seizure-free postoperatively
- No Association With Seizure Outcome
  - Sex
  - Age
  - Side of resection
- Negative Association With Seizure Outcome
  - **Nonlesional epilepsy**
  - **Normal MRI**
  - Preoperative generalized tonic-clonic seizures
  - Intracranial electroencephalographic monitoring
  - Infantile spasms or tonic seizures
- Inconsistent Association With Seizure Outcome
  - Duration of epilepsy
  - Temporal vs extratemporal location
  - Pathology

Jobst, BC and Cascino GD, JAMA. 2015

Evidence on Use of Neuroimaging for Surgical Treatment of Temporal Lobe Epilepsy

Table 1. MRI Findings and Surgical Outcomes in Temporal Lobe Epilepsy

Source	No. of Patients	Imaging Findings	Surgical Outcome
Radhakrishnan et al,[7] 1998	175	Unilateral MRI-identified hippocampal atrophy	MRI findings associated with a favorable outcome ($P = .02$)
Lin et al,[12] 2005	40	MRI volumetric studies for hippocampal atrophy	The "not seizure-free" group had smaller bilateral mean hippocampal volumes and greater ipsilateral atrophy
Roberti et al,[29] 2007	42	MRI-identified hippocampal abnormality	MRI abnormality predictive of excellent surgical outcome ($P < .01$)
Wiesmann et al,[30] 2008	76	MRI-identified hippocampal atrophy	MRI-identified hippocampal atrophy was predictive of favorable surgical outcome ($P = .01$)
Stefan et al,[17] 2009	64	MTS may not reflect severity of MTS or different subtypes	MTS type IB had best operative outcome
Bell et al,[14] 2009	40	All MRIs nonlesional; 11 patients had subtle MRI abnormalities: atrophy without signal change, amygdala enlargement, FLAIR-increased intensity without atrophy	24 Patients (60% of all) were rendered seizure free; patients with subtle medial temporal lobe MRI abnormalities had an improved operative outcome ($P = .03$)
Hajek et al,[28] 2009	35	Concordant MRI and MRS in 25 patients; nonlateralizing MRI and MRS in 6 patients; 4 patients with indeterminate MRI had unilateral MRS findings that correctly lateralized the temporal lobe	MRS may be useful to localize the temporal lobe of seizure origin in the presence of indeterminate or bilateral MRI abnormalities
Schijns et al,[26] 2011	116	MTS alone in 58 patients; MTS plus gray-white matter abnormalities in 58 patients	51 Patients (87.9%) in both groups had a favorable operative outcome; no difference between the 2 MRI groups
Vale et al,[31] 2012	86	All patients had nonlesional MRI studies	47 Patients (55%) had excellent operative outcomes (Engel class I)[a]
Kaubeih et al,[4] 2012	25	MRI-identified MTS in 6 patients, unremarkable in 5 patients, and findings other than MTS in 14 patients	No difference in operative outcome based on MRI findings
Lau et al,[32] 2014	241	MRI assessment of hippocampal pathology	Surgery is less effective in patients with unremarkable MRI vs those with MTS
Miserocchi et al,[21] 2013	68	MRI-identified focal lesion in 44 patients, dual pathology in 13 patients, MTS alone in 8 patients, and extratemporal lesion in 3 patients	Patients with temporal lobe focal lesion or MTS alone had a favorable operative outcome; extratemporal lesions had poorer outcome after temporal lobe surgery
Elsharkawy et al,[18] 2009	434	MRI suggestive of hippocampal atrophy was associated with better outcome ($P = .02$)	MRI showing hippocampal atrophy associated with better surgical outcome

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTS, mesial temporal sclerosis; MTS type IB, pathologically defined severe hippocampal sclerosis.
[a] The Engel classification system is presented in the Findings section.

Jones AL and Cascino GD; JAMA Neurol. 2016

Imaging Safety: CT

- VNS, RNS, pacemakers are all safe
- All Intracranial electrodes are safe for CT, thin sliced and attenuated sequences help with reconstruction
- Pregnancy and Children:
- CT should be reserved for urgent cases or when irreplaceable and necessary by MRI for pregnant women and children
- Teratogenicity risk lower after 1st semester
- decreased by shielding uterus/gonads during Head CTs
- typical radiation doses are well below threshold of "significant risk"
- Contrast agents are contraindicated during pregnancy

Imaging Safety: MRI

- VNS must be turned off prior to structural and function MR scanning (re-interrogated after turning on)
- Ventricular shunts should be adjusted after MRI scan
- Braces and dental works, tattoos on head are safe but cause artifact or heating
- MRI is currently considered unsafe for RNS. some cardiac pacemakers and aneurysm clips are safe, check with radiology techs
- Most platinum-iridium Intracranial electrodes are safe for MRI, will causes some artifact. Negotiate with radiology
- Gadolinium not useful for most established epilepsy cases, comes with minimal risk and scanner time: avoid ordering without thinking.

CME code

Functional Neuroimaging (PET, SPECT, fMRI)

William D. Gaillard, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

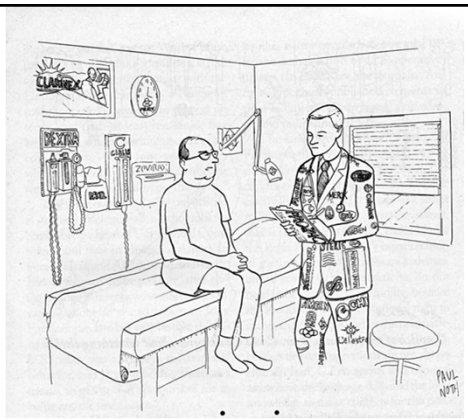
FUNCTIONAL IMAGING PATIENTS WITH EPILEPSY

William Davis Gaillard, MD
Division Chief, Epilepsy, Neurophysiology, & Critical Care Neurology
Director, Comprehensive Pediatric Epilepsy Program
Associate Director, Center for Neuroscience Research
Children's National Health System

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - Supported by Federal Grants R01 NS44280 NINDS, RO1 MH65395 NIMH, P30HD40677 NICHD, U54 MH066417 & Clinical Epilepsy Section NINDS, NIH.
  - Co-Investigator (Not PI, no salary support) - several Pharmaceutical Industry supported AED clinical trials: Rectal Diazepam, Oxcarbazine, Lamotrigine, Zonisimide, Vigabatrin, Tiagabine, Gabapentin, Clobazam, Rufinimide.
  - Advisory Board - GE and laundered funds Ovation and Questor
- Off-Label Usage
  - PET ligands used on a research basis under FDA IND



New Yorker

Question 1

- The single most helpful test for evaluating the cause of epilepsy and for identifying the epilepsy focus is:
- 1. FDG-PET
- 2. functional MRI
- 3. High resolution structural MRI
- 4. Low radiation CT
- 5. HMPAO ictal SPECT
- 6. MEG source imaging

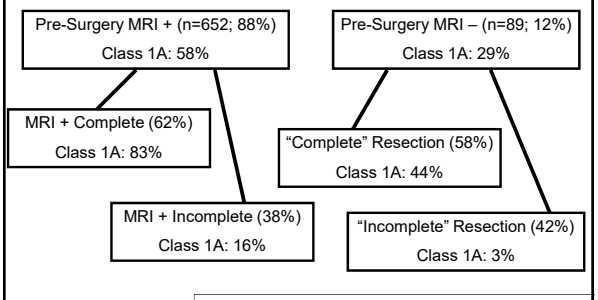
Epilepsy & Functional Imaging

- Direct treatment of Surgical Planning
- Confirmation of focus (critical for epilepsy surgery)
- Identify areas to be spared during epilepsy surgery (cortical and white matter)

Imaging

- PET
- SPECT
- Functional MRI for brain mapping
- DTI for white matter tract identification

Class 1A Seizure Outcome
2004 ILAE Pediatric Outcome Survey



*PET/SPECT/MEG+ 40-60% EI; Image - <20%

Courtesy G Mathern

Question 2

- Which ligand is most common clinically used for PET
- 1. Cyclofoxy
- 2. Flumazanil
- 3. FDG
- 4. O-15 Water

PET Methods

- Radio tracers tagged to compounds designed to target a physiologic process
  - Blood flow, metabolism, neurotransmitter precursor, receptor binding (agonist/antagonist)
- Information gained limited by tracer half life
  - ^{18}F 90 minutes FDG PET Decrease
  - ^{11}C 20 minutes Flumazenil Decrease
  - ά Methyl Trypotphan Increase
- Requires image acquisition shortly after injection

PET (& SPECT) Methods

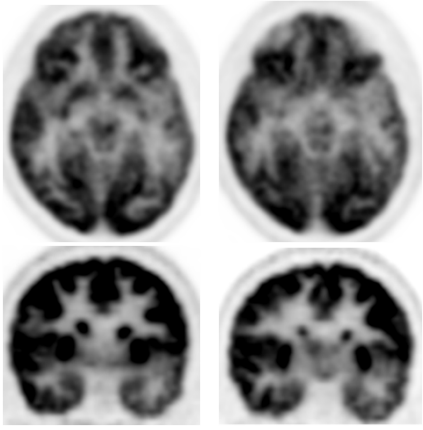
- PET patient studies require EEG
  - Ictal vs. interictal
- Analysis
  - Visual
  - Region of interest (superior to visual analysis adult data, Theodore et al. Ann Neurol 1992) with laterality index
  - Voxel based (e.g. SPM) (beyond 2-3SD mean signal voxle based on Normal ("normal") data

Imaging: FDG-PET

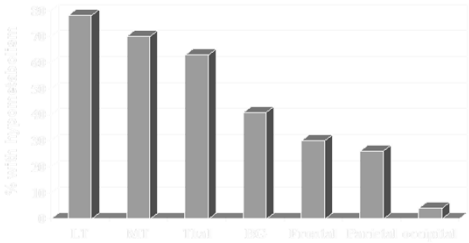
- Measure of metabolic rate: Glucose uptake and consumption
- Ictal FDG-PET uncommon and unreliable
- Interictal: Regional hypometabolism 90% adults with temporal lobe epilepsy (most childhood onset)
- Regional hypometabolism more widespread than epileptogenic zone
- Regional hypometabolism: Good surgical outcome adults with childhood onset epilepsy (class 2)
- Reduces need for invasive (less extensive) recording
- FDG-PET less helpful in neocortical epilepsy (50-60%)

FDG-PET

- Correctly lateralize focus in 60% children with intractable partial epilepsy (including those with normal MRI)
- May be helpful in young, < 2 years, when MRI less sensitive to identifying dysplasia (Class 4)
- Evaluate integrity good hemisphere when considering hemispherectomy (Class 4)

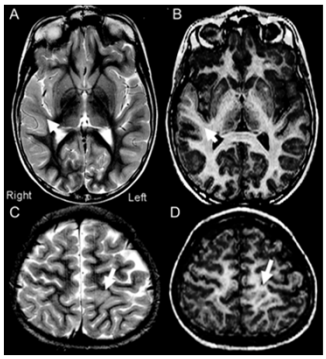


Hypometabolism in TLE



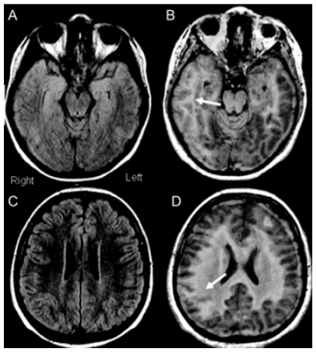
Henry et al, 1993

^{18}FDG-PET Co-Registered with T1 MRI
Type 1 FCD: The second look effect



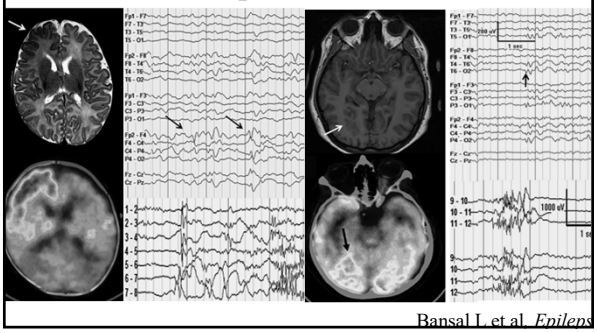
Salamon N, et al *Neurology* 2008

Multilobar FCD I and Normal MRI



Salamon N, et al *Neurology* 2008

PET Hypermetabolism & FCD
2-6% pediatric series



Bansal L et al. *Epileps*

PET: Other Ligands

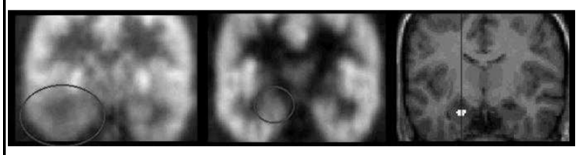
- ^{11}C Flumazenil: Not helpful
  - Benzodiazepine/GABA receptor antagonist
- ^{11}C α- Methyl Tryptophan: For TS
  - Precursor to amino acid transmitters
- ^{18}FC WAY: Experimental
  - $5HT_{1A}$ Antagonist
- ^{11}C-PBR28 PET: Experimental
  - Peripheral Benzodiazepine Receptor Ligand

^{11}C Flumazenil

- Benzodiazepine receptor antagonist, modulating $GABA_A$ receptor ionophore complex most common inhibitory neurotransmitter
- Disordered inhibitory systems implicated in neuronal hyper-excitability
- Anticipated to help identify focus and patho-physiology in human epilepsy
- Does not meet expectations; Limited utility

^{11}C Flumazenil

- More restricted regional abnormalities than FDG
- Rarely abnormal when FDG-Normal
- Lesional studies: abnormalities at margin of lesion
- Correspondence with subdural recordings
- Non-lesional/cortical dysplasia mixed results

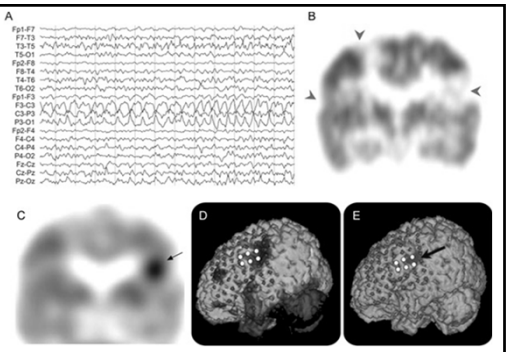


Decreased FDG Decreased FMZ SPM of FMZ

^{11}C α- Methyl Tryptophan

- Precursor to Serotonin synthesis
- Likely precursor to quinolinic and kynurenic acid – implicated as excitatory compounds
- Increased in epileptogenic Tubers TS
- Increased in focal cortical dysplasia
- Increased in non lesional epilepsy, dysplasia, especially young (sensitivity 50%)
- Increase in surgical margins in surgical failures

TS



FDG tubers "Cold", AMT epileptogenic tuber "Hot"
Helpful in one third children with TS (n=191)
Chugani HT et al, *Neurology* 2013

SPECT

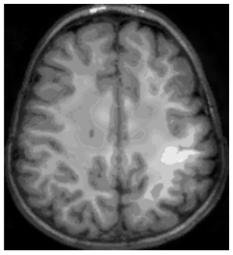
- HMPAO, ECD (99-Technetium)
- Markers of CBF
- Long half life (6 hours)
- Can scan several hours after injection
- Can not quantify
- Always perform with EEG
- Timing of injection in relation to seizure critical

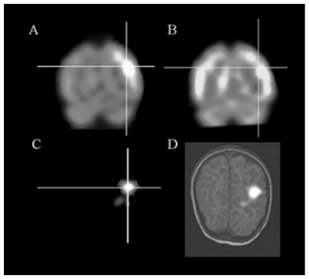
SPECT

- Interictal, SuSPECT: False lateralizing 10%
- Ictal Superior
- Subtraction Inter-Ictal from Ictal (or SPM)
  - Co-registration with structural MRI
  - Increases inter and intra rater agreement from 70 to 85% & localization value 31-74% to 74-93%
  - 80-90% when lesion present (Class 3 adults)
  - 59-76% non lesional (Class 4)
- Reliability depends on timing/delay injection in relation to seizure onset (later injection increases false localization/lateralization)
- Propagation effects

O'Brien et al, 98, 99; Vera et al, 99

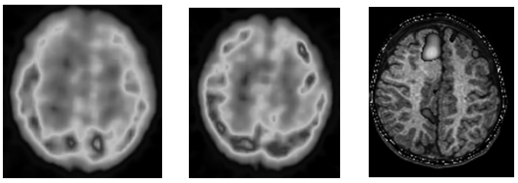
Ictal SPECT
Co-registered with MRI





Courtesy P Jayakar MCH

Courtesy G Cascino. In Wyllie E Principles and Practice of Epilepsy

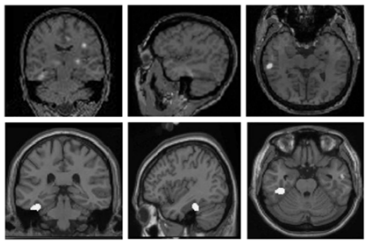


interictal **ictal** **« SISCOM »**

Courtesy C Chiron

SISCOM
κ=0.36
66% all
24% TLE subtype
47% normal MRI

STATISCOM
κ=0.81
84% all
68% TLE subtype
80% normal MRI
Outcomes better



Statistical Ictal SPECT Voxel-Wise Statistical Threshold Difference
N=87; controls =11

Kazemi et al *Neurology* 2009

N=160; 77 iEEG; 72 Seizures; 62 resection; 38 (61%) Engle I
MRI negative (43%), unclear, small FCD NB 1.5T MRI

n		MEG	PET	iSPECT
62	Sensitivity	55		
	Specificity	75		
51	Sensitivity	56	59	
	Specificity	79	79	
34	Sensitivity	38		50
	Specificity	72		72
27	Sensitivity	31	54	62
	Specificity	79	86	86

Knowlton R et al, *Ann Neurol*, 2008

Question 3

- Under what conditions is SPECT (ECD or HMPAO) most reliable
- 1. Inter-Ictal
- 2. Peri-ictal
- 3. Icta-ictal
- 4. Post- ictal

Summary

- Lesional (MRI) studies: PET and SPECT add little
  - Unless wish to localize within large lesion
- FDG-PET: Non-lesional MRI helpful 30-60% (>TLE)
- AMT-PET: Occult dysplasia, TS, young, post-op failure (Increased uptake)
- Ictal (subtraction) SPECT when PET negative or unavailable
- Discordant Results ⇨ Invasive monitoring
- Negative imaging: think genetic or inflammatory causes

Functional MRI (fMRI)

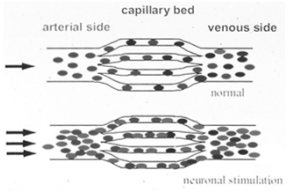
- Identify Epileptogenic Cortex
  - Interictal
  - Ictal
- Identify what to spare during epilepsy surgery
  - Motor
  - Sensory
  - Language
  - Memory

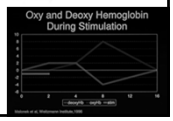
Blood Oxygen Level Dependent signal

↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

BASAL STATE
Normal CBF
Basal level [Hbr]
Basal CBV
Normal MRI signal

ACTIVATED STATE
Increased CBF
Decreased Hbr
Increased CBV
Increased MRI signal





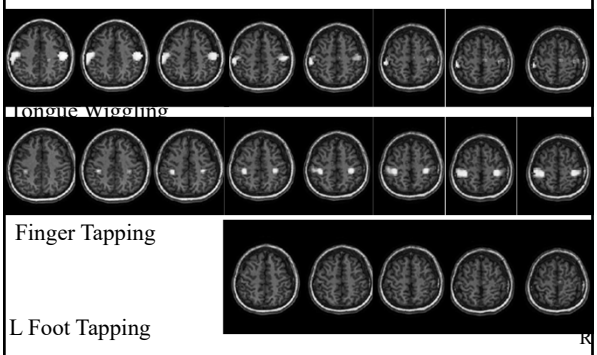
Source: fMRIB Brief Introduction to fMRI

Motor & Sensory Mapping

- Extra-temporal lobe epilepsy
- Lesion (Tumor/AVM)
- Identification of Motor/Sensory strip
- Agreement with Evoked potential & electro-cortical stimulation (<5 mm)

MOTOR	SENSORY
Finger Tapping	Visual Flash (primary visual)
Tongue Wiggling	Tones (primary auditory)
Foot Tapping	Brush (Sensory strip)
	Face, Hand, Foot

Motor Mapping

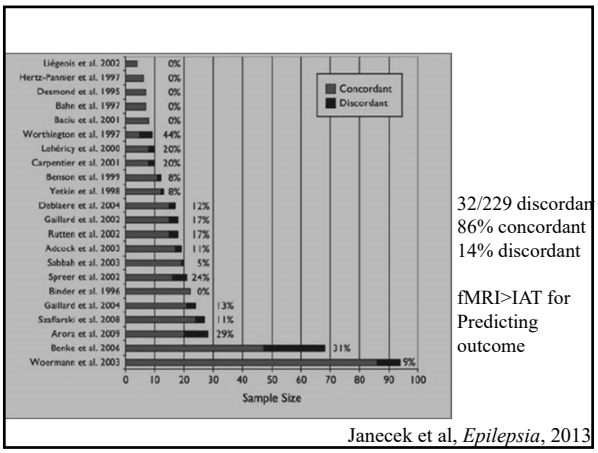


Language Mapping

- 30% patients atypical language (75% acquired L handedness)
  - vs 5% R handed controls and 22% L handed controls
- Selection of Tasks
- Determination of Language Dominance
- Location of Language Function
- Multiple Tasks
- Individual Analysis
- Correlation with Electro-cortical stimulation
- Correlation with Wada
- Resection fMRI negative safe
- Resection fMRI positive some peril

fMRI & Language Lateralization

- Agreement with Wada
  - Over 20 studies, more than 400 patients
  - 85-90% complete agreement
  - 10-15% partial disparity
  - Rare absolute discordance (1%)
- Excellent but not complete agreement with electro-cortical stimulation (localization)
- Predicts post operative language capacity
- fMRI better predictor of outcome than IAT



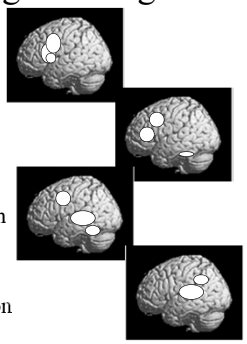
32/229 discordan
86% concordant
14% discordant

fMRI>IAT for Predicting outcome

Janecek et al, *Epilepsia*, 2013

fMRI Language Paradigms

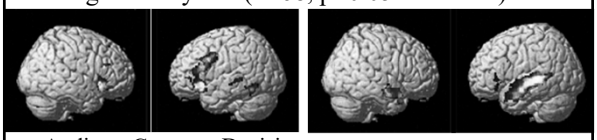
- Verbal Fluency
  - (semantic/ phonologic)
- Semantic Decision
  - (visual/auditory)
- Reading Comprehension
  - (whole language)
- Auditory Comprehension
  - (whole language)



Binder *Neurology* 1996; Benson, *Neurology* 1999; Lehericy *Neurology* 2000; Gaillard *Neurolgy* 2002

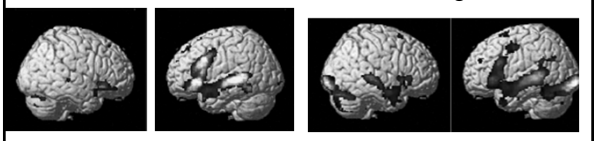
fMRI Language Group Maps for Children

Ages 4-12 years (n=68, p<0.05 corrected)



Auditory Category Decision

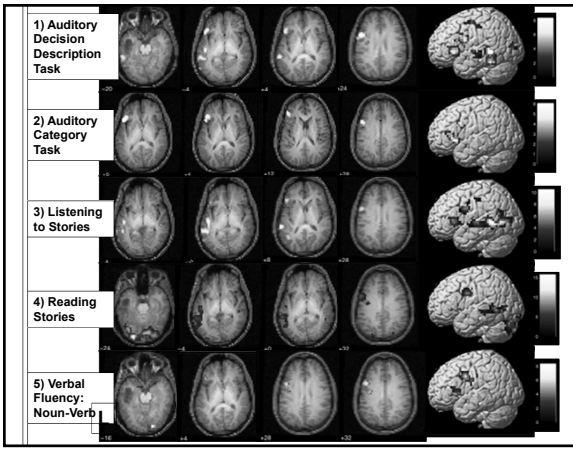
Listening to Stories



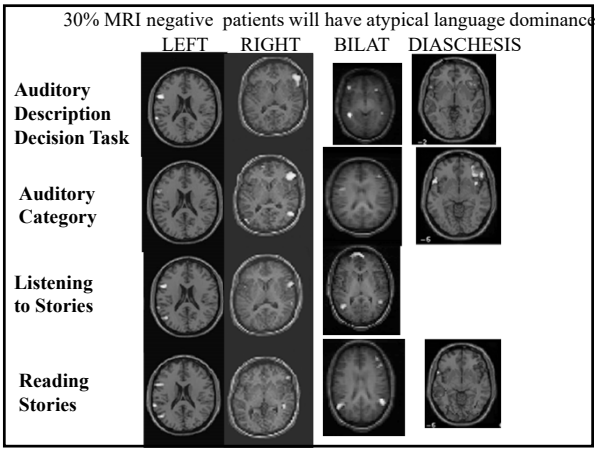
Auditory Description Decision Task

Reading Stories

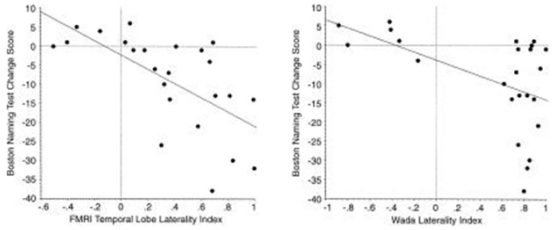
(6-12, n=48)



30% MRI negative patients will have atypical language dominance



fMRI Semantic Decision Task Predicts Post-Op Naming



fMRI AI

Wada LI

AI > 0.4 risk of language measure decline

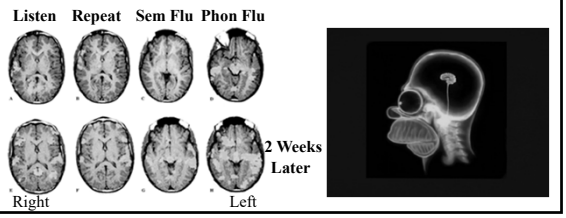
Sabsevitz DS, et al. *Neurology* 2003

fMRI Language

- Activated Areas Involved, **NOT** Critical
- Critical Areas **NOT** always Activated
  - Blood flow response trigger threshold
  - Individual vs. Group analysis
  - Data analysis threshold
- False Lateralization: Homologous non-dominant activation misinterpreted
- Null activation interpreted as no function

Failed fMRI

- Disruption BOLD Signal
  - Glioma, Edema & Mass Effect (Bookheimer et al, 1997)
  - AVM and Vascular Steal (Lehericy et al, 2002)
  - Post-Ictal state (Jayakar et al, 2002)
  - Arterial Stenosis (Rother et al, 2002)

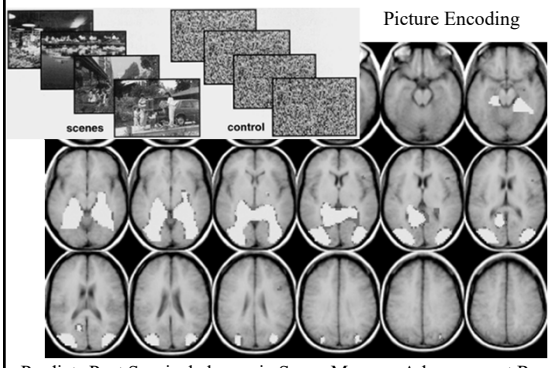


Memory Paradigms: Material Specificity

• Verbal encoding	L>R Activation
• Scene decision or encoding	L=R Activation
• Mental navigation (Roland)	L=R Activation
• Face recognition	R≥L Activation
• Pattern encoding	R>L Activation

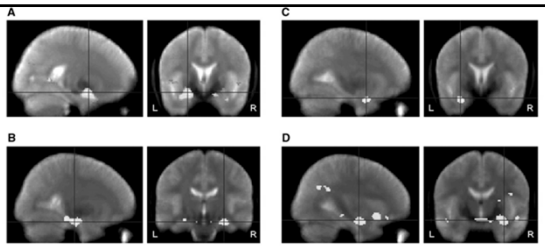
- HF and parahippocampal activation
- Functional Adequacy > Functional Reserve

- Activation linked to performance
- Has not predicted risk of amnesia



Predicts Post Surgical change in Scene Memory Adequacy not Reserve

Rabin et al *Brain* 2004

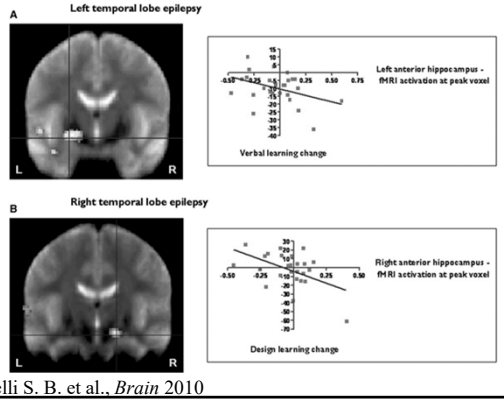


Event related, forced encoding, design
- Verbal encoding
- Face encoding

10 controls; 72 patients (40 left; 68 MTS); 54 resection (29 left)
*Simple Line Picture Encoding little effect

Bonelli S. B. et al., *Brain* 2010

Group Map: HF signal and change in verbal & visual memory

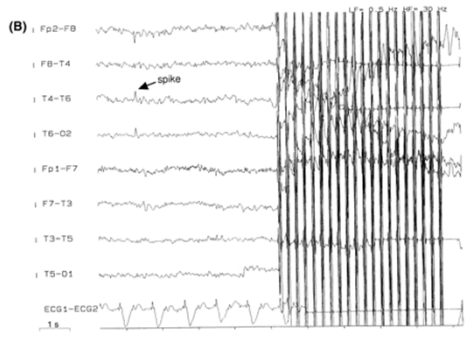


Bonelli S. B. et al., *Brain* 2010

Interictal fMRI

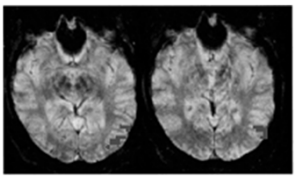
- Event related
  - On line EEG manual fMRI trigger
  - Post hoc analysis with continuous EEG
  - Older literature 50 events (only for patients with frequent spikes)
  - More recent can obtain data from few spikes; may augment by manipulating HDR function to optimize signal
  - ~67 % of patients reliable data
  - Spike or slow wave may be mapped
- Relation to focus uncertain, as in MEG, but good concordance with invasive mapping

EEG Spike Event Related fMRI



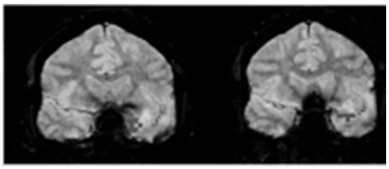
Krakow et al. *Brain* 2000

EEG Spike Event Related fMRI



Neocortical focus

Mesial Temporal Focus



Krakow et al. *Brain* 2000

Question 4

- Functional imaging may be used for all of the following except:
- 1. Identifying eloquent cortex
- 2. Source localization
- 3. Identifying co-morbidities
- 4. Predicting outcomes

Functional MRI: Practical Applications for Epilepsy

- Reliable for language lateralization
  - More tasks the beter/ select task to target area of interest
- Agreement w/ invasive methods
- Predicts surgical outcome language and memory
  Guide for motor, sensory, language localization
- Reliable for Hippocampal memory (Untested for predicting amnesia)
- Interictal localization reliable for selected patients
- Ictal localization rare

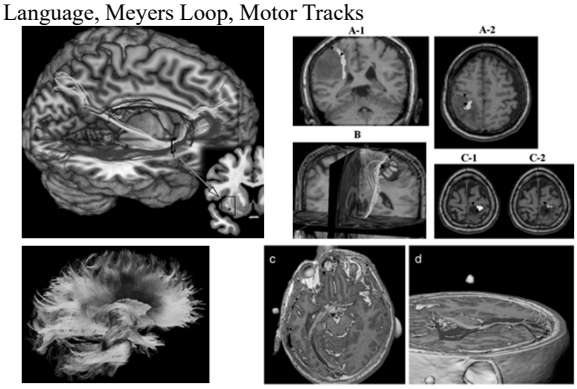
Functional MRI: Practical Applications in Epilepsy

- Conditions where BOLD disrupted and data falsely lateralizing
- No activation is NON Diagnostic
- Repeat Atypical or Null activation studies: confirm with Wada/Electro-cortical stimulation

Diffusion Tensor Imaging

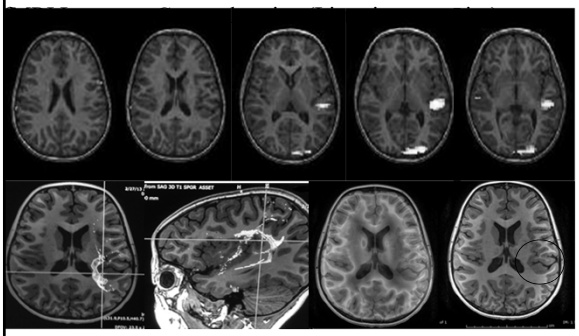
- Diffusability: distance molecule of water will move
- Fractional Aniosotropy: directionality of water molecule movement)
  - to identify long white matter tracts that underlie cortical function
- Seeds
  - fMRI activation
  - Anatomy regions (usually 2)
  - White matter tract strings
- Motor/Sensory, Language, Visual (Meyer's loop)
- Avoid critical white matter tracts to avoid deficits

DTI Tractography: White Matter, Anatomic, Functional Seed Language, Meyers Loop, Motor Tracks



Shinoura, *J Clin Neurosci* 2009; Axer, *Brain & Lang* 2012, Chen, *NeuroImage* 2009

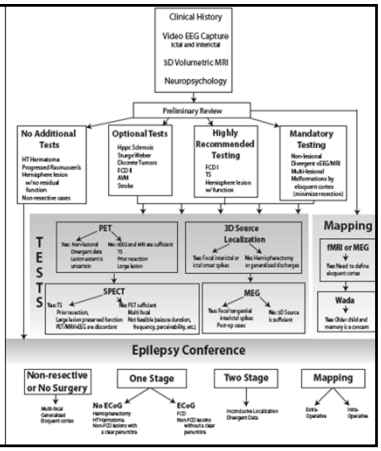
Multi-Modal Imaging



DTI Tractography Arcuate Fasciculus FDG-PET MRI

Epilepsy Surgery Evaluation Protocol

ILAE



Jayakar P. *Epilepsia* 2014

Conclusions: Functional Imaging

- PET (interictal) and SPECT (ictal subtraction) to identify the seizure focus when MRI normal; comparable in utility
- fMRI to identify eloquent cortical areas to spare during epilepsy surgery
- fMRI may be used for source localization
- DTI to identify deep white matter tracts to minimize neurological deficits

Question 5

- A good rule to follow when removing epileptic tissue in normal appearing brain from your hospital CEO family member when electrocaudery is broken, massive bleeding is occurring, & the blood pressure is dropping is
- 1. Always Panic
- 2. Never Panic
- 3. Panic only when safe to do so

MEG and Magnetic Source Localization

Taha Gholipour, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

MEG AND SOURCE LOCALIZATION

Taha Gholipour, MD
Assistant Professor of Neurology
The George Washington University Epilepsy Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Outlines

- Recording data and the Models
- Evoked potentials and Language mapping
- Epileptic focus localization and value in epilepsy surgery

Clinical use for MEG

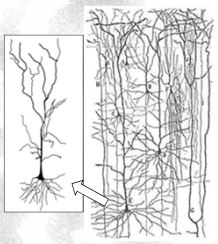
- Epileptogenic zone localization
  - Guide grids or depth placement
- Sensory or motor mapping
- Language lateralization

Outlines

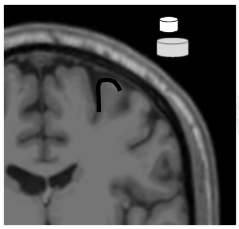
- Recording data and the Models
- Evoked potentials and Language mapping
- Epileptic focus localization and value in epilepsy surgery

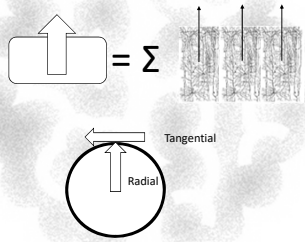
Refresher: source of EEG and MEG signal

- Pyramidal neurons are the most prominent neurons in the cerebral cortex.
- Pyramidal cells are shaped as paralle long tubes aligned perpendicular to the cortical surface
  - **Extracellular** synaptic currents produce the EEG
  - **Intracellular** current flow produces the MEG
- These current flows **summate** and become significant because they are in parallel



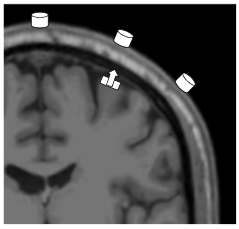
The orientation of the cortical surface orientation changes

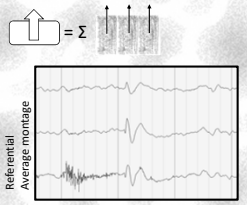




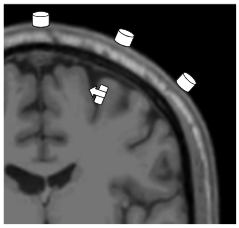
..So does the current dipole

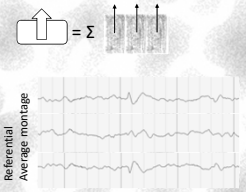
Scalp EEG view of cortical sources



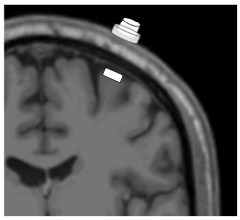


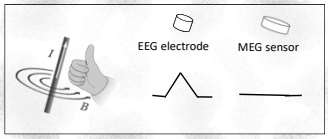
Scalp EEG view of cortical sources



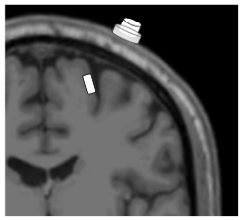


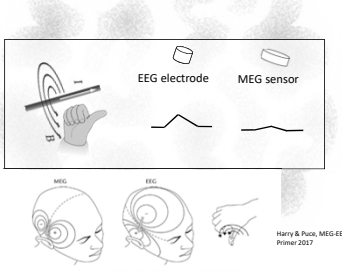
Electricity and Magnetism



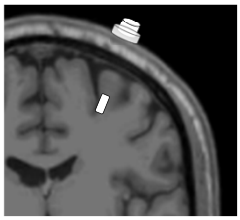


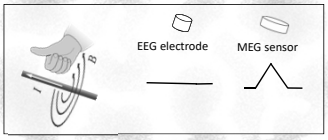
Electricity and Magnetism



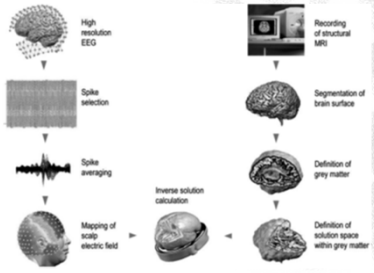


Electricity and Magnetism



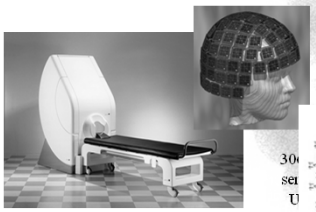


EEG records small electric fields from neural activity (+noise)

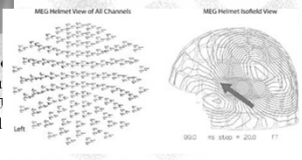


Brodbeck et al., 2011;

MEG records small magnetic fields from neural activity (+noise)



306-channel
sensor array helmet
+ EEG Electrodes

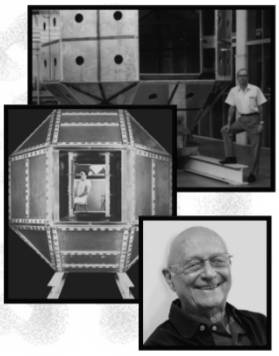


MEG and EEG, lets (not) compare them

- MEG and EEG together are better than either alone, since MEG has advantages over EEG for solving source localization problem
- MEG is less likely to estimate source from radial and deep sources
- MEG signal drops off faster with distance
- Unlike EEG, MEG does not see radial dipoles
- However, MEG sources have tighter dipole fields on the surface
- Unlike EEG, scalp, skull and CSF have little effect on MEG signal

MEG evolution
David Cohen's legacy

- 1967: Cohen measured magnetic field created by cardiac muscle using simple copper coils in a field far from any magnetic noise.
- 1970: SQUID (superconducting quantum interference devices) was developed by James Zimmerman and colleagues
- 1971-2: single SQUID detector recording of MEG in the first multi-layer shield room at MIT
  - First done with the stronger cardiac signal, then brain (aka MEG)



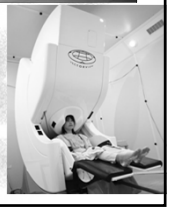
The data collection

- Brain neuromagnetic signals: 100 X 10^{-15} Teslas (100 femtotesla).
- Cooling system essential for super-conductor performance (-269◦C)
- Performed in magnetically shielded room
- Modern helmets have 102 channels (306 sensors planar and axial gradiometers, and magnetometer.

UMontreal.ca
martinos.org

MEG today

- Modern MEG shield room is like a walk in bank vault, which essentially protect from magnetic noise. Urban noise still a problem
- External (outside the helmet) and Internal magnetic interference:
  - cardiac/muscle, VNS, pacemakers, traffic, power lines
  - eyes (blinks, saccades), tongue, metal from surgery, dental work, braces



UMontreal.ca
martinos.org

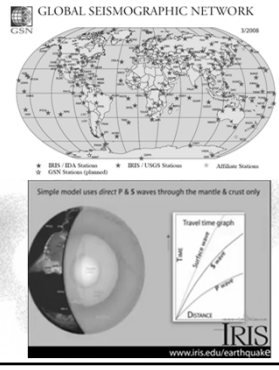
MEG acquisition process

- Test performed sitting or lying down, in resting state or with ability to present stimuli. Perfectly quit!
- Somatosensory, motor, language tasks can be performed
- Multiple short runs (4-5 min) to perform analysis
- Concurrent high-density EEG recorded for correlation with known features
- MRI after the EEG can help with brain model building for some analysis

Baby MEG, Boston Children's Hospital childrenshospital.org

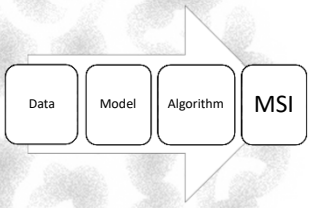
Source localization: Earthquake example

- Many sensors (seismometers) around the surface of the globe
- Data are recorded with location coordinates and throughout a spectrum of frequencies
- Information about Earth crust, continents and oceans (the model)
- Noise (non-seismic shaking)



MEG/EEG Source Localization

- Goal: estimate the location of a dipole-generating spontaneous or evoked activity
- Data: surface measurements and location co-registration
- Model: sphere or simplified head
- Algorithm: iterative search among theoretical dipoles
- **Magnetic Source Imaging (estimation): *Best* dipole to explain data**

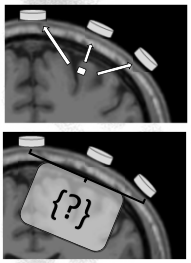


The inverse problem

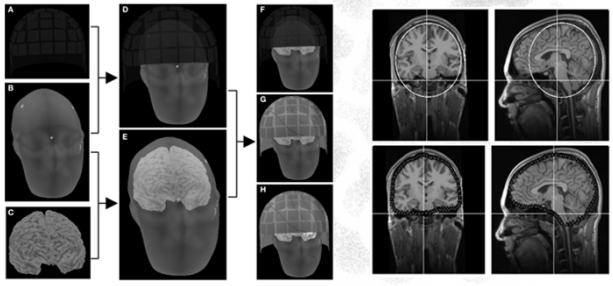
- Forward problem: what is the expected measurements on the surface for a known cortical source? There is a unique answer.
- Inverse problem: what is the cortical source of a set of neuromagnetic measurements? It does not have a Unique answer: there are infinite number of possible solutions
- The problem is "ill-posed"

But:

- ***best*** solutions compatible with the data can be identified under ***constraints*** imposed by electrophysiology, cortical anatomy, and prior assumptions about the generators
- These assumptions are encapsulated in a "*head model*"

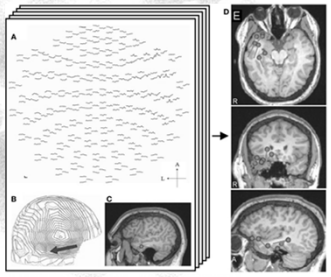


Source localization: location and model



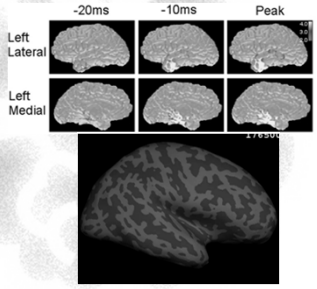
Estimated current dipole (ECD)

- ECD is the traditional method for solving for the inverse problem
- Finds the best estimate that explains the recorded signal
- When there is a tight and uniform cluster of dipoles, the localization is robust and reliable
- Limitation: the best estimate never explains 100% of the measured magnetic field
- Inaccurate when there is a distributed source
- Also, it does not give a good estimate of the time course and propagation of source

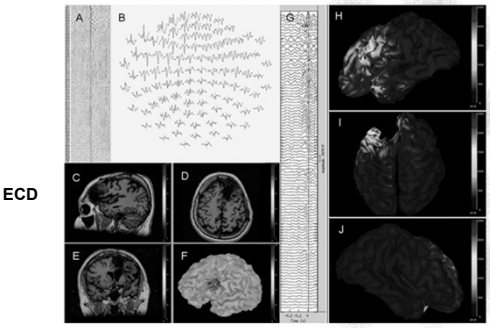


Distributed Source Models (DSM or dSPM)

- Also known by its resulting distributed Statistical Probability map (dSPM "MEG movies)
- DSM uses cortical models and a slightly different approach to normalize the noise
- Can provide an idea of moving sources
- Requires heavy processing and building an inflated cortical model
- Remains valid with post-resection brain models



Tanaka and Stufflebeam, Front. Hum. Neurosci., 2014

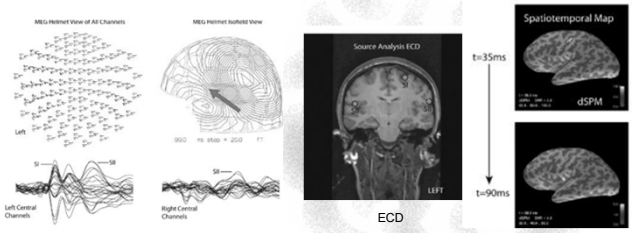


Anderson, et al. Curr Neurol Neurosci Rep., 2014

Outlines

- Recording data and the Models
- Evoked potentials and Language mapping
- Epileptic focus localization and value in epilepsy surgery

Somatosensory evoked potentials

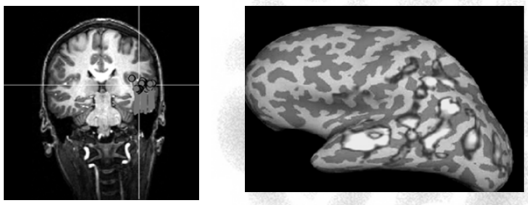


Median nerve electrical stimulation

Language mapping with MEG

- MEG can be used to determine language laterality
- Offers a less specific localization than fMRI, but robust laterality
- Visual language tasks (e.g abstract vs concrete words) can be projected
- Evoked responses are between 150ms-600ms
- For ECD approach: counting ECD dipoles for the evoked responses on left and right to calculate laterality index
- For distributed approach: dSPM map peak activation area calculated and results laterality index and visual map of the language network similar to fMRI.

MEG language mapping examples (abstract vs concrete word task)



ECD dSPM

Courtesy of Steven Stufflebeam, Naoro Tanaka

Outlines

- Recording data and the Models
- Evoked potentials and Language mapping
- Epileptic focus localization and Value in epilepsy surgery

Why neurologists are hesitant to use MEG?

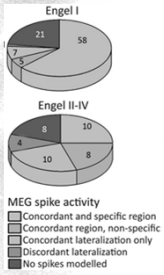
- Difficult to coordinate, not accessible
- Concern for insurance coverage (MEG has CPT codes)
- Predicting results based on EEG
- Unsatisfying experience:
  - Negative results or no additional info
  - Discordant results
  - Confusing or irrelevant reports
- So we should look at the literature..

MEG in Epilepsy literature (1)

- In a study of 455 cases undergoing surgical planning, MSI provided additional information in 35%, in 10% "crucial" information (Stefan et al. 2003).
- Other studies showed that in around one-third of cases MEG provides non-redundant information (Sutherling et al 2008)
- When compared to intracranial EEG and/or surgical outcome; there is strong localization value in MSI (Positive predictive value for MSI 82-90%, Knowlton et al. 2006) .

MEG in Epilepsy literature (2)

- Englot et al. (2015) showed that when MEG is concordant with EEG and MRI data, it can predict a favorable postoperative seizure outcome (Englot et al., 2015)
- Complete resection of IEDs clusters was associated with better seizure outcome in focal epilepsies (Jung et al, 2013, Murakami et al. 2016).



(Englot et al. Epilepsia, 2015)

MEG in Epilepsy literature (3)

- In different studies, MSI was showed to increase diagnostic yield of intracranial EEG, and help change the electrode coverage decisions (Knowlton et al, 2009) including in non-lesional epilepsy (Mohamed et al. 2020).
- MEG adds higher spatial resolution and less signal loss compared to scalp EEG. It can capture tangential dipoles so can provide benefit in those with little or no spiking (Bagic et al. 2009).

MEG in Epilepsy literature (4)

- A prospective MEG and EEG source localization study of 141 patients undergoing epilepsy surgery evaluation found that combining MEG and EEG source imaging provides clinically useful, new information
- The **combined EEG and MEG analysis** affected clinical plan 34% of the patients and 18% benefited from the changes related to EMSI data
- MEG with 306 sensors and high-density EEG (64+ electrodes) used, data analyzed separately with ECD and DSM models.
- EEG analysis using ECD had the highest concordance with intracranial electrode seizure onset localization
- MEG analysis using ECD had the highest correlation with seizure freedom

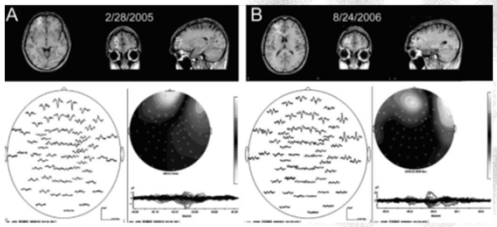
(Duez et al. Neurology 2019)

Clinical use for MEG

- Ictal recording and long(er) duration MEG have been done however clinical MEG has been limited for interictal epileptiform discharges
- MEG interpretation is more challenging for deep sources, particularly mesial temporal lobe and propagated neocortical spikes, but recent studies suggest there are analytical solutions around it (Pizzo et al. 2019).

Robust MSI shouldn't be ignored..

Case shows a right frontal ECD cluster for discharges. Intracranial recording led to R temporal resection with poor outcome, MSI cluster remains stable and proved to be seizure onset in second intracranial recording.



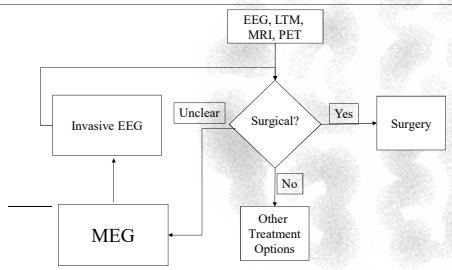
From Sutherling et al. Neurology 2008

Clinical indications for MEG per public payers

- Localizing cortical generators of interictal epileptic spikes in patients being evaluated for epilepsy surgery
- Lateralizing language dominance prior to epilepsy surgery
- Localizing somatosensory cortex prior to epilepsy surgery
- Localizing primary auditory cortex prior to epilepsy surgery

- Note that patient with no (useful) interictal discharges on EEG can have MEG spikes, with better localization.

Surgical Evaluation for Epilepsy Suggested role for MEG



Useful References

- Duez, L., Tankisi, H., Hansen, P. O., Sidenius, P., Sabers, A., Pinborg, L. H., … Beniczky, S. (2019). Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. *Neurology*, *92*(6), 257e–e586. https://doi.org/10.1212/WNL.0000000000006877
- Englot, D. J., Nagarajan, S. S., Imber, B. S., Raygor, K. P., Honma, S. M., Mizuiri, D., … Chang, E. F. (2015). Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery. *Epilepsia*, *56*(6), 949–958. https://doi.org/10.1111/epi.13002
- Jung, J., Bouet, R., Delpuech, C., Ryvlin, P., Isnard, J., Guenot, M., … Mauguière, F. (2013). The value of magnetoencephalography for seizure-onset zone localization in magnetic resonance imaging-negative partial epilepsy. *Brain : A Journal of Neurology*, *136*(Pt 10), 3176–3186. https://doi.org/10.1093/brain/awt213
- Knowlton, R. C., Elgavish, R., Howell, J., Blount, J., Burneo, J. G., Faught, E., … Kuzniecky, R. I. (2006). Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. *Annals of Neurology*, *59*(5), 835–842. https://doi.org/10.1002/ana.20857
- Knowlton, R. C., Razdan, S. N., Limdi, N., Elgavish, R. A., Killen, J., Blount, J., … Kuzniecky, R. (2009). Effect of epilepsy magnetic source imaging on intracranial electrode placement. *Annals of Neurology*, *65*(6), 716–723. https://doi.org/10.1002/ana.21660
- Murakami, H., Wang, Z. I., Marashly, A., Krishnan, B., Prayson, R. A., Kakisaka, Y., … Alexopoulos, A. V. (2016). Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. *Brain*, *139*(11), 2935–2947. https://doi.org/10.1093/brain/aww215
- Stefan, H., Hummel, C., Scheler, G., Genow, A., Druschky, K., Tilz, C., … Romstöck, J. (2003). Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. *Brain : A Journal of Neurology*, *126*(Pt 11), 2396–2405. https://doi.org/10.1093/brain/awg239
- Sutherling, W. W., Mamelak, A. N., Thyerlei, D., Maleeva, T., Minazad, Y., Philpott, L., & Lopez, N. (2008). Influence of magnetic source imaging for planning intracranial EEG in epilepsy. *Neurology*, *71*(13), 990–996. https://doi.org/10.1212/01.wnl.0000326591.29858.1a

CME code

Clinical Neuropsychology

Antonio N. Puente, PhD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

CLINICAL NEUROPSYCHOLOGY AND ITS UTILITY IN EPILEPSY

Antonio N. Puente, PhD
Assistant Professor of Psychiatry
The George Washington University

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Clinical Neuropsychology and its utility in Epilepsy

ANTONIO N. PUENTE, PHD

JULY 17, 2020

Objectives

1. Who we are?
2. What we do?
   - What is included in a neuropsychological assessment?
3. Utility in Epilepsy
   - How are they useful for pts with epilepsy?
   - What factors influence test performance in epilepsy?
   - Who is considered a "good" surgical candidate?

Who are we?

- Doctoral educated psychologists
  - ~80% PhDs
    - PsyD
- Clinical psychology
  - Brain-behavior relationships

Table 6. Comparison of sample characteristics across time

Characteristics	2005			2010			2015		
	Mean	*SD*	Min–Max	Mean	*SD*	Min–Max	Mean	*SD*	Min–Max
Age	47.2	9.5	29.0–82.0	47.4	10.5	28.0–85.0	46.2	11.6	28.0–82.0
	Frequency	%		Frequency	%		Frequency	%	
Degree	(*n* = 972)			(*n* = 1582)			(*n* = 1577)		
Ph.D.	865	89.0		1312	82.9		1271	80.6	
Psy.D.	93	9.6		217	13.7		261	16.6	
Ed.D.	9	.9		9	.6		6	.4	
Other	5	.5		44	2.8		39	2.5	

What do we do?

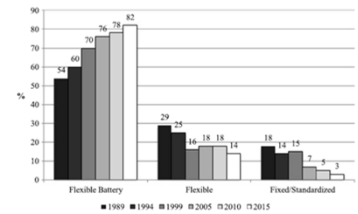
- Clinical Neuropsychologists
  1. Assessment
  2. Treatment
     - Psychotherapy
     - Cognitive Rehabilitation

Assessment

- ➢Medical Records Review
- ➢Clinical Interview
  - ➢Personal history & presenting symptoms
- ➢Mental Status Exam
- ➢Comprehensive battery of tests

Assessment

- ➢Comprehensive Battery of tests
  - ➢Motor functions
  - ➢IQ
    - ➢Cognition
      - ➢Language
      - ➢Attention
      - ➢Executive functions
      - ➢Memory
  - ➢Emotional functioning and personality
  - ➢Effort or validity measures

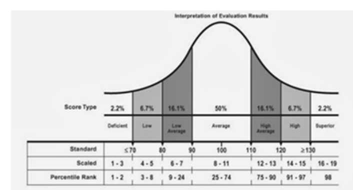


Assessment

- ➢Factors that determine battery
  1. Inpatient or Outpatient
  2. Referral Question
     1. Treatment planning?
        - ➢ Academic
        - ➢ Vocational
          - ➢ Cognitively Disabled?
        - ➢ Pre-surgical
     2. Diagnosis?
        - ➢ Additional neurological disorder
        - ➢ Psychiatric illness

Assessment

- ➢Full day for outpatient
  - ➢Data is scored and integrated into a report
  - ➢Age or demographic referenced scores



Neuropsychological Evaluation

Patient's Name: *Paula Smith*
Date of Birth: xx/xx/1975
Date of Assessment: xx/xx/2015
Education: B.A. in English
Occupation: *Government contractor*

Procedures Administered:

Clinical Interview, Wechsler Adult Intelligence Scale (3rd edition), Wide Range Achievement Test (4th edition) Word Reading, Spelling, and Math Computation subtests, Boston Naming Test, Word List Generation (guided by initial letter and by meaning), Bakker-Brandt Naming Test, Token Test, Hopkins Verbal Learning Test – Revised, Brief Visuospatial Memory Test – Revised, Logical Memory Subtest of WMS-III, Faces Subtest of WMS-III, Hopkins Board, Brief Test of Attention, Stroop Color-Word Test, Trail Making Test, Grooved Pegboard Test, Edinburgh Handedness Inventory, Personality Assessment Inventory, and Quality of Life in Epilepsy.

Introduction:

Paula Smith is a 39 year-old, right-handed, married, Caucasian woman who was referred for neuropsychological evaluation by Dr. Gregory Bergey, of the Johns Hopkins Epilepsy Center in the Department of Neurology. Ms. *Smith* has a history of complex partial seizures with occasional secondary generalization. This evaluation was performed in the context of her presurgical workup.

Brief History:

Ms. *Smith* was born in and raised in XXXX, VA. Her mother is a 65 year-old retired sales representative who is generally healthy. Her father is a 65 year-old attorney who is generally healthy. Ms. *Smith* has a brother and two sisters with whom she is close. There is no family history of epilepsy.

Ms. *Smith* attended Boston College and graduated in 1998 with a degree in English. After graduation, she enrolled in Teacher Corps. She taught 10th and 11th grade in an impoverished public high school. After two years, she returned to the DC area, and has worked as a *government contractor*.

Ms. *Smith* lives with in XXXX, VA her husband. He is a healthy 41 year-old who works for the Department of Defense. Together they have a 2 ½ year-old son and a 1 year-old daughter. When she is not working, Ms. *Smith* spends most of her time with her children. She also enjoys exercising.

Ms. *Smith* has a history of complex partial seizures that date back to 2000. She has been tried on numerous antiepileptic medications, and she is currently taking Onfi, Trileptal, and Vimpat. Although this combination of medications has been most successful, she still has 1-2 complex partial seizures a month. Several seconds before her seizures, she "feels weird and as if something is not right." She also often hears a repetitive phrase about America. During her seizures, she has altered awareness and speaking difficulties. Her seizures typically last for 30 seconds; however, she sometimes remains confused for up to 30 minutes after the seizure. Her brain MRI scan in July 2014 was normal. Her PET scan (November 2014) revealed bilateral temporal lobe hypometabolism. VEEG in July 2014 captured 13 seizures, which indicated onsets in the left posterior and left anterior temporal regions.

Ms. *Smith* sustained a head injury in a MVA when she was 3 years old. She was unsure if she lost consciousness. She denied the use of tobacco or illicit drugs. On special occasions, Ms. *Smith* will have an alcoholic beverage.

Ms. *Smith* denied having any history of a psychiatric disorder, though she met briefly with a mental health professional at age 11 or 12 when her parents divorced. Currently, she frustrated about not being able drive, and is concerned about the effect of her seizures on her children. The thought of neurosurgery for her epilepsy is concerning for her.

Interview Behavior and Mental Status:

Ms. *Smith* arrived on time with her husband to the evaluation. She was well groomed with shoulder length black hair. She was casually dressed in a black puffer coat (which she kept on), blue jeans, and running shoes. She ambulated normally and displayed no abnormal movements. Her conversational language and memory for autobiographical events appeared to be entirely normal. However, she appeared anxious throughout the evaluation. Her face was often blushed, and she was fidgety. During testing, Ms. *Smith* remained friendly and pleasant.

Test Results:

Test	Functions Assessed	Score	%ile for Age	Comments
Wechsler Adult Intelligence Scale (3rd edition)	Psychometric intelligence	Similarities = 11 Arithmetic = 13 Digit Span = 17 Information = 11 L/N Sequencing = 18 Picture Completion = 11 Digit Symbol Coding = 13 Block Design = 13 Symbol Search = 16 Verbal Comprehension Index = 105 Perceptual Organiz. Index = 111 Working Memory = 136 Processing Speed = 125 Verbal IQ = 119 Performance IQ = 115 Full Scale IQ = 119	63 84 99 63 >99 63 84 84 98 63 77 99 95 90 84 90	High average global intellect; very superior working memory and superior processing speed
Wide Range Achievement Test (4th edition)	Basic academic skills	Word Reading = 103 Spelling = 107 Math Computation = 121	58 68 92	Superior computational ability
Boston Naming Test	Visual confrontation naming	51/60	12	Normal recognition, trouble finding names of lower-frequency items
Word List Generation	Guided by initial letter Guided by meaning	FAS = 53 (22, 12, 19) Animals = 24 Supermarket = 39 Tools = 9	81 68 99 16	Normal
Bakker-Brandt Naming Test	Auditory and visual confrontation naming	Auditory Naming = 13/20 Auditory Recognition = 7/7 Visual Naming = 18/20 Visual Recognition = 1/2	14 37	Slightly impaired naming of environmental sounds
Token Test	Ability to follow instructions	40/44	24	Intact
Hopkins Verbal Learning Test-Revised	Learning, recall, and recognition of a word list	Trials 1-3 = 32 (8, 12, 12) Delayed Recall = 12/12 Recog. = 12 hits, 0 false-positive	82 ≥82 ≥73	Exceptional auditory-verbal and visuospatial learning and memory.
Brief Visuospatial Memory Test-Revised	Learning, recall, and recognition of geometric designs	Trials 1-3 = 32 (10, 10, 12) Delayed Recall = 11/12 Recog. = 6 hits, 0 false-positive Copy = 12/12	88 76 >16 --	
Logical Memory Subtest of WMS-III	Learning and memory of a text passage	Logical Memory I = 54/75 Logical Memory II = 31/50 Percent Retained = 82% Recognition = 26/30	84 75 50 50	

Test	Functions Assessed	Score	%ile for Age	Comments
Faces Subtest of WMS-III	Learning and memory of faces	Faces I SS = 14 Faces II SS = 10	91 50	
Hopkins Board	Naming, learning and memory of items and their spatial location	Object Naming = 9/9 Trials to Criterion = 3 Errors to Criterion = 1 Item Recall = 9/9 Location Recall = 9/9	>16 66 66 ≥76 ≥65	Normal
Brief Test of Attention	Auditory divided attention and working memory	20/20	≥74	Exceptional auditory working memory
Stroop Test	Processing speed and inhibition of prepotent responses	Word T = 50 Color T = 50 Color/Word T = 55 Interference T = 54	50 50 69 66	
Trail Making Test	Visual scanning, mental tracking, and graphomotor speed	Part A = 30", 0 errors Part B = 36", 0 errors	51 88	
Grooved Pegboard Test	Manual speed and dexterity	Dominant (right hand) = 64" Nondominant hand = 66"	45 54	Normal
Edinburgh Handedness Inventory	Self-report assessment of handedness	Total = +60		Predominantly right handed
Personality Assessment Inventory	Self-reported symptoms of psychopathology	Inconsistency T= 43 Infrequency T = 47 Neg. Impression Mgmt T = 47 Pos. Impression Mgmt T = 61 Somatic Concerns T = 65 Anxiety T = 62 Anx. Related Disorders T = 55 Depression T = 57 Mania T = 36 Paranoia T = 36 Schizophrenia T = 62 Borderline Features T = 45 Antisocial Features T = 41 Alcohol Problems T = 41 Drug Problems T = 42 Aggression T = 37 Suicidal Ideation T = 51 Stress T = 45 Nonsupport T = 37 Treatment Rejection T = 55 Dominance T = 29 Warmth T = 56	24 38 38 86 93 88 69 76 08 08 88 31 18 18 21 10 54 42 10 69 02 73	Ms. *Smith* has major concerns about her health and physical well-being, but does not display somatization behavior. She complains of difficulties with attention and focusing her thoughts, leading to a minor elevation on the "schizophrenia" scale; she does not have psychotic experiences (except ictally) and has normal social attachments. She acknowledges that she is frequently tense and anxious, and tends to be extremely submissive in interpersonal interactions.
Quality of Life in Epilepsy	Self-reported quality of life related to epilepsy	Seizure Worry T = 46 Overall Quality of Life T = 53 Emotional Well-being T = 50 Energy/Fatigue T = 43 Cognitive T = 51 Medication Effects T = 46 Social Function T = 34 Total T = 43	33 61 52 23 55 36 05 26	Ms. *Smith's* seizures prevent her from driving, and also limit her socially and vocationally.

Summary, Formulation, and Recommendations:

Paula Smith is 39 year-old woman who has had seizures since 2000. They appear to be arising from left temporal regions. Ms. *Smith* has about one to two seizures a month that prevent her from driving and interfere with her social and occupational functioning.

This neuropsychological evaluation reveals a woman of high average global intellect who performed normally across most cognitive and motor tests. In fact, she had exceptional working memory and processing speed, information-processing domains often affected in persons with epilepsy taking medications. In addition, she had exceptionally strong auditory-verbal as well as visual-spatial learning and memory (immediate and delayed). However, Ms. *Smith's* auditory and visual confrontation naming were both lower than expected. Together, these findings strongly suggest to us that her brain is maximally dysfunctional in the left lateral neocortex rather than the left mesial/limbic areas. Recording from brain surface electrodes, as is planned, would likely be particularly helpful for seizure onset localization. Ms. *Smith* is probably at increased risk for noticeable memory decline from a conventional left temporal lobectomy/hippocampectomy.

Ms. *Smith* describes herself as generally anxious, but is understandably concerned about her health and the prospects of neurosurgery. If she wants to learn about the experiences of other patients who have undergone surgical treatment for epilepsy, the nurses in the Epilepsy Center might facilitate the contacts. Although her anxiety not suggestive of a psychiatric disorder, she may benefit from some short-term counseling.

If Ms. *Smith* proceeds to surgery, neuropsychological re-evaluation is recommended 6 to 12 months postoperatively to assess for any cognitive or emotional changes.

____
Antonio N. Puente, Ph.D.
Fellow in Medical Psychology

This patient was personally seen by me. A credentialed psychology associate assisted with test administration, but the clinical interpretations and decisions are entirely mine. Dr. Puente and I jointly prepared this report. The total time required for this evaluation – including record review, interview and mental status examination, test administration, scoring and interpretation, and report preparation – was 8 hours [CPT 96116 (1 hr.), 96118 (1 hr.), and 96119 (6 hrs.). ICD-9: 345.41

____
Jason Brandt, Ph.D., ABPP(CN)
Professor of Psychiatry and Behavioral Sciences
Professor of Neurology
JHH ID# 4254

Assessment

- Comprehensive Battery of tests
  - IQ
    - Premorbid IQ
      - HART
    - Current IQ
      - WAIS-IV

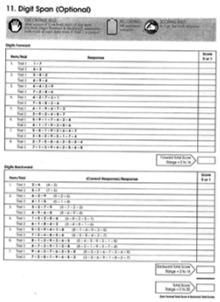
- https://www.commondataelements.ninds.nih.gov/Epilepsy.aspx#tab=Data_Standards

Test Battery

- Motor
  - GPT
  - TMT
  - WAIS-IV

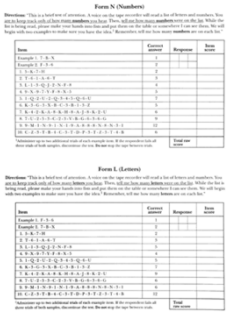
Test Battery

- Attention
  - Simple auditory attention
    - Digits Forward
  - Working Memory
    - Digits Backward



Test Battery

- Attention
  - Divided auditory attention
    - BTA



Test Battery

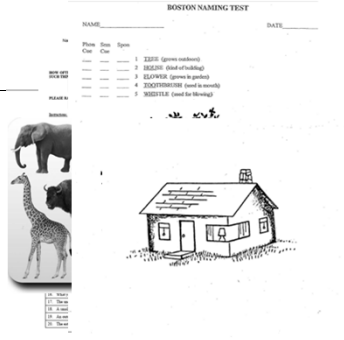
- Attention
  - Sustained Visual Attention

Test Battery

- Executive Functions
  - Set-shifting
    - TMT-B
  - Concept formation and problem solving
    - WCST

Test Battery

- Language
- Verbal Fluency
  - Letters
  - Categories
- Naming
  - Confrontation Naming
  - Auditory Naming

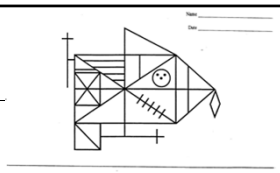


Test Battery

- Visuospatial abilities
- Perception
  - JOLO
  - WAIS-IV

Test Battery

- Visuospatial abilities
- Construction
  - Rey-CFT
  - BVMT-R



Test Battery

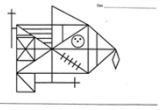
- Memory
- Visuospatial
  - Designs
    - BVMT-R
  - Faces
    - WMS-III Faces

Test Battery

- Memory
- Auditory verbal
  - Rote
    - HVLT-R/RAVLT
  - Contextual
    - Logical Memory

Neuropsychology and Epilepsy

- Factors that test performance
  1. Lesion
     - Mesial temporal lobe structures
       - New learning and memory deficits
       - Naming deficits
         - Lateral temporal
     - Right parietal
       - Visuoperceptual and constructional deficits
     - Left parietal
       - Visuospatial, reading, writing, and calculation

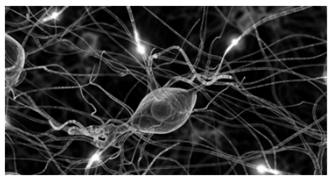


Factors that test performance

1. Lesion
   - Prefrontal
     - Executive dysfunction
       - Problem solving, mental flexibility, planning, and letter guided verbal fluency
   - Occipital lobe
     - Visual-perceptual deficits

Factors that test performance

2. Seizure frequency
   - Greater frequency = greater cognitive impairment
     - Intractable
       - Temporal lobe epilepsy
         - Progressive temporal and extratemporal damage



Factors that test performance

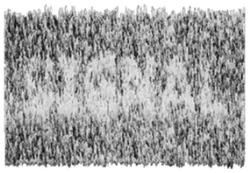
3. Seizure severity
   - More severe = greater cognitive impairment
     - More episodes of status epilepticus
     - Primary generalized tonic-clonic vs complex partial seizures
     - Multiple seizure types vs single seizure type

Factors that test performance

4. Age of Onset
   - Earlier age of onset
     - Worse neuropsychological performances

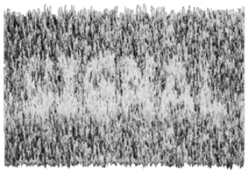
Factors that test performance

5. Noise
   - Antiepileptic drugs (AEDs)
     - ↓ seizure likelihood ↓ neuronal excitability
       - Attention and processing speed
     - Dose dependent
     - Older AEDs
       - Topamax



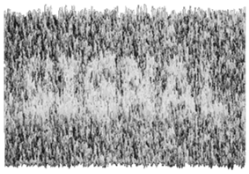
Factors that test performance

5. Noise
   - Transient cognitive impairment
     - Subclinical epileptiform discharges
   - Postictal
     - Brief vs prolong delay
       - ~20 minutes vs 24 hours
         - Seizure type
         - Complex partial seizure
           - 24 hrs



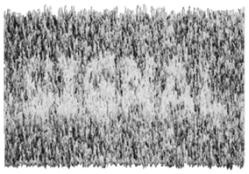
Factors that test performance

5. Noise
   - English language
     - Non-English speaker
     - Fluent English bilinguals ↓ than English monolinguals on tests of language



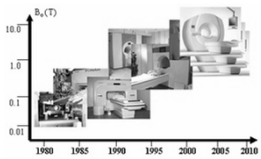
Factors that test performance

5. Noise
   - Motivation/Effort
     - Qualitative and quantitative measurement



Pre-surgical planning

- Lateralization and Localization
- Costs vs benefits



Lateralization and Localization

- Lateralization
  - 66-73%
- Localization
  - Influencing factors
    - Known seizure focus?
      - Location
        - Temporal
          - BNT-70%
        - Diffuse

Pre-surgical planning

- Costs vs benefits
  - Seizure control vs cognitive impairment
- Seizure control
  - Focal deficit
    - Consistent with EEG and MRI
    - Seizure relief
- Postoperative cognitive impairment?
  - Prediction of Memory Loss and Language impairment

Prediction of Memory Loss

1. Memory performance
   - Material specific
   - Relative to seizure focus/area to be resected
     - Verbal > nonverbal
     - Left > right
   - Left temporal lobectomy
     - ~60% of pts have verbal memory decline
   - Right temporal lobectomy
     - ~20 – 25% of pts experience non-verbal memory decline

Prediction of Memory Loss

2. Presence of MTS
   - Seizure focus or contralateral
- Poor Candidate if:
  1. Normal verbal memory
  2. Seizure focus is not MTS and is L medial temporal lobe

Prediction of Language impairment

1. Language performance
   - Relative to seizure focus/area to be resected
   - Dominant much more likely to decline
     - Acute aphasia few days/weeks postoperatively
     - Left temporal lobectomy
       - 25 to 40% of pts will have anomia
         - Mild verbal IQ decline (4-5 pts)

Prediction of Language impairment

2. Temporal lobe epilepsy
   - Type of surgery
     - Traditional resection vs laser ablation
     - 19 (laser) vs 39 (traditional) pts
     - 10 vs 22 dominant
     - 0/10 vs 21/22 declined

Better object recognition and naming outcome with MRI-guided stereotactic laser amygdalohippocampotomy for temporal lobe epilepsy

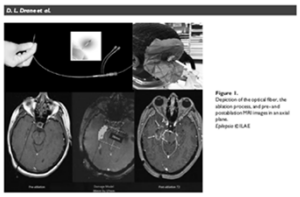


Figure 1.
Depiction of the optical fiber, the ablation process, and pre- and postablation MRI images in a axial plane.
Epilepsia © ILAE

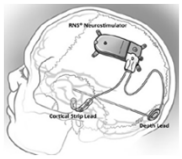
Cognitive Outcome

- Focal deficit
  - Consistent with EEG and MRI
  - Area proposed for surgical resection
    - Seizure Control
    - Cognitive decline less likely
      - Increased likelihood for cognitive gains
        - Attention and processing speed
    - Post-operative cognitive assessment
      - ~1 year

Pre-surgical planning

- Poor surgical candidate?

Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy



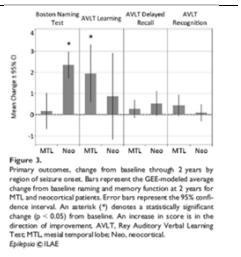


Figure 3.
Primary outcomes, change from baseline through 2 years by region of seizure onset. Bars represent the GEE-modeled average change from baseline naming and memory function at 2 years for MTL and neocortical patients. Error bars represent the 95% confidence interval. An asterisk (*) denotes a statistically significant change ($p < 0.05$) from baseline. An increase in score is in the direction of improvement. AVLT, Rey Auditory Verbal Learning Test; MTL, mesial temporal lobe; Neo, neocortical.
Epilepsia © ILAE

Conclusions

- Who we are?
  - Doctoral educated clinical psychologists
    - Brain-behavior relationships
- What we do?
  - Assessment
    - Record review, clinical interview, mental status exam, and comprehensive test battery

Conclusions

- Utility in Epilepsy
  - How are they useful for pts with epilepsy?
    1. Treatment planning
    2. Diagnostic clarification
  - What factors influence test performance in epilepsy?
    1. Lesion
    2. Seizure Frequency
    3. Seizure Severity
    4. Age of Onset
    5. Noise

Conclusions

- Utility in Epilepsy
  - Who is considered a "good" surgical candidate?
    1. Focal deficit that is consistent with imaging and area proposed for resection
       - ↓ Seizure likelihood and ↓ cognitive decline

Thanks for Listening!

Questions?

AEDs I: The Sodium Channel

Bassel W. Abou-Khalil, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

AEDs I: SODIUM CHANNEL

Bassel Abou-Khalil, MD
Professor of Neurology
Director of the Epilepsy Center
Vanderbilt University Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **Use of lacosamide for status epilepticus**

ASMs acting on the sodium channel

Bassel Abou-Khalil, M.D.

Objectives

- Review the mechanism of blocking sodium channels
- Review pharmacokinetics of classical sodium channel blockers PHT, CBZ, OXC, ESL, LTG, LCM, RFM
- Review key interactions of above
- Review main adverse effects of above
- Review clinical use of classical sodium channel blockers

ASM main mechanisms of action

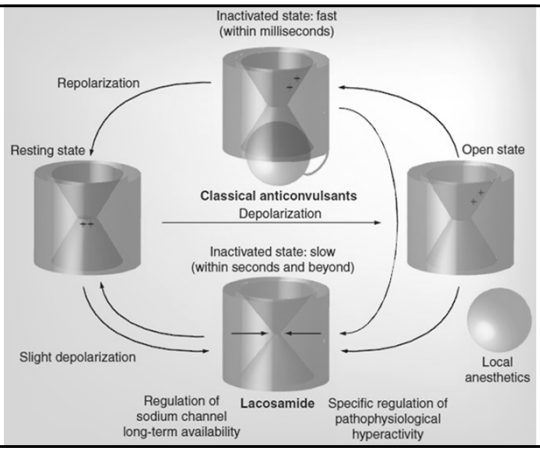
- **Na channel blocking**
- Enhancing GABA
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Modulation of intracellular calcium
- Binding synaptic vesicle protein SV2A
- Carbonic anhydrase inhibition

Blocking voltage-gated sodium channels as an ASM mechanism

- Sodium channels open in response to membrane depolarization, allowing positive sodium ions into the neuron, which increases neuronal depolarization and facilitates the spread of action potentials
- After the channel closes, it remains inactive for a certain period - a refractory period- during which membrane depolarization cannot reopen it.
- During seizures, neurons undergo depolarization and fire action potentials at high frequencies. Inhibition of high frequency firing is thought to be mediated by decreasing the ability of sodium channels to recover from inactivation.
- Drugs that increase the refractory period decrease the frequency of action potentials

Fast versus slow inactivation of VGSC

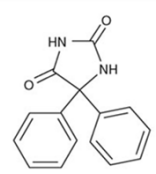
- Fast inactivation occurs on a time scale of milliseconds.
- Slow inactivation occurs over the time course of seconds to minutes.
  - involves modification of the shape of the sodium channel



ASMs and Na channel blocking

- Enhancement of fast inactivated state- blocking of sustained repetitive firing:
  - Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide, eslicarbazepine
- Selective enhancement of slow inactivation of voltage-gated sodium channels
  - Lacosamide
- Multiple mechanisms, including effect on sodium channels
  - Valproate, felbamate, topiramate, zonisamide, cenobamate

Phenytoin (PHT)



- In use since 1938 when Houston and Merritt discovered its efficacy in the MES model
- MOA: binds to the active state of the sodium channel, slows recovery rate of inactivated channel, and reduces high frequency firing (as might occur during a seizure) while allowing normal action potentials to occur.
- Available as oral preparations and parenteral solution

PHT- Absorption, distribution

- **Rate and extent of absorption may differ among different formulations and is affected by many factors, including age and food** (decreased in neonates, with NG feedings, calcium, antacids).
- Limited absorption in the stomach. **Absorption primarily in the duodenum**, where the higher pH increases PHT solubility.
- Tmax 4-8 hours (up to 12 hours), sooner with immediate release
- V_d= 0.78 L/Kg
- **Protein binding: ~90%**

PHT- Metabolism

- **Major pathway of elimination is hydroxylation mediated mainly by the cytochrome P450 enzyme CYP2C9> CYP2C19.**
- **Nonlinear kinetics**- small changes in CYP2C9 activity may have clinically significant effects. Some alleles are associated with reduced clearance.
- Importance of CYP2C19 increases with higher levels. Some alleles and inhibitors (e.g. ticlopidine or isoniazid) may lead to accumulation

PHT- Elimination

- PHT follows nonlinear elimination kinetics, unlike other ASMs
- **$T_{1/2}$ is dependent on serum concentration**. Initial $T_{1/2}$ = ~ 22 h (range 8–60).
- The half-life will increase as the serum concentration increases within and above the recommended therapeutic range (10-20 mg/L).
- ~95% is excreted in urine and feces as metabolites, ≤ 5% unchanged PHT

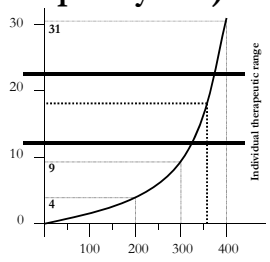
PHT- Nonlinear elimination kinetics

- Enzymes responsible for most of PHT elimination are partially saturated at concentrations within the recommended therapeutic range (with individual variation as to concentration at which this phenomenon starts).
- These enzymes are not able to increase their activity in proportion to PHT concentration as the concentration increases to the recommended therapeutic range.
- Steady-state PHT level increases disproportionately as the maintenance dose is increased within and above the recommended therapeutic range.

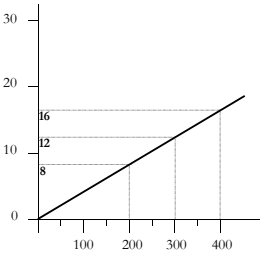
Phenytoin nonlinear kinetics- Example of consequences

- Example 1: a daily dose of 300 mg per day results in a serum concentration of 9 mg/L. Increasing the dose to 400 mg per day (1/3 increase) would have increased the steady state concentration by 1/3 to 12 mg/L if phenytoin were to follow linear elimination kinetics. With its nonlinear kinetics, the concentration may increase disproportionately by >300% to 31 mg/L with associated toxicity
- Example 2: a patient presents with phenytoin toxicity and a serum concentration of 40 mg/L. The $T_{1/2}$ was previously estimated at 24 hours. However, after phenytoin was stopped it took 3 days for the serum concentration to go below 20 mg/L

Non-linear kinetics (ex: phenytoin)



Linear kinetics (other ASMs)



PHT- Formulations

- Extended release capsules contain phenytoin sodium
- Immediate release tablets contain phenytoin, so they are not exactly equivalent.

PHT- Interactions

- **PHT affected by drugs that**
  - **Decrease absorption (e.g. NG tube feedings)**
  - **Compete for protein binding (VPA)**
  - **Enzyme inducers or inhibitors**
- PHT is **a potent enzyme inducer** that reduces the efficacy of other ASMs metabolized by p450 enzyme system

Select drugs that reduce PHT clearance

- Acute alcohol intake
- Amiodarone
- Azoles (fluconazole, ketoconazole, etc…)
- H2- antagonists (e.g. cimetidine)
- Several ASMs (ethosuximide, methsuximide, felbamate, oxcarbazepine, topiramate, cenobamate)
- Fluoxetine, fluvoxamine
- Isoniazid
- Others

PHT- Protein binding

- **PHT is ~90% protein bound, 10% free**
- **Free level is responsible for therapeutic effect and for toxicity**
- **Free fraction increases in presence of low protein state, renal failure, hepatic failure, old age, or with co-administration of VPA.**

PHT- Adverse effects

- Concentration-dependent AEs: nystagmus, ataxia, incoordination, diplopia, dysarthria, drowsiness.
- **Exacerbation of seizures may occur with levels above 30 mcg/ml**.
- Some may experience prominent AEs within the recommended therapeutic range, including cognitive AEs.

PHT- Idiosyncratic AEs

- Idiosyncratic reactions may be related to formation of an arene oxide, a reactive metabolite that forms due to inadequate epoxide hydrolase activity.
- Allergic rash occurs in up to 8.5% of patients
  - Stevens Johnson syndrome, toxic epidermal necrolysis less common
- 'Hypersensitivity syndrome" with rash, fever, lymphadenopathy, eosinophilia, elevated liver enzymes, renal failure is very uncommon.

PHT- Long-term AEs

- Gingival hyperplasia, hirsutism, acne
- Cerebellar atrophy (may also occur after acute high dose)
- Reduced bone density
- Reduced folate levels, anemia, macrocytosis
- Teratogenicity

AEs- IV solution

- **Local reactions**
  - Pain and burning at infusion site
  - Phlebitis
  - Cellulitis or necrosis from extravasation
  - Purple glove syndrome with discoloration then petechial rash
- Cardiovascular AEs related in part to vehicle (propylene glycol), can be avoided with slowing of infusion rate (max 50 mg/min)
  - hypotension, conduction abnormality, arrhythmia

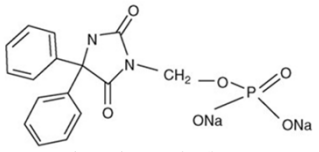
PHT- Efficacy and Clinical Indications

- Effective against focal (partial) onset seizures and generalized tonic-clonic seizures. Efficacy against tonic and atonic seizures less well established.
- **Not effective against generalized myoclonic or absence seizures** (and may exacerbate them).
- The most frequently used ASM for many years, but its use has declined considerably since the appearance of newer-generation ASMs with improved tolerability.

PHT- Acute loading

- Oral loading dose can be given (18 mg/Kg divided into three doses given 2 to 3 hours apart.
- IV loading dose for status epilepticus is 18-20 mg/Kg. Should be diluted in normal saline, not dextrose 5% in water; max rate 50 mg per minute into a large vein. ECG and BP monitoring recommended.
- **Intramuscular injection not recommended due to slow and erratic absorption, and crystallization at injection site causing pain.**

Fosphenytoin



- Phenytoin pro-drug
- Can be given IV or IM
- Rapidly and completely converted to phenytoin (by cleavage of the phosphate group by nonspecific phosphatases). Conversion $T_{1/2}$ is ~8-18 minutes. Conversion is complete in a little more than 1 hr.
- Highly bound to serum albumin (95% to 99%)- displaces phenytoin from protein binding sites after IV administration, increasing unbound phenytoin concentrations as a function of fosphenytoin concentration.

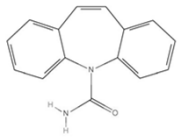
Fosphenytoin indications/dosing

- Indicated for replacement of oral PHT or for IV or **IM loading**
- Marketed in phenytoin equivalents (PE), so loading dose is equivalent to phenytoin loading dose. Loading dose 18-20 mg PE/Kg, max rate 150 mg PE/min
- Therapeutic PHT level usually reached within 10 min after IV loading, within 30 min after IM administration.

Fosphenytoin AEs

- Lower incidence of local reactions.
- IV administration commonly associated with **paresthesias/ itching**, most often in the groin/ perianal region, on the trunk, or the back of the head; this is related to infusion rate and subsides rapidly after the end of infusion. It is not seen with IM administration.

Carbamazepine (CBZ)



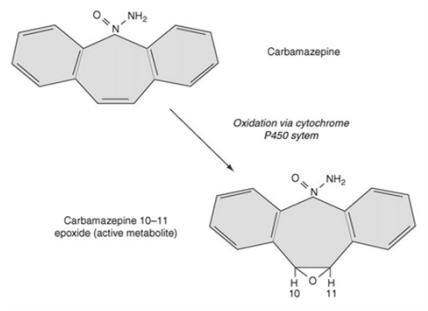
- Similar in structure to tricyclic antidepressants.
- MOA: reduces high frequency neuronal firing through action on the sodium channel, in both a voltage- and use-dependent fashion

CBZ- Absorption, distribution

- Bioavailability ~ 80-90%
- T max = 3-4 hours.
- Lipophilic- crosses the blood-brain barrier readily
- Poorly water soluble; IV preparation approved in 2016 for short-term replacement therapy
- V_d= 0.8-2 L/Kg
- **Protein binding: 75%**

CBZ- Metabolism, elimination

- **Cleared almost entirely via hepatic metabolism.**
- Major pathways are epoxide-diol pathway, aromatic hydroxylation, and conjugation.
- **Most important product is CBZ-10,11-epoxide** (via oxidation through CYP3A4 and CYP2C8). It is active and also responsible for some adverse effects.
- **Induces its own metabolism (autoinduction)**, with increasing clearance, shortening of $T_{1/2}$ and lowering of serum concentration over time (process takes 2-4 weeks). Cannot be started on target maintenance dose.



CBZ- Interactions

- **Potent inducer of p450 enzyme system** (CYP3A4, CYP2C9, CYP2C19, and CYP1A2), increasing clearance of agents metabolized by these enzymes
  - Hormonal contraceptives
  - Warfarin
  - Simvastatin
  - Valproate, lamotrigine, etc..

CBZ- Interactions

- **Affected by agents that induce or inhibit CYP3A4 isoenzymes**
  - **Inhibitors include erythromycin and related antibiotics (not azithromycin), fluoxetine, propoxyphene, verapamil, diltiazem, grapefruit juice,** etc...
- CBZ-epoxide increased by concomitant use of valproate, felbamate, oxcarbazepine, zonisamide

CBZ- Adverse effects

- Most common AEs are nausea, GI discomfort, headache, dizziness, incoordination, unsteadiness, vertigo, sedation, tiredness, blurred vision, diplopia, nystagmus, tremor.
- Leukopenia is common (10-20%)- most often transient but may be persistent.
- Hyponatremia
- Cognitive impairment on neuropsychological testing
- Weight gain
- Decreased bone density
- Increased sex hormone binding globulin and decreased testosterone

CBZ- Idiosyncratic AEs

- Rash
- Stevens-Johnson syndrome, and toxic epidermal necrolysis are rare.
- Rare hypersensitivity syndrome, with fever, rash, and organ involvement.
- SLE rare
- Hepatotoxicity rare
- Aplastic anemia rare (1 per 200,000)

CBZ- Idiosyncratic AEs

- **Strong association between the HLA-B*1502 allele and CBZ-induced Stevens- Johnson syndrome in Asian populations** and individuals of Asian descent
- FDA issued an alert and updated product labeling recommending genetic testing of HLA-B polymorphisms to predict carbamazepine-induced serious skin reactions in individuals of Asian descent.

CBZ- Efficacy and indications

- Effective against focal (partial) onset seizures and against generalized tonic-clonic seizures
- **May exacerbate absence and myoclonic seizures** as well as atonic seizures.
- Recommended therapeutic range 4-12 mg/L

CBZ- Place in therapy

- Had the best balance of efficacy and tolerability in the large cooperative VA study. As a result, it became the standard treatment for focal seizures.
- No drug has been demonstrated to be more effective than CBZ, but its use has declined with the marketing of new ASMs with pharmacokinetic advantages.
- LTG, OXC, GBP had better tolerability than immediate release CBZ. However, **comparative trials using extended release CBZ have failed to show superior tolerability of LTG, LEV, ZNS, ESL or LCM**.
- Nevertheless, enzyme induction and pharmacokinetic interactions have been issues favoring newer ASMs. On the other hand, economic considerations favor the less-expensive CBZ.

Comparison of CBZ, PHB, PHT, or PMD in partial and secondarily generalized tonic-clonic seizures

Mattson et al, N Engl J Med. 1985

- 10-center, double-blind trial to compare the efficacy and toxicity of four ASMs [carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), or primidone (PMD)] in partial and secondarily generalized tonic-clonic seizures (SGTCS)
- 622 adult patients were randomly assigned to CBZ, PHB, PHT, or PMD and were followed for two years or until the drug failed due to uncontrolled seizures or unacceptable side effects
- **Overall treatment success was highest with CBZ or PHT, intermediate with PhB, and lowest with PMD** ($p<0.002$). PMD caused more intolerable acute toxic effects (nausea, vomiting, dizziness, sedation, decreased libido, impotence)
- **Control of SGTCS did not differ significantly with the four drugs.**
- **CBZ provided complete control of partial seizures more often than PMD or PhB** ($p<0.03$).
- "Overall, CBZ and PHT are recommended drugs of first choice for single-drug therapy of adults with partial +/- SGTCS."

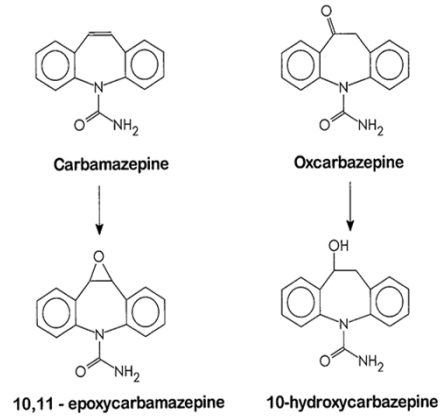
Seizure Freedom

Treatment Group	12 months	12 months SGTCS only	12 months Partial only
CBZ	47%	48%	43%*
PhB	36%	43%	16%
PHT	38%	43%	26%
PMD	35%	45%	26%

* Significantly better at every 6-month point for all 36 months

Oxcarbazepine (OXC)

- Structurally related to CBZ, but different from CBZ in metabolism and induction of metabolic pathways- rapidly and extensively metabolized to an active monohydroxy derivative (MHD)- no epoxide formation
- MOA similar to CBZ



OXC- Absorption, distribution

- Oral absorption is virtually complete (bioavailability ~99%)
- MHD Tmax 4-6 hours after OXC dose (OXC Tmax 1-3 hours)- 7 hrs after extended release
- MHD V_d= 0.7-0.8 L/Kg
- **MHD Protein binding: 40%** (OXC 60%)

OXC- Metabolism, elimination

- OXC **rapidly converted to the active metabolite monohydroxyderivative (MHD)**, which is then further metabolized
- MHD T½= 8-10 hrs (OXC T½= 1 to 3.7 hrs)
- **Does not induce its own metabolism**

OXC- Interactions

- MHD level decreases with enzyme inducing ASMs (EIASMs)
- **Does not induce metabolism of other ASMs or warfarin**
- **Weakly induces CYP3A4 responsible for estrogen metabolism**
- **Weakly inhibits CYP2C19, raising PHT level at high doses**
- **Is not affected by erythromycin, fluoxetine, propoxyphene, grapefruit juice,** etc..

OXC- Adverse effects

- Most common are somnolence, headache, dizziness, blurred vision, diplopia, fatigue, nausea, vomiting, ataxia
- **Hyponatremia; more likely in older age or in association with diuretic intake**
- Rash- ~2-4%
- Does not have CBZ effect on SHBG and testosterone

OXC- Efficacy and clinical indications

- Effective against **focal-onset seizures**
- **Multiple comparative monotherapy trials for new onset partial epilepsy**
  - OXC equal in efficacy to PHT and CBZ, but with less adverse effects/ superior tolerability
  - OXC equal in efficacy and tolerability to VPA
- **May exacerbate absence and myoclonic seizures**

OXC- Conversion from CBZ

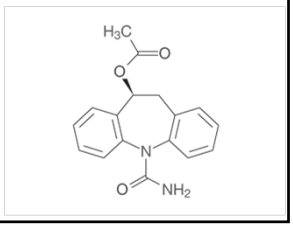
- Conversion from CBZ can be made overnight using a 1.5 to 1 ratio at a CBZ dose of $\leq$ 800 mg. Lower conversion ratio advisable at higher CBZ doses.
- **Conversion from CBZ to OXC will be accompanied by enzyme de-induction** and possible elevation of other medication levels.
- **Sodium level may decrease after conversion from CBZ**

Eslicarbazepine Acetate (ESL)

- Approved for marketing in the USA in 2014.
- A prodrug of eslicarbazepine- rapidly converted to the active metabolite (S)-licarbazepine by hydrolytic first-pass metabolism. (S)-licarbazepine is the active enantiomer of the monohydroxy derivative, which is the active metabolite for oxcarbazepine. The monohydroxy derivative from oxcarbazepine is a racemic mixture of the active (S)-licarbazepine and the inactive (R)-licarbazepine.
- Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage gated sodium channel.

ESL- Absorption, distribution

- Bioavailability >90%
- T max 1-4 hours post-dose.
- Food has no effect on absorption
- Protein binding <40%
- Vd= 0.87 L/Kg



ESL- Metabolism, elimination

- Eslicarbazepine is metabolized to inactive compounds. It is not subject to autoinduction.
- Renal excretion, 60% unchanged, 30% glucuronide conjugate, 10% other metabolites.
- **T1/2 ~ 13-20 hours in plasma, 20–24 hours in CSF**

ESL- Interactions

- **Moderate inhibitory effect on CYP2C19**
  - can cause increased plasma concentration of phenytoin and other drugs metabolized by CYP 2C19
- **Can induce CYP3A4**, decreasing plasma concentrations of estrogen and drugs metabolized by CYP 3A4
- No apparent autoinduction
- Enzyme inducers may reduce level of eslicarbazepine

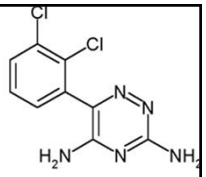
ESL- Adverse effects

- Most common are dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, ataxia, blurred vision, and vertigo
- Hyponatremia (≤ 125 mEq/L) reported in up to 1.5% at 1200 mg per day
- Rash- up to 3% at 1200 mg per day

ESL- Efficacy and clinical indications

- Effective against **focal seizures**
- FDA indication: adjunctive and monotherapy of partial-onset seizures in patients ≥4 years
- Should be avoided in IGE.
- Theoretical considerations suggest ESL could be considered as first-line monotherapy for focal seizures, with tolerability advantages over immediate-release oxcarbazepine (but financial considerations may be an obstacle).

Lamotrigine (LTG)



- Approved in the USA in 1995, licensed in Europe in 1991
- Mechanism of action: blocking sodium channels; secondarily blocks release of glutamate; inhibits high-voltage–activated calcium channels

LTG- Absorption, distribution

- Oral bioavailability ~98 %
- Tmax = 1-1.5 hours (4-11 hours for XR)
- Protein binding: ~55%
- V_d = 0.9-1.3 L/Kg

LTG- Metabolism, elimination

- Metabolism: **extensively metabolized in the liver** predominantly by glucuronidation (to lamotrigine 2-N-glucuronide), then excreted by the kidney
- Elimination: in urine (94%, ~90% as glucuronide conjugates and ~10% unchanged)
- $T_{1/2}$ = ~24 hours in monotherapy; 48–60 hour with valproate; 12 hours with enzyme inducers

LTG- Interactions

- LTG associated with mild autoinduction
- Weak inhibitor of dihydrofolate reductase
- LTG slightly increases TPM level (15%), decreases VPA level (25%)
- **LTG clearance increased in the presence of enzyme-inducing drugs, estrogen containing oral contraceptives, pregnancy**
- **LTG clearance markedly decreased by valproate**

LTG- Adverse effects

- Dose-related AEs: dizziness, ataxia, blurred vision, diplopia, nausea, and vomiting.
- Headache, tremor
- **Rash (~3%)-** higher risk in children, with co-administration of valproate, faster titration, higher dose)
- **Hypersensitivity- Stevens-Johnson syndrome or TEN; hypersensitivity syndrome (~1 in 4,000)**
- **Hemophagocytic lymphohistiocytosis- very rare**

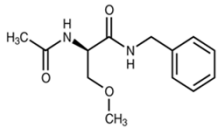
LTG- Efficacy, clinical use

- LTG is a **broad spectrum ASM** effective against focal seizures as well as generalized tonic-clonic seizures. It is indicated as adjunctive therapy for Lennox-Gastaut syndrome.
- **Efficacy against absence is less than valproate and ethosuximide**. Efficacy against myoclonic seizures is variable, and may exacerbate myoclonic seizures in some individuals.

LTG- FDA indications

- Adjunctive therapy in patients aged ≥2 for
  - Partial-onset seizures
  - Primary GTC
  - Generalized seizures of LGS
- Monotherapy- conversion to monotherapy for partial-onset seizures
- Maintenance treatment of bipolar I disorder to delay mood episode

Lacosamide (LCM)



- Approved in USA in 2008.
- MOA: enhances slow inactivation of Na channels
- Available in oral and IV formulations

LCM- Absorption, distribution

- Oral bioavailability: ~100 %
- Tmax = 1-4 hours
- Protein binding: <15%
- V_d = ~0.6 L/Kg

LCM- Metabolism, elimination

- **Metabolized by demethylation in the liver to inactive O-desmethyl-metabolite via CYP-2C19**
- 95% excreted in urine (40% as unchanged drug, 30% as O-desmethyl-metabolite)
- **$T_{1/2}$ ~ 13 hours**

LCM- interactions

- No known pharmacokinetic interactions, despite CYP-2C19 metabolism
- Pharmacodynamic interaction with other ASMs acting on sodium channel

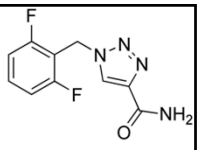
LCM- Adverse effects

- Dose-related AEs: dizziness, headache, nausea, diplopia, sedation (more likely when used in conjunction with other Na-channel blockers)
- Small, asymptomatic increase in PR interval

LCM- Efficacy, clinical use

- Narrow spectrum ASM against focal seizures
- FDA indication: adjunctive therapy and monotherapy of partial-onset seizures in patients $\geq$ 4 years of age. Injection is indicated as short-term replacement when oral administration is not feasible
- Greater efficacy and better tolerability if combined with a non-sodium channel drug
- Efficacy against generalized tonic-clonic seizures under investigation

Rufinamide (RFM)



- Approved in USA in 2008.
- MOA: Binds to sodium channels; prolongs the inactive state of Na channels

RFM- Absorption, distribution

- Oral absolute bioavailability: ~85 % with food; less without food (food increases absorption by >30%)
- Tmax = 4-6 hours
- Protein binding: ~ 35%
- V_d = ~0.77 L/Kg

RFM- Metabolism, elimination

- Metabolism by enzymatic hydrolysis to an inactive metabolite (not dependent on p450 system)
- Elimination by excretion in urine (metabolites are inactive)
- $T_{1/2}$ = 6-10 hours

RFM- Interactions

- RFM is a weak inhibitor of CYP 2E1 (increases olanzapine level) and a weak inducer of CYP 3A4 enzymes (decreases OCP efficacy).
- RFM is a weak inducer of UDP-GT (increases clearance of LTG)
- Addition of enzyme-inducing ASMs increase RFM clearance and decrease RFM levels
- **Addition of VPA decreases RFM clearance and increases RFM levels up to 70%**

RFM- Adverse effects

- Dizziness, fatigue, somnolence, headache in adults
- Somnolence, vomiting, headache in children
- **Short QT interval**

RFM- Efficacy, clinical use

- FDA indication: adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 1 year and older and in adults
- Efficacy against focal seizures demonstrated in trials

AEDs II: The GABA System

Bassel W. Abou-Khalil, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

AEDs II: THE GABA SYSTEM

Bassel Abou-Khalil, MD
Professor of Neurology
Director of the Epilepsy Center
Vanderbilt University Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - Use of clobazam outside of Lennox-Gastaut syndrome (LGS)
  - Use of CBD outside of LGS and Dravet syndrome

ASMs acting on the GABA system

Bassel Abou-Khalil, MD

Objectives

- Review the mechanism of action of GABA-acting antiseizure medications
- Review pharmacokinetics of drugs with main mechanism related to GABA
- Review key interactions of above ASMs
- Review main adverse effects of above ASMs
- Review clinical use of above ASMs

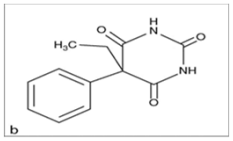
ASM main mechanisms of action

- Na channel blocking
- **Enhancing GABA**
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Modulation of intracellular calcium
- Binding synaptic vesicle protein SV2A
- Carbonic anhydrase inhibition

Enhancing GABA as a mechanism of ASM action

- **Irreversible inhibition of GABA transaminase: vigabatrin**
- **Inhibition of GABA reuptake at the synapse: tiagabine**
- **Prolongation of GABA-mediated chloride channel openings: phenobarbital**
- **Increased frequency of GABA-mediated chloride channel openings: benzodiazepines**, topiramate (different binding site- also increases GABA levels in the brain by MRS)
- Other: valproate, felbamate, cannabidiol, cenobamate
- Some ASMs are associated with acute elevation of brain GABA by MRS after single doses: 70% for topiramate, 48% with gabapentin (but gabapentin does not interact with the GABA receptor).

Phenobarbital (PB)



- In use since 1912
- MOA: **enhances postsynaptic $GABA_A$ receptor-mediated chloride currents, prolonging the opening of the Cl^- channel**. May also have other actions (HVA Ca channels and glutamate receptors).
- Available as oral preparations and parenteral solution

PB- Absorption, distribution

- **Oral absolute bioavailability is > 90%**
- Tmax = 2-4 hours
- **Protein binding: ~45%**
- V_d = ~0.6 L/Kg

PB- Elimination

- Elimination: **20-25% eliminated renally, unchanged; rest metabolized in the liver**
- $T_{1/2}$ = **80-100 hours in adults**; ~100-150 hours in newborns; 60-70 hours after that, before age 5

PB- Interactions

- PB is a **potent inducer of p450 enzymes**. Accelerates metabolism and reduces levels of ASMs processed by this enzyme system
  - Reduces valproate, ethosuximide, lamotrigine, etc..
  - Reduces levels of CBZ (but may increase CBZ-epoxide to CBZ ratio)
  - Reduces efficacy of warfarin, steroids, oral contraceptive
  - Variable effect on phenytoin (due to competition for metabolism)
- Phenobarbital **level is increased by inhibitors valproate, felbamate, cenobamate**

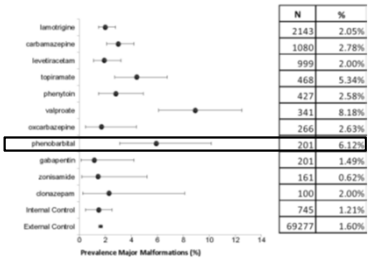
PB- Adverse effects

- **Sedation**
- **Mood changes (depression)**
- **Hyperactivity/irritability in children**
- **Decreased memory and concentration**
- **Long term use associated with decreased bone density and connective tissue disorders**
  - Dupuytren's contractures
  - Plantar fibromatosis
  - Frozen shoulder

PB- Efficacy/clinical indication

- Effective against focal seizures, generalized tonic-clonic seizures, other generalized-onset seizures except absence.
- IV preparation may be used against status epilepticus
- Not drug of choice in developed countries
- May be the only affordable ASM in much of the developing world

PB- Teratogenicity



N	%
2143	2.05%
1080	2.78%
999	2.00%
468	5.34%
427	2.58%
341	8.18%
266	2.63%
201	6.12%
201	1.49%
161	0.62%
100	2.00%
745	1.21%
69277	1.60%

North American AED Pregnancy Registry- Rate of major malformations in monotherapy- Updated 2018 data

- Increased risk of cardiac malformations
- Reduced cognitive abilities in exposed male offspring

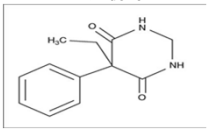
PB- Monitoring

- "Therapeutic" concentration: 15-40 mg/L

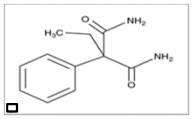
Primidone (PRM)

- Converted to phenobarbital (PB) and active metabolite phenyl-ethyl-malonamide (PEMA)
- MOA:
  - Does not have a direct effect on GABA receptors.
  - PB acts on the $GABA_A$ receptor to prolong opening of the chloride channel
  - PRM acts synergistically with PB to reduce sustained, high-frequency, repetitive firing at clinically relevant concentrations
- PEMA action unknown and modest

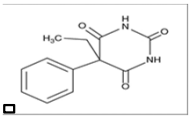
Primidone



Phenylethylmalonamide (PEMA)



Phenobarbital



PRM- Absorption, distribution

- **Oral bioavailability is fairly complete (~92%)**
- Tmax = ~3 h
- V_d = 0.54 (single dose)-0.86 L/Kg
- **Poorly soluble, precluding IV preparation**
- **Protein binding: <10%** for PMD and PEMA

PRM- Metabolism and elimination

- **PEMA is first detected metabolite**
- **~25% of oral PRM is converted to PB** (dose of PRM required for certain PB level ~4-5 x dose of PB required for same level)
- In monotherapy $T_{1/2}$= 10-15 hours- with enzyme inducers $T_{1/2}$= 6.5-8.3 hours.
- After one dose 64% excreted unchanged in absence of induction, ~40% excreted unchanged with induction.

PRM- Interactions

- Co-administration of inducers (particularly PHT) reduces ratio of PRM to PB due acceleration of PRM to PB conversion.
- PRM and PB are potent enzyme inducers
- All PB interactions are present by necessity

PRM- Adverse effects

- **Acute toxic reactions different from PB**
  - Transient drowsiness, dizziness, ataxia, nausea, and vomiting that can be debilitating.
  - Tolerance to acute AEs develops rapidly within hours to days.
  - Long-term PB therapy protects from acute PRM toxicity
- Chronic AEs same as PB

PRM- Efficacy and indications

- Effective against same seizure types as phenobarbital
- Equal efficacy, but lower tolerability in comparison to PB, PHT, CBZ

PRM- Monitoring

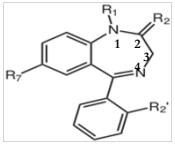
- "Therapeutic plasma concentration" of PRM 5-12 mg/L.
- Phenobarbital level may also be monitored (15-40 mg/L)
- Since ~25% of oral PRM is converted to PB, dose of PRM required for certain PB level ~4-5 x dose of PB required for same PB level

Comparison of CBZ, PHB, PHT, or PMD in partial and secondarily generalized tonic-clonic seizures Mattson et al, NEJM 1985

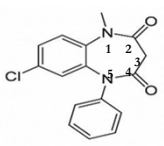
- 10-center, DB trial to compare efficacy and toxicity of four ASMs [carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), or primidone (PMD)] in partial and secondarily generalized tonic-clonic seizures (SGTCS)
- 622 adults patients randomly assigned to CBZ, PHB, PHT, or PMD and followed for 2 years or until the drug failed due to uncontrolled seizures or unacceptable side effects
- **Overall treatment success was highest with CBZ or PHT, intermediate with PhB, and lowest with PMD** ($p<0.002$). PMD caused more intolerable acute toxic effects (nausea, vomiting, dizziness, sedation, decreased libido, impotence)
- **Control of SGTCS did not differ significantly**
- **CBZ provided complete control of partial seizures more often than PMD or PhB** ($p<0.03$).
- "Overall, CBZ and PHT are recommended drugs of first choice for single-drug therapy of adults with partial +/- SGTCS."

Benzodiazepines

- Mechanism of action: Increased frequency of GABA-mediated chloride channel openings



Most benzodiazepine



Clobazam

Benzodiazepines

- **Diazepam** and **lorazepam** primarily used for acute seizure emergencies (status epilepticus and acute repetitive seizures)
- **Clonazepam**, **clorazepate**, **clobazam** used mainly for chronic epilepsy management

Benzodiazepines- Absorption and distribution pharmacokinetics

- Most benzodiazepines have oral bioavailability >80% (except 40% for midazolam, due to metabolism in intestinal epithelium).
- All benzodiazepines rapidly cross BBB, diffusion rate and onset of action determined by lipid solubility.
- Large volumes of distribution, characterized by two-compartment model.
- Highly protein bound.

Distribution by one vs ≥2 compartment model

- A one-compartment distribution model exists if the final concentration equilibrium is reached rapidly following IV administration
- ≥2 compartment distribution model applies if after initial rapid distribution in one compartment the drug diffuses into a second or more compartments.
- The total V_d will correspond to the sum of the compartments.
- An example is diazepam redistributing to adipose tissue. The true $T_{1/2}$ is 36 hours, but the redistribution half-life is ≤ 1 hour

Benzodiazepine metabolism

- Benzodiazepines vary considerably in their metabolism and elimination rate.

Benzo	Primary metabolic pathway	Active metabolite	T1/2 of parent drug (hrs)	T1/2 of active metabolite (hrs)
Diazepam	Demethylation, hydroxylation, glucuronidation	**Desmethyldiazepam (DMD)**, oxazepam, temazepam	21-70	**DMD: 49-179** Oxazepam: 6-24 Temazepam: 8-24
Lorazepam	Glucuronidation	None	7-26	NA
Clonazepam	Nitroreduction, acetylation, hydroxylation	None	19-60	NA
Clorazepate	Decarboxylation	**DMD**, oxazepam	NA	**DMD: 20-160** Oxazepam: 6-24
Clobazam	Demethylation	N-desmethylclobazam	10-30	36-46

Benzodiazepine drug interactions

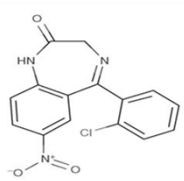
- Both pharmacokinetic and pharmacodynamic interactions occur
- Interactions depend on specific metabolic pathway
- Inhibition of major pathway may cause accumulation, but inhibition of minor pathway has limited effect
- Induction of major or minor pathways will reduce concentration
- Clinical effect of induction and inhibition also dependent on active metabolites and their metabolic pathways

Enzymes involved in metabolism of select ASMs

Enzyme	DZP	LZP	CZP	CLZ	CLB
1A2					
2A6					
2B6	X				X
2C8					
2C9	X				
2C18					X
2C19	X			X*	X
2E1					
3A4	X		X	X*	X
3A5	X				
3A7					
4B1					
UGT		X			
NAT			X		

UGT= uridine diphosphate glucuronosyltransferase
NAT= N-acetyltransferase
*- applies to DMD

Clonazepam (CZP)



- Bioavailability>90%
- Tmax= 1-4 hours
- V_d= 3.0 L/Kg
- Protein binding: 85%
- Metabolism: hepatic
- $T_{1/2}$= 20-40 hours
- Minimal interactions- clearance increased by inducers

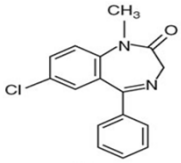
CZP- Adverse effects

- Drowsiness (tolerance to AEs develops)
- Nystagmus, incoordination, ataxia, dysarthria with higher doses
- Behavior disturbances more common in children- aggression, hyperactivity, paranoia
- Withdrawal seizures with abrupt discontinuation

CZP- Clinical use

- Used for long-term treatment as well as acute management- only oral form available in USA
  - Myoclonic seizures
  - Wide spectrum of efficacy against focal and generalized seizure types
- Dose: children- 0.01 to.0.02 mg/kg per day; adults up to 8 mg per day in two or three divided doses.
- Tolerance may develop to therapeutic effect

Diazepam (DZP)



- Bioavailability >90%
- Tmax: 1 hour
- V_d= 1-2 L/Kg
- Protein binding: 95%
- **$T_{1/2}$ = 36 hrs; initial $T_{1/2}$ = 1 hr**
- Liver metabolism- active metabolites with long $T_{1/2}$
- Induces CYP2B
- VPA increases free level through displacement from protein binding

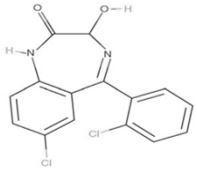
DZP- Adverse effects

- Sedation
- Fatigue, amnesia, ataxia, falls in the elderly
- Blurred vision, diplopia
- Respiratory depression with IV use
- Withdrawal seizures after chronic use

DZP- Clinical use

- Available in oral tablet and liquid form, rectal gel, and parenteral solution
- **Acute use for status epilepticus (but short duration of action requires additional agent), acute repetitive seizures (oral or rectal)**
- **Usually not adequate for chronic use, except that courses can be used in some syndromes such as Landau-Kleffner syndrome and electrical status epilepticus during sleep (ESES)**

Lorazepam (LZP)



- Bioavailability >90%
- Tmax: 1.5-2 hours
- V_d= 1 L/Kg
- Protein binding: 90%
- $T_{1/2}$ = 15 hrs
- Metabolized in the liver through glucuronidation and excreted by the kidneys
- **Clearance reduced by VPA and other inhibitors**

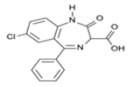
LZP- Adverse effects

- Sedation, dizziness, vertigo, weakness, unsteadiness, dysarthria
- Disorientation, depression, headache, agitation or restlessness, emotional disturbances, hallucinations, delirium
- Impaired psychomotor performance, anterograde amnesia
- Mild respiratory depression with IV use
- Withdrawal seizures from sudden discontinuation

LZP- Clinical use

- Available in oral and parenteral forms
- Can be given sublingually
- Usually not appropriate for chronic use
- **Status epilepticus (longer duration of action than DZP despite shorter half-life**, and less respiratory depression makes it preferable)
- Acute repetitive seizures

Clorazepate (CLZ)



- Bioavailability 100%
- Tmax= 0.5-2 hours
- Protein binding: 96%
- Prodrug, rapidly decarboxylated in the stomach to form the active desmethyldiazepam (DMD- also called nordiazepam) with an average $T_{1/2}$ of ~ 2 days

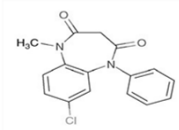
CLZ- Adverse effects

- Drowsiness
- Dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, mental confusion.
- Dependence
- Withdrawal symptoms with discontinuation

CLZ- Clinical use

- FDA approved for management of anxiety disorders and as adjunctive therapy in the management of partial seizures.
- Available in immediate and extended release preparations

Clobazam (CLB)



- **Only 1,5-benzodiazepine ASM**
- Bioavailability >90%
- Tmax= 1-4 hours
- Protein binding: 85%
- $T_{1/2}$= 10-30 hours
- Metabolized in the liver to the active N-desmethylclobazam (T1/2= 42 hrs)
- N-desmethylclobazam is metabolized by CYP2C19- accumulates in presence of inhibitors (such as cannabidiol or cenobamate)

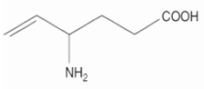
CLB- Adverse effects

- **Less sedation than with 1,4-benzodiazepines**
- Drowsiness, fatigue, ataxia, dizziness, memory disturbance, aggressiveness
- Tolerance may develop, but less than with 1,4-benzodiazepines
- Seizures may occur with acute withdrawal

CLB- Clinical use

- Available in tablets and syrup
- Widely used for long-term treatment of epilepsy
- FDA indicated for Lennox-Gastaut syndrome (adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥2 years)
- Broad spectrum of efficacy, as with other benzodiazepines

Vigabatrin (VGB)



- Initially licensed in Europe in 1989. First approved in the USA in 2009.
- MOA: irreversible inhibition of GABA transaminase (designer drug)

VGB- Absorption, distribution

- Oral bioavailability nearly complete
- Tmax = 1 hour for children and adults, 2.5 hours for infants
- Protein binding: none
- V_d = ~0.8 L/Kg

VGB- Metabolism, elimination

- Not significantly metabolized
- Elimination by excretion in urine, unchanged
- $T_{1/2}$ = 10.5 hours in young adults, 5–6 hours in infants.

VGB- Interactions

- VGB is a weak inducer of CYP2C9
- PHT levels decrease ~20% with addition of VGB

VGB- Adverse effects

- Sedation, fatigue, dizziness, ataxia
- Irritability, behavioral changes, psychosis, depression
- Weight gain
- **Bilateral concentric visual field constriction,** progressive and permanent (up to 30 %- risk increases with dose and duration of Rx)
- **MRI changes in infants-** increased T2 and restricted diffusion in deep white matter, basal ganglia, thalamus, and corpus callosum (asymptomatic and reversible)

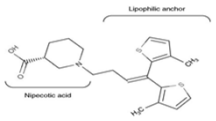
VGB- Efficacy/ Clinical indications

- Effective against focal seizures; may worsen absence and myoclonic seizures in IGE
- FDA indications
  - "Adjunctive therapy for adults and pediatric patients ≥10 years with refractory complex partial seizures who have responded inadequately to several alternative treatments"
  - "Monotherapy in infants with infantile spasms 1 m to 2 yrs of age, for whom the potential benefit outweighs the potential risk of vision loss"

VGB- Monitoring

- **Periodic visual assessment is recommended (at baseline and every 3 months)**
  - perimetry in cooperative adult and pediatric patients.
- Additional optional testing may include electroretinography (ERG) and retinal imaging with optical coherence tomography (OCT)
- Treatment should not be continued if therapeutic benefit is insufficient

Tiagabine (TGB)



- First approved in the USA in 1997.
- MOA: inhibition of GABA uptake at the synapse.
- Requires slow titration

TGB- Absorption, distribution

- Oral bioavailability: 90-95%
- Tmax = 1-1.5 hours
- **Protein binding: 96%**
- V_d = ~1 L/Kg

TGB- Elimination

- Extensively metabolized in the liver; mainly by cytochrome P450 enzyme CYP3A
- 63% excreted in feces, 25% in urine (<2% unchanged)
- $T_{1/2}$ = **7–9 h in monotherapy** (normal volunteers); 2-5 hours with enzyme inducers (epilepsy patients), requiring tid dosing

TGB- Interactions

- TGB does not affect other medications.
- Even though TGB is highly protein bound, levels are low and this is not a source of interaction.
- **TGB metabolism is accelerated by enzyme-inducing drugs.**

TGB- Adverse effects

- Most commonly reported AEs: dizziness, asthenia, nervousness, tremor, depression, emotional lability.
- AEs more common during titration- requires slow titration and tid dosing.
- **Nonconvulsive status epilepticus/ encephalopathy-** dose dependent. **May occur in the absence of epilepsy.**

TGB- Efficacy/ clinical indication

- Effective against focal seizures
- Not effective against, and may exacerbate generalized absence or myoclonic seizures
- FDA approved for adjunctive therapy in adults and children $\geq$12 years in the treatment of partial seizures

Stiripentol

- Approved by FDA in 2018 for the treatment of seizures associated with Dravet syndrome in patients also taking clobazam.
- Mechanism of action may involve both direct interaction with the $GABA_A$ receptor and inhibition of CYP enzyme activity resulting in increased concentration of clobazam and its active metabolite.

AEDs III: Miscellaneous (with Carbonic Anhydrase Inhibition)

Bassel W. Abou-Khalil, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

AEDs III: AEDs WITH CARBONIC ANHYDRASE INHIBITION

Bassel Abou-Khalil, MD
Professor of Neurology
Director of the Epilepsy Center
Vanderbilt University Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - Dosing schedule of zonisamide

ASMs with Carbonic Anhydrase Inhibition

Bassel Abou-Khalil, MD

Objectives

- Review the mechanism of carbonic anhydrase inhibition
- Review pharmacokinetics of TPM, ZNS, AZM
- Review key interactions of above
- Review main adverse effects of above
- Review clinical use of above

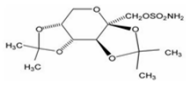
ASM main mechanisms of action

- Na channel blocking
- Enhancing GABA
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Modulation of intra-cellular calcium
- Binding synaptic vesicle protein SV2A
- **Carbonic anhydrase inhibition**

Carbonic anhydrase inhibition

- Increases carbon dioxide, which may increase seizure threshold.
- Increase in brain carbon dioxide has been associated with an increase in GABA.
- Likely a minor mechanism

Topiramate (TPM)



- Sulfamate-substituted monosaccharide
- Approved in USA in 1996.
- MOA: **multiple mechanisms**, including
  - blocking of voltage-gated sodium channels
  - augmentation of GABA activity
  - antagonism of AMPA/kainate receptors
  - inhibition of high-threshold activated Ca channels
  - weak inhibition of carbonic anhydrase activity

TPM- Absorption, distribution

- Oral bioavailability ~80-95 %
- Tmax = 1.5-4 hours
- Protein binding: 15-40%
- V_d = ~0.7 L/Kg

TPM- Metabolism, elimination

- Metabolism: **not extensively metabolized**
- **70% eliminated unchanged in the urine**
- hepatic metabolism by P450 enzyme system- metabolites formed via hydroxylation, hydrolysis, and glucuronidation.
- There is **evidence of renal tubular reabsorption**
- $T_{1/2}$ = ~21 hours

TPM- Interactions

- Drug interactions are minimal.
- Enzyme inducing ASMs may reduce TPM levels by up to 50%
- **Mild inhibitor of CYP2C19** (may increase PHT levels at higher dose) and a **mild inducer of CYP3A4** (may decrease OCP efficacy at dose ≥200 mg/day)
- **May cause hyperammonemia when co-administered with VPA**

TPM- Adverse effects

- Sedation, fatigue, dizziness, ataxia (helped by slower titration)
- **Memory disturbance; word finding difficulty; cognitive slowing- patients may not be aware of these**
- Depression
- Kidney stones (1.5%)
- **Acute myopia and secondary angle closure glaucoma**
- **Paresthesias** (decrease over time- helped by K supplementation)
- **Oligohydrosis**, hyperthermia (in children)
- **Metabolic acidosis**
- Weight loss
- Increased risk of birth defects in exposed infants, mainly oral clefts- lip or palate; low birth weight

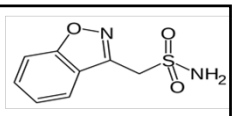
TPM- Clinical use and efficacy

- **Broad spectrum ASM, but not effective against absence** in a controlled randomized trial
- FDA indications:
  - Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures
  - Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)
  - Prophylaxis of migraine in adults and adolescents ≥12 years
- **Requires slow titration to improve tolerability** (25 mg/wk, up to 100-400 mg)

TPM- Monitoring

- Suggested therapeutic range: 5–20 mg/L

Zonisamide (ZNS)



- Structurally related to sulfonamides
- Approved in Japan in 1989. First approved in the USA in 2000.
- MOA: **multiple mechanisms:** blocks sodium channels (blocks sustained repetitive firing), **reduces T-type Ca currents**, weakly inhibits carbonic anhydrase (100-200 times less potent than acetazolamide)

ZNS- Absorption, distribution

- Oral absolute bioavailability: ~100 %
- Tmax = 2-5 h after oral dosing, 4-6 h with food
- Protein binding: 40-50%
- V_d = 0.9–1.4 L/kg

ZNS- Metabolism, elimination

- **Hepatic metabolism** by acetylation and reduction (mediated by CYP 3A4), then glucuronidation- metabolites inactive
- Cleared by renal excretion
- **$T_{1/2}$ = ~ 60 hours**

ZNS- Interactions

- Not a hepatic enzyme inducer or inhibitor- has no effect on pharmacokinetics of other commonly used ASMs
- **Affected by CYP 3A4 inducers or inhibitors**
  - Addition of enzyme-inducing ASMs decreases ZNS half-life and plasma level
  - ZNS concentration increased by CYP3A4 inhibitors (e.g. ketoconazole, cyclosporine)

ZNS- Adverse effects

- Sedation, ataxia, dizziness, nausea, anorexia, fatigue, agitation/irritability
- Weight loss
- **Cognitive slowing**, difficulty with concentration
- **Kidney stones** (up to 4%)
- Depression, psychosis
- Rare serious rash (SJS and TEN)
- **Oligohydrosis and hyperthermia** (in children)
- Metabolic acidosis

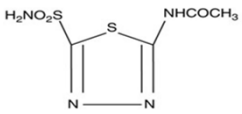
ZNS- Efficacy/clinical indication

- Broad spectrum agent; class I trials only for focal epilepsy
- FDA indication: adjunctive therapy in the treatment of partial seizures in adults with epilepsy
- In Europe it is indicated as initial monotherapy for partial seizures. In Japan it is also indicated as monotherapy for generalized seizures (tonic, tonic-clonic, and atypical absence)
- Start at 100 mg daily, titrate Q 2 weeks- long $T_{1/2}$ allows once daily dosing off label

ZNS- Monitoring

- Suggested therapeutic range: 10-40 mg/L

Acetazolamide (AZM)



- Carbonic anhydrase inhibitor
- **Bioavailability complete with low dose, decreases with increasing dose**
- Tmax= 2–4 hrs
- **Protein binding: 90–95%**
- V_d: 1.8 L/kg
- $T_{1/2}$= 10–12 h
- Partially metabolized; 80% excreted by tubular secretion

AZM- Adverse effects

- Altered taste perception (flat), loss of appetite, drowsiness, paresthesias
- Renal stones particularly in combination with topiramate, zonisamide, or ketogenic diet
- Metabolic acidosis
- Rare idiosyncratic: rash, hypersensitivity reactions, Steven Johnson syndrome, toxic epidermal necrolysis
- Rare muscle weakness, hepatic dysfunction

AZM- Clinical use

- Adjunctive therapy for refractory focal and generalized epilepsies, particularly absence [FDA indication "centrencephalic epilepsies (petit mal, unlocalized seizures)]
- Adjunctive therapy for catamenial epilepsy, starting 2 days before predicted exacerbation
- Start at 250 mg/day and increase weekly based on response, up to 500–1,000 mg/day in 2-3 divided doses.
- Evidence for efficacy class 4 or anecdotal.

AEDs IV: Miscellaneous

Bassel W. Abou-Khalil, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

AEDs IV: MISCELLANEOUS AEDs

Bassel Abou-Khalil, MD
Professor of Neurology
Director of the Epilepsy Center
Vanderbilt University Medical Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - Use of valproic acid for myoclonic and tonic-clonic seizures
  - Use of perampanel for myoclonic seizures

Objectives

- Review the mechanism of remaining ASMs
- Review pharmacokinetics of VPA, ESM, FBM, GBP, PGB, LEV, BRV, PER, CBD, CNB
- Review key interactions of remaining ASMs
- Review main adverse effects of remaining ASMs
- Review clinical use of remaining ASMs

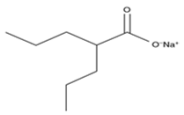
ASM main mechanisms of action

- Na channel blocking
- Enhancing GABA
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Modulation of intracellular calcium
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Binding synaptic vesicle protein SV2A
- Carbonic anhydrase inhibition

Key known ASM mechanisms

ASM	Block Na Channels	Enhancing GABA	Glutamate antagonism	T Ca channels	α2δ Ca Ch subunit	SV2A	Other	Carbonic anhydrase
Phenobarbital/ primidone		X	X					
Phenytoin	X							
Ethosuximide				X				
Clonazepam/ Clobazam		X						
Carbamazepine	X							
Valproate	X	X		X				
Felbamate	X	X	X					
Gabapentin/ Pregabalin					X			
Lamotrigine	X							
Topiramate	X	X	X					X
Tiagabine		X						
Levetiracetam/ Brivaracetam						X		
Oxcarbazepine/ Eslicarbazepine	X							
Zonisamide	X			X				X
Lacosamide	X							
Rufinamide	X							
Vigabatrin		X						
Perampanel			X					
Cannabidiol		X					X	
Cenobamate	X	X						

Valproate-divalproex (VPA)



- Serendipitous discovery (was used as solvent for ASMs in testing).
- Short-chain, branched fatty acid
- MOA: multiple mechanisms including blocking of Na channels, GABA potentiation, blocking T-calcium channels
- Main form used clinically is divalproex sodium, a complex composed of equal parts of VPA and sodium valproate

VPA- Formulations

- Preparations include immediate-release VPA capsules, tablets, and syrup; delayed release enteric coated tablets of divalproex sodium (rapid release after coating dissolved) ; divalproex sodium enteric-coated sprinkles; extended release (ER) divalproex sodium; parenteral sodium valproate.

VPA- Absorption, distribution

- Bioavailability almost complete; 90% for ER
- **Tmax depends on preparation**
  - ~2 hrs after syrup; 3-8 hrs after enteric coated divalproex DR; 4-17 hours after divalproex ER
- V_d= 0.13-0.19 L/kg in adults and 0.20-0.30 L/kg in children.
- **Protein binding ~90%; free fraction increases with increasing total concentration.**
  - 30% at 150 mg/L

VPA- Metabolism, elimination

- Metabolized by p450 enzyme system
- $T_{1/2}$ depends on inducing co-medication
  - Adults: 13 -16 hours without induction; 9 hours with EIASMs.
  - Children: 11.7 and 7 hours
- Most abundant metabolites glucuronide and 3-oxo-VPA.

VPA- Interactions

- Its metabolism is induced by PHT, CBZ, PB
  - Levels increase after withdrawal of EIASMs
- It can inhibit metabolism of PB, LTG, RFM, CBZ-epoxide
- **It may compete for protein binding with PHT**
- Its levels increase with co-administration of felbamate and clobazam

VPA- Adverse effects

- Gastric irritation with nausea, vomiting, GI distress, anorexia (less with enteric coated and ER formulation).
- Tremor
- Weight gain
- Hair loss
- Peripheral edema
- Thrombocytopenia
- Drowsiness, lethargy, confusion
- Reversible dementia and brain atrophy- more in seniors
- Encephalopathy with polytherapy
- Hyperammonemia, carnitine deficiency

VPA- Idiosyncratic AEs

- Fatal hepatotoxicity (risk factors are polytherapy and young age- high risk with POLG mutation)
  - 1:600 at < 3 y; 1:8,000 at 3-10 y, 1:10,000 at 11-20 y; 1:31,000 at 21-40 y; 1:107,000 at >40 y
- Pancreatitis

VPA- Teratogenicity

- Dose-related teratogenicity rate higher than any othermarketed AED
  - Risk of major malformations >30% at doses greater than 1100 mg/d
- In utero exposure also associated with dose-dependent reduced verbal IQ and autism

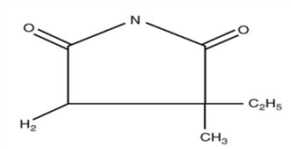
VPA- Efficacy and clinical indications

- **Official FDA indication is for generalized absence and partial-onset seizures**
- **Broad spectrum of efficacy against focal and all generalized-onset seizures, including myoclonic seizures.**
- **Most effective ASM for IGE with generalized tonic-clonic seizures, but should be avoided in women of child-bearing potential**
- Also indicated for migraine prophylaxis and bipolar disorder

A comparison of VPA with CBZ for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. **Mattson et al, NEJM 1992**

- Multicenter, DB trial of VPA vs CBZ in 480 adults with CPS or SGTCS
- Patients randomly assigned to CBZ or VPA at doses adjusted to achieve blood levels in the mid-therapeutic range.
- Patients followed for 1-5 years, until seizures became uncontrollable, treatment had unacceptable adverse effects, or both.
- **For control of SGTC, CBZ and VPA were comparably effective**.
- For CPS, 4/5 measures favored CBZ: total # of seizures, # of seizures per month, time to first seizure, and seizure-rating score.
- CBZ was superior according to a composite score of seizure control and adverse effects. VPA was associated with weight gain >12 lb, hair loss, and tremor. Rash was more common with CBZ.
- **VPA is as effective as CBZ for treatment of SGTC, but CBZ provides better control of CPS and has fewer long-term adverse effects.**

Ethosuximide (ESM)



- MOA: **blockade of T-type calcium currents in thalamus**

ESM- Absorption, distribution

- **Oral bioavailability 90% to 95%**
- Tmax= 1-4 hours
- Vd= 0.65 L/Kg
- **Protein binding: <10%**

ESM- Metabolism, elimination

- Extensive hepatic oxidative biotransformation to inactive metabolite by CYP3A>> CYP2El.
- **$T_{1/2}$= 30-60 hours** (shorter in children)

ESM- Interactions

- No effect on hepatic p450 enzymes and low protein binding predict low potential for causing interactions.
  - reduced VPA level in one study
- Susceptible to interactions from inducers and inhibitors of p450 enzyme system.
  - Clearance increased with enzyme inducers
  - Clearance may decrease with VPA, isoniazid

ESM- Adverse effects

- Most AEs are dose related- helped by dividing dose and administration with meals
  - Nausea, abdominal discomfort, anorexia, vomiting. and diarrhea
  - Drowsiness, insomnia, nervousness, dizziness, hiccups, fatigue, ataxia, and behavior changes (aggression, irritability, hyperactivity)
  - Granulocytopenia
- Headaches, psychosis, depression, hallucinations (visual or auditory) not clearly dose related

ESM- Idiosyncratic AEs

- Rash, Stevens-Johnson syndrome, SLE
- Aplastic anemia, thrombocytopenia, agranulocytosis (rare)
- Autoimmune thyroiditis (rare)

ESM- Efficacy and clinical indications

- **First-line monotherapy against typical absence seizures.**
- Comparative trial favored its tolerability over valproate and efficacy over lamotrigine.
- Narrow spectrum ASM- not effective against any other seizure type.

ESM- Monitoring

- Therapeutic range: 40-100 mg/L
- CBC can be checked before and after 2-3 months of treatment. Continued routine monitoring of CBC not useful.
- CBC should be obtained if there are signs or symptoms of infection. If the WBC count < 3.5 K or granulocytes less than 25% of the total WBC count, consider reducing ESM dose

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy

- **Double-blind, randomized, controlled clinical trial to compare the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine** in 453 children with newly diagnosed childhood absence epilepsy
- ASM doses were increased until child was free of seizures, maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met
- **The primary outcome measure was freedom from treatment failure after 16 weeks of therapy**
- **Secondary outcome measure was attentional dysfunction**

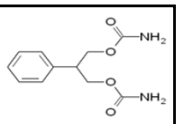
Glauser et al, NEJM 2010

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy- Results

- 453 children randomly assigned to ethosuximide (156), lamotrigine (149), or valproic acid (148)
- **After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar (53% and 58%, respectively) and were higher than the rate for lamotrigine (29%)**
- There were no significant differences among the three drugs in discontinuation because of adverse events
- **Attentional dysfunction was more common with valproic acid than with ethosuximide** (in 49% of the children vs. 33%; P=0.03)
- **Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects**

Glauser et al, NEJM 2010

Felbamate (FBM)



- Approved in USA in 1993.
- FDA indication: monotherapy or adjunctive therapy for partial epilepsy in adult and pediatric patients, adjunctive therapy for Lennox-Gastaut syndrome
- MOA: **NMDA antagonism**, enhancing GABA, blocking sodium channels, blocking high voltage activated calcium channels

FBM- Absorption, distribution

- Oral bioavailability: >90%
- Tmax = 2-6 hours
- Protein binding: ~25%
- V_d = ~0.75 L/Kg

FBM- Metabolism, elimination

- Metabolism: hepatic via CYP3A4
- ~ 40-50% of absorbed dose appears unchanged in urine, and the rest as inactive metabolites and conjugates.
- $T_{1/2}$ = **20-23 hours** (shorter in children or with enzyme induction)

FBM- Interactions

- FBM is an **inhibitor of CYP2C19**, CYP1A2, and ß-oxidation
  - Inhibits metabolism and increases levels of PB, PHT, VPA, CBZ-epoxide, and coumadin
- FBM **induces CYP3A4**
  - Decreases CBZ level
  - Decreases OCP efficacy
- Enzyme-inducing ASMs decrease FBM level

FBM- Adverse effects

- Common:
  - Anorexia, nausea, vomiting, weight loss.
  - Insomnia, irritability, headache
- Serious idiosynchratic
  - **Aplastic Anemia** (estimated risk 1 in 5,000-8,000, not reported below age 13)- onset after 2.5-6 months
    - Risk factors: prior cytopenia, allergy or significant toxicity to an ASM, underlying autoimmune disease.
  - **Hepatic Failure** (estimated risk: 1 in 26,000-34,000)- onset after 25-939 days (mean 217)

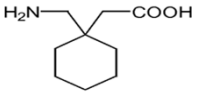
FBM- Efficacy, clinical use

- Broad spectrum ASM
- FDA indications:
  - not indicated as a first line treatment.
  - recommended only in those who respond inadequately to alternative treatments and whose epilepsy is so severe that risk of aplastic anemia and/or liver failure is deemed acceptable.
  - written, informed consent
  - either monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

FBM- Monitoring

- CBC and LFTs should be obtained prior to starting FBM, monitored regularly, Q2 weeks initially, Q 2-3 months after 6 months, then every 6 months after the first year.
- Felbamate suggested therapeutic range: 40-100 mg/L

Gabapentin (GBP)



- Approved in USA in 1994
- FDA indications:
  - adjunctive therapy in adult and pediatric (≥3 years) patients for partial seizures
  - management of postherpetic neuralgia in adults
- MOA: binds to α2δ subunit of voltage-gated Ca channels (reducing influx of calcium and reducing neurotransmitter release under hyper-excitable conditions)
- No interaction with GABA receptors

GBP- Absorption, distribution

- **Transport into blood by L-amino acid transport system, which is saturable**
- **Oral bioavailability low**, with considerable inter-subject variability, and **decreases with increasing GBP dose** (60% after 300 mg, 29% for 1600 mg tid, 36% for 1200 mg Qid)
- Tmax = 2-3 hours
- **Protein binding: <3%**
- V_d = 0.6-0.8 L/Kg

GBP- Metabolism, elimination

- **Not metabolized in humans**
- **Eliminated unchanged in the urine**
- $T_{1/2}$ = 5-7 hours
- Requires dose reduction with renal impairment

GBP- Interactions

- Antacids including aluminum hydroxide or magnesium hydroxide taken within 2 hours before GBP may decrease GBP bioavailability by up to 20%
- No known interactions (predicted by absence of metabolism, absence of enzyme induction or inhibition, and absence of protein binding)

GBP- Adverse effects

- Sedation
- Dizziness, ataxia, asthenia
- Weight gain
- **Myoclonus**
- Cognitive slowing in elderly
- Emotional lability, hostility in children

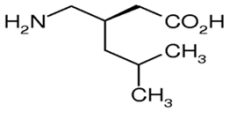
GBP- Efficacy, clinical use

- Under-dosed in clinical trials- dose can go to 4800 mg per day (3-4 divided doses)
- Narrow spectrum agent against focal seizures
- **Failed trials against absence and 1ary GTC seizures**
- May cause exacerbation of myoclonic seizures
- FDA approved for adjunctive therapy for partial seizures and for postherpetic neuralgia- extended release preparation (GBP enacarbil) for RLS and another (gastroretentive dosage form) for postherpetic neuralgia
- Primarily used off label for pain and other nonepileptic indications

GBP- Monitoring

- Optimal therapeutic plasma concentration not established
- Suggested therapeutic plasma concentration range: 2–20 mg/L

Pregabalin (PGB)



- Approved in USA in 2005
- MOA: binds to α2δ subunit of voltage-gated Ca channels (reducing influx of calcium and reducing neurotransmitter release under hyper-excitable conditions)

PGB- Absorption, distribution

- Oral bioavailability: ≥90 %, **independent of dose**
- Tmax = 1 hours (delayed to 3 hours with food)
- **Protein binding: none**
- V_d = ~0.5 L/Kg

PGB- Metabolism, elimination

- **Not metabolized in humans**
- Excreted unchanged in the urine (requires dose reduction with renal impairment)
- $T_{1/2}$ = ~ 6 hours

PGB- Interactions

- No known pharmacokinetic interactions (which is predicted by absence of metabolism, absence of enzyme induction or inhibition, and absence of protein binding)

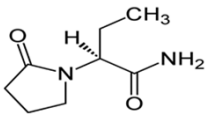
PGB- Adverse effects

- Somnolence
- Dizziness, ataxia, blurred vision, asthenia
- **Increased appetite, weight gain**
- **Peripheral edema**
- **Myoclonus**

PGB- Efficacy, clinical use

- **Narrow spectrum against focal-onset seizures**
- FDA indications:
  - Adjunctive therapy for adult patients with partial onset seizures
  - Neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, fibromyalgia
- Optimal therapeutic level unknown. Range of concentration at effective doses of 300-600 mg per day: 2.8–8.2 mg/L

Levetiracetam (LEV)



- Approved in USA in 1999
- MOA: **binding to the synaptic vesicle protein SV2A**
  - seems to result in nonspecific decrease in neurotransmitter release.
  - functional correlation between SV2A binding affinity and anticonvulsant potency of levetiracetam analogs
- Available in oral and IV formulations.

LEV- Absorption, distribution

- Oral absolute bioavailability ~100 %
- Tmax = ~1 hour (1.5 hours with food)
- **Protein binding: <10%**
- V_d = ~0.6 L/Kg

LEV- Metabolism, elimination

- **No hepatic metabolism**
- Partly hydrolyzed to inactive compounds
- 66% excreted unchanged in the urine
- $T_{1/2}$ = 6-8 hours (shorter in children, longer in the elderly)

LEV- Interactions

- No known significant pharmacokinetic interactions
- Some studies have suggested lower LEV levels in presence of enzyme inducers

LEV- Adverse effects

- Somnolence
- Dizziness, asthenia
- **Irritability**, hostility (more common in children)- pyridoxine supplementation may be helpful anecdotally
  - Risk factors for behavioral adverse effects: symptomatic generalized epilepsy, history of psychiatric diagnosis, faster LEV titration
- Rare psychosis

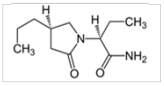
LEV- Efficacy, clinical use

- Broad spectrum agent
- Official FDA indications:
  - adjunctive therapy for partial onset seizures in adults and children ≥ 1 month.
  - adjunctive therapy for myoclonic seizures in adults and adolescents > 12 years with juvenile myoclonic epilepsy.
  - adjunctive therapy for primary generalized tonic-clonic seizures in adults and children > 6 years of age and older with idiopathic generalized epilepsy.
- Approved for initial monotherapy in Europe

LEV- Monitoring

- Optimal therapeutic level unknown
- One study suggested 11 mg/L may be a threshold concentration for a therapeutic response. Upper limit of therapeutic range unknown.

Brivaracetam (BRV)



- Approved in USA in 2016
- MOA: binding synaptic vesicle protein 2A (SV2A) with ~20-fold higher affinity for than levetiracetam
- Higher brain permeability than levetiracetam
- Broad spectrum in preclinical models

BRV- Pharmakokinetics

- Bioavailability ~100%
- Weakly bound to plasma proteins (~17.5%)
- Half-life ~ 9 h
- Renally excreted following extensive metabolism, primarily by hydrolysis and to a lesser extent by CYP-dependent hydroxylation (main isoenzyme responsible for hydroxylation is CYP2C19)

BRV - Interactions

- Enzyme inducers (PHT, CBZ, PhB) reduce BRV levels
- BRV may increase CBZ-epoxide; may increase PHT concentration by up to 20%

BRV- Clinical Studies

- 100 and 200 mg doses more effective than placebo for all outcome measures; responder rates 38.9 and 37.8% (Klein et al, 2015)
- 20 and 50 mg efficacy inconsistent across studies
- Not effective in patients taking levetiracetam
- Efficacy numbers better in levetiracetam naïve patients that in patients who failed levetiracetam (but could be because latter group is more drug-resistant)

BRV- Adverse effects

- Somnolence, dizziness and fatigue most common AEs
- The incidence of irritability was 0.4% PBO; 3.2% BRV 100 mg/day, 2.8% BRV 200 mg/day

Reduction of behavioral adverse events (BAEs) associated with LEV by switching to BRV

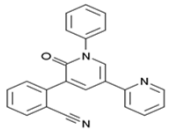
Yales et al, Epilepsy & Behavior 2015

- 27/29 (93.1%) patients switched to BRV had clinically meaningful reductions in BAEs.
- HRQoL scores improved.
- Patients experiencing BAEs associated with LEV may benefit from switching to BRV.

BRV - Clinical Use

- Broad spectrum agent (but only approved for focal seizures)
- FDA indication: treatment of partial-onset seizures in patients $\geq$ 4 years of age (FDA extrapolation policy).
- Available in oral tablets (10, 25, 50, 75, 100 mg), oral solution (10 mg/ml), injection (10 mg/ml) for oral replacement
- Injection is FDA approved only in adult patients ($\geq$16 years of age)

Perampanel (PER)



- Approved in USA in 2012
- MOA: noncompetitive antagonism of AMPA glutamate receptor

PER- Absorption, distribution

- Oral absolute bioavailability: ~100%
- Tmax = 1 hour
- **Protein binding: ~95%**
- V_d= ~77 L

PER- Metabolism, elimination

- Extensively metabolized by primary oxidation mediated by CYP3A followed by glucuronidation
- Excretion: as inactive metabolites, 30% in the urine and 70% in the feces.
- $T_{1/2}$ = **105 hours** (average).

PER- Interactions

- PER does not have a clinically significant effect on other ASMs
- PER dose of 12 mg (not 8 mg) reduces levonorgestrel by ~40%
- Enzyme-inducers decrease PER levels

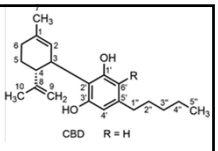
PER- Adverse effects

- Dizziness, somnolence, headache, fatigue, ataxia, blurred vision most common
- Aggression, hostility (black box warning- 20% at 12 mg)

PER- Efficacy and clinical use

- Broad spectrum agent
- FDA indication
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older
  - Adjunctive therapy for primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older
- Case series suggest potentially dramatic efficacy in progressive myoclonic epilepsies

Cannabidiol (CBD)



- First marketed in the USA in 2018.
- Cannabinoid, but does not interact with the cannabinoid receptor CB1
- Does not share THC psychoactive properties
- May enhance GABA activity through allosteric modulation of the $GABA_A$ receptor and enhancement of currents elicited by low GABA concentrations
- Modulates intracellular calcium
- Possible anti-inflammatory effects (adenosine)

CBD- Absorption, distribution

- Oral bioavailability is low: administration with a high-fat/high-calorie meal increased Cmax by 5-fold, AUC by 4-fold
- Tmax = 2.5 to 5 hours
- **Protein binding: >94%**

CBD- Elimination

- Extensively metabolized primarily in the liver by CYP2C19 and 3A4, and UGT1A7, 1A9, and 2B7, to an active (7-OH-CBD) and then inactive metabolite (7-COOH-CBD)
- Excretion: in feces, with minor renal clearance.
- $T_{1/2}$= 56-61 hours

CBD- Interactions

- CBD clearance is increased by CYP2C19 and CYP3A4 inducers and decreased by inhibitors
- Potential to inhibit CYP2C8, CYP2C9, and CYP2C19 as well as UGT1A9 and UGT2B7
- Most important interaction is with clobazam
  - CBD increased clobazam active metabolite, N-desmethylclobazam up to 3-fold
  - CLB increased CBD active metabolite 7-OH CBD
- No interaction with valproate

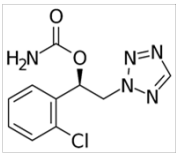
CBD- adverse effects

- Sedation, fatigue
- Decreased appetite, diarrhea
- Increased liver enzymes, particularly when used with valproate
  - check liver enzymes, bilirubin before, and 1, 3, and 6 months after starting treatment

CBD- efficacy, clinical indications

- FDA indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older based on blinded controlled trials.
- Open-label trials also suggest efficacy for other forms of epilepsy.
- Artisanal cannabidiol formulations are used without prescription by many patients with epilepsy in the United States.

Cenobamate (CNB)



- Approved in 2019
- MOA:
  - Sodium channel antagonism- reduces repetitive neuronal firing by inhibiting voltage-gated sodium currents.
  - Enhancing GABA- positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel.

CNB- Absorption, distribution

- Oral absolute bioavailability: ~88%
- Tmax = 1-4 hour
- **Protein binding: ~60%**
- V_d= ~40-50 L

CNB- Metabolism, elimination

- Extensively metabolized by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.
- Excretion: 87% in urine, mostly as inactive metabolites- 6.4% unchanged
- $T_{1/2}$ = **50-60 hours**.

CNB- Interactions

- Phenytoin, an enzyme inducer, reduces CNB level
- CNB inhibits **CYP2C19 (increased concentrations of phenytoin, phenobarbital, N-desmethylclobazam)**
- CNB induces **CYP3A4 (affects oral contraceptives, carbamazepine),** CYP2B6
- CNB decreases lamotrigine concentration
- CNB not a substrate for drug transporter proteins

CNB- Adverse effects

- Somnolence, dizziness, headache, fatigue, ataxia, diplopia, constipation, nausea
- Rare cases of DRESS syndrome, not seen after slowing the titration rate

CNB- Efficacy and clinical use

- FDA indication
  - Treatment of partial-onset seizures in adult patients
- Unusual efficacy against focal seizures
  - Seizure-free rate: study 1: 27.5% CNB 200 mg vs 9.1% placebo; study 2: 11% CNB 200 mg, 21% CNB 400 mg vs 1% placebo
- Slow titration required: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, with 2 weeks for each step; the dose can be increased again by 50 mg every 2 weeks, up to 400 mg per day

Principles of Management I & II

Pavel Klein, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

Principles of Management I

Pavel Klein, MD
Neurologist, Mid-Atlantic Epilepsy and Sleep Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **Consulting Fee (Member/Medical Advisory Board) - Alliance**
  - **Speaker Fee - Aquestive, Eisai, Sunovion;**
  - **Consulting/Speaker Fee - UCB Pharma**
- **Off-Label Usage**
  - **Treatment of epilepsy**

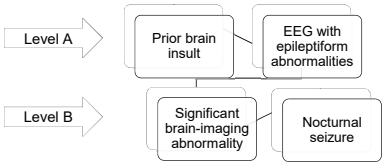
1st Unprovoked Seizure: Risk of Seizure Recurrence

- 24-74% within 5 years
  - Idiopathic & normal EEG: 24%
  - Remote symptomatic, with + EEG: 74%
  - 75+% after 2nd seizure
- ↑ Risk Factors:
  - + Family History, exam, EEG, MRI
  - Etiology: remote symptomatic, CNS lesion
  - Seizure at night/in sleep
  - Pre-treatment seizure number
- Unimportant: seizure duration (adults)

Berg AT. Neurology 1991;41:965-72
Hauser WA NEJM 1998;338:429-434

AES/AAN Guidelines: Management of an unprovoked first seizure in adults

Recurrence risk is greatest early in the first 2 years (21%–45%) Clinical variables associated with increased risk:



- Immediate medical therapy, compared with treatment delay until a second seizure, reduces recurrence risk in the first 2 years but may not improve quality of life

Krumholz A, et al, Neurology. 2015;84:1705–1713.

Krumholz A,Neurology 2015;84:1705-13

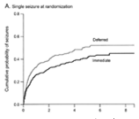
1st Unprovoked Seizure: Timing of Recurrence

- 50% of recurrence occurs within 6 months after initial seizure,
- 80% within 2 years
- Interval between 1st and 2nd seizure: 10-18 weeks
- When treatment is delayed, # of seizures before treatment correlates negatively with long term treatment outcome

Berg AT. Neurology 1991;41:965-72
Hauser WA NEJM 1998;338:429-434

1st Seizure – to Treat or not to Treat

- Treatment reduces recurrence by 35-50%
- No difference in long term outcome for 2 years remission after 5 years follow up
- Recommendation: No treatment until second seizure

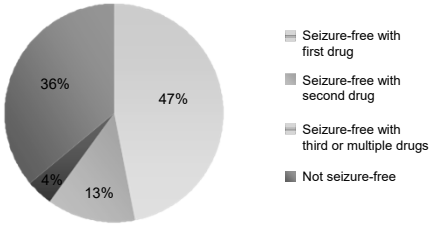


1. AED treatment does not prevent epilepsy
2. May be considered where the benefits of a second seizure prevention outweigh the risks:
   + FH, Exam, EEG, MRI;
   social considerations

Hirtz D et al.Neurology. 2003;60:166-75
1st Seizure Trial Group.Neurology 1993;43:478-483
[1]Marson et al. Lancet 2005;365:2007-13

Success with AED Treatment

Previously untreated patient with epilepsy (N = 470)



Kwan P, et al. N Engl J Med. 2000;342:314-319.

Sz Relapse Risk after AED Withdrawal (1)

- Higher if AEDs are withdrawn after 1 year remission but same if after 2 or 4 years
- Seizure freedom for > 2 years: 60% chance of successful AED withdrawal
- At 4 years, the rates are identical

Shinnar S. Ann Neurol 1994;35:534-45

Predictors of Seizure Freedom after AED Withdrawal

- Favorable factors:
  Sz controlled easily, e.g. one drug at low dose
  Normal exam, EEG, MRI
  PGE except JME
  "Benign" syndrome (Rolandic etc.)
- Poor factors:
  High # of seizures before treatment; "seizure density"
  Long epilepsy duration, several failed AEDs
  Previous unsuccessful withdrawal
  Abnormal EEG before withdrawal
  Remote symptomatic epilepsy
  + Family History

Shinnar S. Ann Neurol 1994;35:534-45

Timing of AED withdrawal and Sz Relapse

- When relapse occurs, it occurs early
  - 50% within 6 months of AED withdrawal
  - 60-90% 1 year
- Late recurrences are uncommon
- Speed of taper: 6 weeks vs. 9 months had similar relapse rates at 2 years
- Consider relative risks/benefits (e.g., driving, pregnancy)

Sirven J. Cochrane Database Syst rev.2001;3:CD001902

Treatment Goals

- Seizure Freedom
- No side effects

- Monotherapy
- Easy regimen to follow

Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2011.

Treatment Concepts

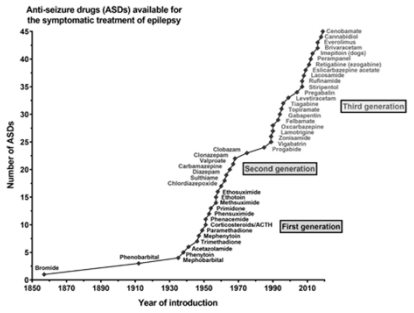
- Initiate treatment with a single drug
- Least possible side effects for given patient
- Compliance - qd vs bid vs tid
- Assess treatment based on clinical response (+/- lab monitoring)
- Treat till: seizure control or toxicity
- In Rx failure, substitute 2nd drug; then possibly a third, or polypharmacy x1, then evaluate for surgery

Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2011.

History of Antiepileptic Drug Therapy in the US

1857 – bromides
1912 – phenobarbital (PB)
1937 – phenytoin (PHT)
1944 – trimethadione
1954 – primidone
1958 – ACTH
1960 – ethosuximide (ESM)
1963 – diazepam
1974 – carbamazepine (CBZ)
1975 – clonazepam (CZP)
1978 – valproate (VPA)
1993 – felbamate (FBM), gabapentin (GBP)
1995 – lamotrigine (LMT)
1997 – topiramate (TPM), tiagabine (TGB)
1999 – levetiracetam (LEV)
2000 – oxcarbazepine (OXC), zonisamide (ZNS)
2005 - pregabalin (PGB)
2009 – lacosamide (LCM), rufinamide (RUF) vigabatrin (VGB)
2011 – clobazam (CBZ)
2012 - ezogabine (EZB) perampanel (PMP)
2014- eslicarbazepine (ESL)
2016- brivaracetam (BRV)
2018 – cannabidiol (CBD) everolimus
2019- stiripentol, cenobamate

AEDs: 1858-2020

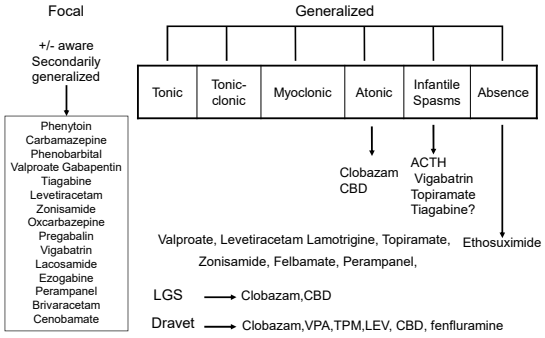


Loscher W, Klein P. Neuropharmacology 2020;

AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

AED Options



AED Treatment by Epilepsy/ Seizure Type

- **Primarily Generalized Epilepsies:** valproate, levetiracetam, lamotrigine, topiramate, zonisamide, ethosuximide (absence only), clobazam (atonic), felbamate, perampanel
- **Focal epilepsies:** All except ethosuximide
- **Special syndromes: Infantile spasms:** ACTH, Vigabatrin
  LGS: clobazam, cannabidiol
  Dravet's: CLB, VPA,TPM, LEV, cannabidiol, fenfluramine

Possible Seizure Exacerbation by AEDs

	CBZ	PHT	LTG	GBP	VGB	TGB	BDZ	VPA
Absence	+	+		+	+	+		
Myoclonic	+	+	+	+	+			
Juvenile myoclonic epilepsy	+	+	+					
Lennox-Gastaut syndrome	+	+	+	+	+		+	
Benign epilepsy of childhood with centro-temporal spikes	+							
Severe myoclonic epilepsy in infancy (Dravet syndrome)	+	+	+	+	+			
Landau-Kleffner syndrome/ electrical status epilepticus during slow sleep	+	+						

Bourgeois BF. Epilepsia. 2003;44(suppl 2):27-32.

AED Selection Criteria

- **Epilepsy type**
- **Mechanism of action**

In monotherapy, it does not matter!

In pharmacoresistance - Rational Polypharmacy?

AED Mechanisms of Action

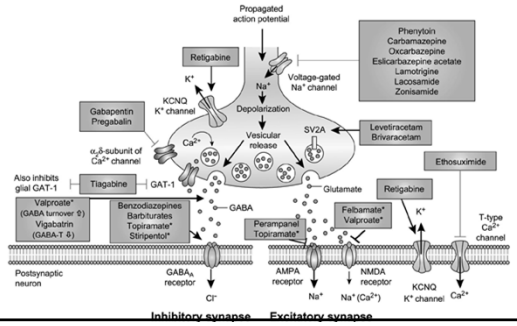
Often have multiple MOAs

- Sodium channel blockers: Phenytoin, Carbamazepine, Oxcarbazepine, Eslicarbazepine Lamotrigine, Topiramate Lacosamide, Cenobamate
- K channel opener: Ezogabine (withdrawn from market 6/2017)
- Ca channel blockers: Ethosuximide (T), Gabapentin, Pregabalin (α-2δ)
- GABA-potentiators: Benzodiazepines (incl. Clobazam), Barbiturates, cenobamate Valproate, Tiagabine,
- Anti-glutamatergic: Felbamate, topiramate, perampanel (AMPA)
- SV2A protein: Levetiracetam, Brivaracetam
- M-Tor inhibition: Everolimus
- Uncertain: CBD
- Multiple: Topiramate,Felbamate

AEDs: different mechanisms of action

	Mechanism of action	AED
1	Na channel	PHT, CBZ, LMT, OXC, Esli
	Na channel, slow inactivation	Lacosamide
	Na channel, persistent current	Cenobamate
2	GABA	PB, VPA, TGB, Benzodiazepines, clobazam
3	Ca channel, T type	Ethosuximide
4	Ca channel, α2/δ receptor	GBP, PGB
5	*K channel, M current*	*Ezogabine*
6	Sv2A	Lev, Briv
7	Glutamate- AMPA	Perampanel (topiramate,felbamate)
8	Multiple	TPM, FBM
9	Uncertain	CBD

Mechanism of Actions of AEDs



AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

AED Monotherapy Selection Criteria by Efficacy

- Absence: Ethosuximide > VPA > LMT
- PGE (other): VPA > TPM/LEV
- Atonic: Clobazam, CBD
- Dravet: Fenfluramine: ~ 50% 75% responder rate, 8% seizure freedom,
- Focal: PHT, CBZ, VPA, OXC, LM, TPM, LEV,ZN,PGB, LCM,EZG – all similar

  PB, GBP,TGB, RUF – less effective?

  Cenobamate: ~ 20% seizure freedom in DRE

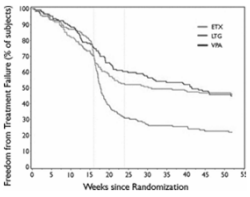
AES/AAN Guidelines: New Treatment in New Onset Epilepsy

- Clobazam (CLB)
- Eslicarbazepine
- Felbamate (FBM)
- Gabapentin (GBP)
- Lacosamide
- Lamotrigine (LTG)
- Levetiracetam (LEV)
- Oxcarbazepine (OXC)
- Perampanel
- Pregabalin (PGB)
- Rufinamide
- Tiagabine
- Topiramate (TPM)
- Vigabatrin (VGB
- Zonisamide (ZNS)

Recommendations for monotherapy in adults with new-onset epilepsy with focal epilepsy or unclassified tonic-clonic seizures

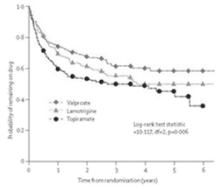
Level	Recommendation
Level B	LTG use should be considered to decrease seizure frequency.
Levels B and Level C	LTG use should be considered (**Level B**) and GBP use may be considered (**Level C**) to decrease seizure frequency in patients aged ≥60 years.
Level C	LEV use may be considered to decrease seizure frequency.
Level C	ZNS use may be considered to decrease seizure frequency.
Level C	VGB use appears to be less efficacious than immediate-release carbamazepine (CBZ) use and may not be offered; furthermore, toxicity profile precludes VGB use as first-line therapy.
Level C	PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d.
Level U	Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ.
Level U	Evidence is insufficient to consider TPM instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic (GTC) seizures, or generalized epilepsy (GE) presenting with GTC seizures.
Level U	Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy.
Level U	Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures.

Response to Ethosuximide, VPA and lamotrigine in Childhood Absence Epilepsy



Glauser T.Epilepsia 2013;54:141-155

Response to VPA,LMT and Topiramate in Generalized and unclassifiable epilepsy



Marson AG.Lancet 2007; 369:1016-26

Seizure Freedom on Monotherapy double-blind comparative trials in newly diagnosed LRE Patients

12 months after Treatment onset

Guerreiro MM, et al. Epilepsy Res. 1997;24:205-213
Bill PA, et al. Epilepsy Res 1997;27:195-204
Christe W, et al. Epilepsy Res. 1997;26:451-60
Dam M, et al. Epilepsy Res. 1989;3:70-76

Efficacy of AEDs in Focal Epilepsy

- Pivotal FDA approval studies are adjunctive treatment in refractory LRE
- Median Seizure reduction 25-50%
- Responder rate (% patients with >50% seizure reduction) 25-50%
- Pivotal RDBPC[1] studies of different AEDs are not comparable – different inclusion criteria, background AEDs, methodology, background patient population, doses used etc.
- Seizure freedom/efficacy stand-outs: Cenobamate for focal seizures (21%), fenfluramine for Dravet syndrome (8%)

P-Slide 28

[1]Randomized Double Blind Placebo-Controlled

AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

AED Side Effects

- Phenytoin: Dizziness, fatigue, drowsiness, osteopenia, rash, Stevens-Johnson, ↑ liver enzymes, gum hypertrophy, marrow suppression
- Phenobarbital: Dizziness, fatigue, drowsiness, osteopenia, rash, Stevens-Johnson, ↑ liver enzymes,
  Cognitive slowing
- Carbamazepine: Dizziness, fatigue, drowsiness, osteopenia, rash, Stevens-Johnson, ↑ liver enzymes,
  Cognitive slowing, aplastic anemia (1/200,000)
- Valproate: DFD, osteopenia, alopecia, tremor, weight gain, leg swelling, hyperandrogenism; polycystic ovarian syndrome/metabolic syndrome, thrombocytopenia, hepatitis/pancreatitis, teratogenicity, fetal neurocognitive development

AED Side Effects (2)

- Lamotrigine: DFD, diplopia. Rash: 3/10,000: fast titration, + VPA, more in children, previous drug-rashes. Tremor
- Topiramate: DFD. Paraesthesiae memory/cognitive/speech impairment: 10%. Dose dependent. renal stones 1-2%. Weight loss
- Oxcarbazepine: DFD. Rash. Hyponatremia/+/-encephalopathy/↑ szs: 3-7%,↑in elderly, concomitant diuretics, ACE inhibitors
- Zonisamide: DFD. Renal stones. Weight loss Aplastic anemia, hepatitis

AED Side Effects (3)

- Levetiracetam: DFD. Irritability/anger: 10%. Depression: 5%. Psychosis/hallucinations: 1%.
- Pregabalin:DFD. Weight gain – 10%. Leg swelling. Euphoria
- Lacosamide: Dizziness, headache, nausea, diplopia. ↑PR interval/1st degree heart block (a fib, bradycardia)
- Rufinamide: DFD, short QT
- Clobazam: DFD, diplopia, rash, SJS, irritability/anger
- Ezogabine: DFD, diplopia, nausea. Urine retention (2%). QT prolongation. Confusion (4%) psychosis/ hallucination (<1%). Pigmental discoloration/retinal pigmentation.

AED Side Effects (4)

- Perampanel: DFD. Ataxia. Hostility/anger/aggression/homicidal ideation. Schedule 3
- Eslicarbazepine: DFD. Hyponatremia (1-2%)
- Brivaracetam: DFD. Irritability: 3%
- Vigabatrin: DFD. Visual field constriction, memory, depression, hyperactivity
- Cannabidiol: Somnolence, decreased appetite, diarrhea, nausea/vomiting, URTI/fever
- Everolimus: Stomatitis, diarrhoea, nasopharyngitis, URTI/fever
- Cenobamate: DFD; diplopia, ataxia, rash (1.5%), DRESS
- Fenfluramine: ↓ appetite, diarrhea, fatigue, somnolence, weight loss

AED Side Effects (non-neurol)

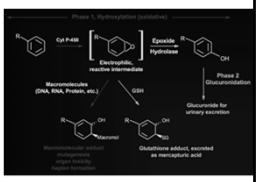
Side Effect	AEDs
Rash/allergy/SJS	PHT,PB,CBZ,OXC,LMT, CLB
Marrow suppression	CBZ (aplastic anemia), PHT, FB, ZN, VPA (platelets)
Hepatitis/↑ LFTs	VPA (+pancreatitis), CBZ, PHT, ZN,
Cognition	TPM, PB,CBZ
Psychiatric --	LEV, PB (depression), EZG, PMP, CLB, BRV (irritability)
Weight Gain	VPA, GBP, PGB, VGB
Weight Loss	TPM, ZN, FB, CBD, fenfluramine
PCOS, DM	VPA
↓ Na	CBZ, OXC, ESL
Renal Stones	TPM, ZN
Teratogenicity	VPA, PB, TPM, PHT
Osteoporosis	PB, PHT, CBZ, VPA
Neuropathy/cerebellar atrophy	PHT, CBZ (neuropathy)

AED Side Effects (ctd)

Side Effect	AEDs
Paraesthesiae	TPM, ZN
Hyposexuality (M&F)	PB/PM,PHT,CBZ
Tremor	VPA,LM
Dizziness,ataxia, fatigue, Drowsiness/sedation	All
Diplopia, nausea	PHT,CBZ,LM, LCM, EZG,CLB,cenobamate

AED Hypersensitivity Syndrome

Rash, systemic involvement: SJS,TEN,DRESS
Arene oxide intermediates - aromatic ring
CBZ: Lack of epoxide hydrolase
Cross-reactivity
- Phenytoin
- Phenobarbital
- Carbamazepine (HLA-B*1502 in Han Chinese) HLA-A*3101 in Japanese + Europeans
- Oxcarbazepine
- Lamotrigine

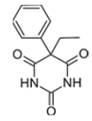


- Rash: ca 15%
- Severe cutaneous reaction (SCR: SJS,TEN): 1/10,000 (LMT 3/10,000)

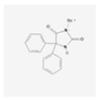
HLA-A*1502 in Han Chinese: 9-10% prevalence, 100% in CBZ-SCR +, 3% in CBZ SCR -.
No association with mild maculo-papular rash
HLA-A*3101 in Japanese : 15% population prevalence; 61% in CBZ-rash +, 13% in CBZ-rash -
Europeans: 2-5% prevalence, 26% in CBZ-SCR +, 4% in CBZ-SCR –

Chung WH Nature 2004;428
Ozeki T. Human Med Gen 2011:20:1034-41
Pichler Int Arch Allerg Immunol 2015; 168:13-24
McCormack M. NEJM 2011;364:34-43
Pichler, WAOJ, 2008;

Arene Oxide Intermediates- Aromatic Ring



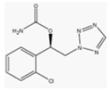
Phenobarbital



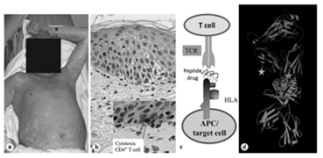
Phenytoin

Carbamazepine

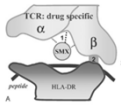
Lamotrigine



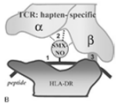
AED Hypersensitivity Syndrome (2)



Drug interacts with molecules other than target molecule, e.g. with immune receptors, including T cell receptor +/- HLA
>> Results in T cell stimulation
>> Results in delayed type hypersensitivity
Drugs bind preferentially or exclusively to certain HLAs or certain TCRs
Drug binding to HLA generates a drug-modified HLA which stimulates T cells directly



1.Drug binds to TCR
2.T cell stimulation is enhanced by additional interaction with MHC molecule



1.Drug binds to HLA
2.The complex is recognized by T cells via TCR
3. +/OR may activate T cell directly

Pichler, W WAOJ, 2008; Pichler Int Arch Allerg Immunol 2015; 168:13-24

Drug	Therapeutic Area	HUGO Symbol	Referenced Subgroup	Labeling Sections
Carbamazepine (1)	Neurology	HLA-B	HLA-B*1502 allele carriers	Boxed Warning, Warnings and Precautions
Carbamazepine (2)	Neurology	HLA-A	HLA-A*3101 allele carriers	Boxed Warning, Warnings and Precautions
Phenytoin	Neurology	HLA-B	HLA-B*1502 allele carriers	Warnings

AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

Co-morbidities/Special Populations

- Migraine : valproate, topiramate
- Bipolar/Depression/anxiety: Valproate, lamotrigine, tiagabine, +/- pregabalin, CBZ/OXC
- Obesity: topiramate, zonisamide, (felbamate)
- Insomnia: phenobarbital, pregabalin,(gabapentin), perampanel
- Elderly: levetiracetam, pregabalin, gabapentin, lamotrigine, ?Lacosamide
- Pregnancy: lamotrigine, levetiracetam, carbamazepine, oxcarbazepine

AED Choice by Co-Morbidity

Condition	Use
Anxiety	PB, LM, PGB, GBP
Bipolar Affective Disorder/mood stabilization	VPA, LM, CBZ, OXC, TPM
Obesity/T2DM	TPM, ZN (FB)
Migraines	VPA, TPM
Insomnia	GBP, PGB, PB
Painful neuropathy	GBP, PGB, CBZ, OXC
Trigeminal Neuralgia	OXC, CBZ
Fibromyalgia	PGB (GBP)
Restless leg syndrome	CBZ, GBP, PGB
Essential Tremor	Primidone

AED Avoidance by Co-Morbidity

Condition	Avoid
Behavioral/mood problems	LEV, PMP
Obesity (+OSA)	VPA, PGB, GBP
Cognitive issues	TPM, PB
Renal Stones	TPM, ZN
Osteoporosis	PB/PM, CBZ, PHT, VPA
Diabetes	VPA
Elderly on diuretics/ ACE inhibitors (↓ Na)	OXC, CBZ, ESL
Glaucoma	TPM

AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

Pharmacokinetics

Pharmacokinetics: determines relationship between dose and concentration

- Absorbtion: entry of drug into blood
- Distribution
- Elimination: removal of active drug from the blood by metabolism and excretion

PHARMACOKINETIC PARAMETERS OF ANTIEPILEPTIC DRUGS

AED	F (%)	Protein binding (%)	$T_{1/2}$ (hour)	Routes of elimination renal hepatic isozymes involved (%)	Active metabolite
Carbamazepine	70–80	75	12–17	<1 CYP3A4 (major), CYP1A2, 2C8	Yes
Clobazam	87	85–93	10–30	Nk CYP2C19, 3A4	Yes
Clonazepam	90	85	22–40	<1 CYP3A4	Yes
Ethosuximide	>90	0	25–60	20 CYP3A4 (major), 2E1	No
Felbamate	>90	22–25	20–23	50 UGT, CYP3A4 (20%), 2E1	No
Gabapentin	30–60	0	5–9	>90 none	No
Lacosamide	100	<15	13	40 not identified	No
Lamotrigine	98	55	12–60	<1 UGT1A4	No
Levetiracetam	100	<10	6–8	66 Amidase	No
Oxcarbazepine	>90	40–60	1–2.5	<1 Cytosolic arylketone reductase	Yes
MHD	–	33–40	8–11	20 UGT	No
Phenobarbital	80–90	20–60	36–118	20 Glucosides, CYP2C9, 2C19, 2E1	No
Phenytoin	70–100	88–93	7–42	2 CYP2C9 (major), CYP2C19	No
Pregablin	>90	0	5–6.5	>95 none	No
Primidone	>90	20–30	3–7	0 CYPs, isozyme not identified	Yes
Rufinamide	85	34	6–10	<2 non-CYP dependent hydrolysis	No
Stiripental	25	99	13	<1 UGT and CYPs, isozymes not identified	No
Tiagabine	90	96	3–8	<2 CYP3A4 (22%),	No
Topiramate	80	9–41	21	30 not identified	No
Valproate	90	5–15	6–17	<5 β-oxidation, UGT1A6, 1A9, 2B7, CYP2C9, 2C19	Yes
Vigabatrin	50–60	0	5–8	>90 none	No
Zonisamide	>90	40–60	27–70	35 NAT2 (15%), CYP3A4 (major), CYP2C19	No
Eslicarbazepine	<40%		20	CYP 3A4	No
Perampanel	95%		105	CYP 3A4/5	No
Brivaracetam	<20%		9	CYP 2C19, 2C9	No
Cannabidiol	>90%		10-17	CYP 2C19, 3A4	No
Cenobamate	60%		50-60	UGT2B7/B4,CYP2E1, 2A6, 2B6, 2C19 3A4/5	No

Anderson G. In Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 5th ed. 2011

Pharmacokinetics: Oddbins to Remember

- Absorbtion:
  Near complete for all except:
  Gabapentin: saturable amino acid transport system: 900 mg= 60% absorbed
  2400= 34%, 3600= 33%
- Distribution:
  Protein binding: > 85% binding= clinically significant
  PHT, CBZ, VPA, TGB, midazolam, perampanel, cannabidiol
  Linear except for VPA: at 100 µg/ml > free level rises more than total because protein binding is saturated
  Binding is important in: neonates, elderly, pregnancy, hepatic and renal disease because of low albumin. With decreased albumin AED total concentration decreases more than unbound concentration > total concentration underestimates free concentration.
  Check total &. free concentrations

  NB Perampanel: 95% protein bound, but no protein-binding based drug-drug interaction because PMP blood concentration is in nanomolar range, not micromolar

Pharmacokinetics: Oddbins (2)

- Elimination:
  Linear except PHT: 0 order elimination pharmacokinetics: metabolism is saturated
  $T_{1/2}$ x 4-5 results in elimination of >90% of drug>>steady state = $5xT_{1/2}$

  AEDs with long $T_{1/2}$: PB (53-118), PHT (18), ZN (105), CBZ (10-20), PMP (105), ESL (20), CLB (18; NDM-CLB: 50); CBD (10-24), CNB (50-60)
  Renally eliminated drugs: Reduce dose in the elderly and in RF:
  LM, GB,PGB, Lev, LCM
  Liver Metabolism/CYP-450 inducers: Changes in metabolism over time (auto-induction) or with polytherapy (enzyme induction or inhibition):
  PB,PHT,CBZ: auto-induction, levels fall 4 weeks after starting
  induce metabolism of each other and other AEDs
  VPA: inhibits UGT 1A9,1A4; CYP-450> increases levels of LMT, PHT, PB
  ESL: inhibits CYP-2C19>increases levels of PHT
  CLB: inhibits CYP-2C19>increases levels of active CBD metabolite, 7-OH-CBD
  CBD: inhibits CYP-2C19>increases levels of n-desmethyl-CLB (active CLB metabolite)
  CNB: inhibits CYP-2C19 >increases levels of n-desmethyl-CLB, PHT

AED Metabolism by the Liver

- AEDs are metabolized by the cytochrome p450 (CYP) and Uridine glucuronosyl transferase (UGT) enzymes
- CYP-450: 3 families of individual isoenzymes : CYP1-3.
- AEDs are metabolized by 4 isoenzymes, CYP3A4/5, CYP2C9, CYP2C19
- CYP3A4 accounts for 30% of all hepatic CYP & metabolism of >50% of all drugs
- A drug may be substrate for > 1 enzyme
- Uridine Glucoronyl Transfearses (UGT): 2 families:
- UGT1: glucuronidate drugs, xenobiotics and endobiotics;
- UGT2: glucuronidate endobiotics including steroids

CYP-450 & UGT Inducers/Inhibitors

- CYP-450: Inducers:
  PB,PHT,CBZ: CYP 1A2, A28/9, 3A4, (+2A6,2B6)
  OXC,TPM, FB, ESL, Cenobamate: CYP 3A4
- CYP-450: Inhibitors:
  VPA, FB,CNB: 2C19: ↑concentrations of PHT,PB
  TPM, OXC, ESL: 2C19: ↑concentrations of PHT
  CBD: ↑concentrations of CLB/n-des-methyl CLB
- UGT: Inhibitors:
  VPA: UGT1A9: ↑concentrations of LMT, lorazepam
  UGT1A4: ↑concentrations of LMT
  UGT2B7: ↑concentrations of lorazepam

AEDs Metabolized by Liver Isozenzyme

AED	CYP3A4	CYP2C9	CYP2C19	UGT
CBZ	+	+		
PHT	+	+	+	
VPA		+	+	+
PB	+	+		
ZNS	+			
TGB	+			
OXC	+		+	
LTG	+			+
TPM	+		+	
LCM			+	
CBL	+		+	
PMP	+			
ESL	+			
BRV		+	+	
CLB	+		+	
Everolimus	+			
CNB	+		+	+

AED Pharmacogenomics

- There is genetic polymorphism in the expression of CYP1A2, 2B6, 2C8, 2C9, 2D6, 3A5, and UGT1A1
- Poor metabolizers: monozygous for the mutant gene. High AED level
- Extensive metabolizers: homozygous or heterozygous for the gene. Low AED level
- Ultra-metabolizers: have multiple copies of the gene; only described for CYP 2D6 polymorphism.
- CYP2D6: predominant variant in Asians and African Americans are alleles with reduced enzyme activity >> ethnic variability in proportion of poor metabolizers
- AEDs affected: PHT, CBZ, VPA
- NB HLA-B*1502 in south east Asians (Taiwanese); and HLA-A*3101 in Europeans/Japanese: CBZ Stevens-Johnsons

PK in Renal and Liver disease

- Renal disease:
  ↓ albumin concentration:↓ AED protein binding > ↑ free drug level
  ↓ renal clearance: ↑ level of renally excreted drugs
- Liver disease:
  ↓ CYP-450 synthesis: ↑ AED levels of CYP-metabolized AEDs

  CYP2C19 activity is first affected with mild liver disease, 3A4 and 2C9 activity in severe liver disease

  ↓ albumin synthesis: ↓ AED protein binding

Pharmacokinetics in the Elderly

- Absorption - unchanged
- Distribution
  ↓ in albumin: ↑ free fraction: may have low total levels of PHT,CBZ,VPA, but normal free levels
- Metabolism - ↓ hepatic enzyme content and blood flow
- Excretion - ↓ renal clearance: ↓ dose of GBP,PGB, LMT, LEV,

Pharmacokinetics in Pregnancy

- Increased volume of distribution
- ↓ serum albumin – may ↑ free concentrations of protein bound AEDs: PHT,CBZ,VPA
- Faster metabolism
- ↑ Renal clearance and ↑ activity of UGT & CYP3A4, 2D6, 2C9
  > ↑ LMT, LEV metabolism and clearance,
  ↓ LMT, LEV levels (up to 50%) during pregnancy > risk of seizures,
  ↑ post-partum levels > risk of toxicity

Pharmacokinetics in Pregnancy (2)

- ↓ CYP1A2 & 2C19 activity
  May cause ↑ in CBZ, PHT levels
- AED management:
  Check levels monthly (+/- free levels for VPA,PHT, CBZ)
  Adjust dose as needed
  Consider more frequent dosing
  Return to pre-pregnancy conditions rapidly (within 2 weeks) after delivery

Pennell PB. Epilepsy Curr. 2012;12:63-5

AEDs in Breast Milk

Excretion of drug into breast milk is determined by drug's lipophilicity, protein binding and ionization

AEDs	Breast milk/maternal concentration	Adult half-life	Neonate half-life
CBZ	0.36–0.41	8–25	8–36
PHT	0.06–0.19	12–15	15–105
PB	0.36–0.46	75–125	100–500
ESX	0.86–1.36	32–60	32–38
PRM	0.72	4–12	7–60
VPA	0.01–0.1	6–20	30–60
LTG	0.5–0.77	30	—
ZNS	0.41–0.93	63	61–109
TPM	0.86	21	24
GBP	0.7–1.3	7–9	14
OXC	0.5–0.65	19.3	17–22
LEV	0.8–1.3	6–8	16–18

Anderson G. In Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 5th ed. ; 2011

Administration of i.v. injectable AEDs

AED	Dosage/Rate of Infusion
fosphenytoin	Status epilepticus: Loading Dose: 15-20 mg PE/kg IV (PE = phenytoin equivalent) Non-emergent: Loading Dose: 10-20 mg PE/kg IV or IM; MD: 4-6 mg PE/kg/day IV or IM Infusion Rate: Should not exceed 150 mg PE/minute
Levetiracetam	>16 y/o. No recommended Loading Dose Infusion Rate: Dilute in 100 ml of normal saline (NS), lactated ringers (LR) or dextrose 5% and infuse over 15 minutes
Phenytoin	Loading Dose: 10-15 mg/kg; up to 25 mg/kg has been used clinically. IM not recommended; dilute in NS or LR, DO NOT MIX WITH DEXTROSE, do not refrigerate, use within 4 hrs. Use inline 0.22-5 micron filter Infusion Rate: Should not exceed 50 mg/min; elderly/debilitated should not exceed 20 mg/min
Valproic acid	No Loading Dose: 20-40 mg/kg Infusion Rate: Administer over 60 minutes (<= 20 mg/min); rapid infusion over 5-10 minutes as 1.5-3 mg/kg/min
Lacosamide	No Recommended Loading Dose: Infusion Rate: IV formulation is 10 mg/ml, can be administered with or without diluents over 30-60 minutes
Brivaracetam	No Recommended Loading Dose: can start at maximum dose, 200 mg/d Administered as either 2 min bolus or 15 min infusion with or without diluents

AED Selection Criteria

- Epilepsy type
- Mechanism of action
- Efficacy profile
- Side effect profile
- Comorbidity
- Pharmacokinetics
- Drug-drug interaction
- Compliance
- Ease of Use
- Refractory Seizures/polytherapy
- Special populations: women
- Elderly
- Brand vs. generic

Drug Interactions Are Common

AEDs	Effect of Drug/Condition on AEDs: Enzyme-Inducing Drugs (phenobarbital, phenytoin, carbamazepine)	Effect of Drug/Condition on AEDs: Enzyme-Inhibiting Drugs (valproate)	Effect of AED on Oral Contraceptives: Oral Contraceptive Drugs
Phenytoin	↓	↑/↓	↓
Carbamazepine	↓	↑	↓
Phenobarbital*	↓	↑/↓	↓
Valproate	↓	-	NC
Felbamate	↓	NC	↑/NC
Gabapentin	NC	NC	NC
Lamotrigine	↓	↑	↓/↑
Topiramate	↓	↓	↓
Tiagabine	↓	↑	NC
Levetiracetam	NC	NC	-
Oxcarbazepine	↓	↓	↓
Zonisamide	↓	NC	-
Pregabalin*	NC	NC	NC

↓ = decreases serum concentration; ↑ = increases serum concentration; NC = no change in serum concentration.

*Based on internal assessment. PI not available. †For doses >200 mg/d.
Physicians' Desk Reference®. 58th ed. Montvale, NJ: Thompson PDR; 2004.

AEDs with no Significant Drug-Drug Interactions

- Gabapentin
- Pregabalin
- Levetiracetam
- Lacosamide
- Brivaracetam (rifampin reduces BRV levels by 45%)

When Does Drug-Drug Interaction Occur?

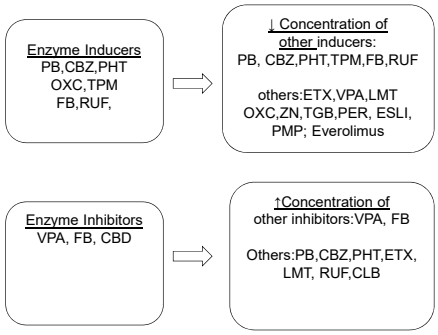
- Metabolism:
  Medication is a substrate for or affects Cytochrome P450 or UDP-glucoronidation isoenzymes
- Protein binding:
  Has significant protein binding (>60%)
- Drug interactions may occur with:
  Addition of a new medication when inducer/inhibitor is present
  Addition of an inducer/inhibitor
  Removal of an inducer/inhibitor
- Same with protein binding medication

AED Drug-Drug Interactions

- Hepatic Enzyme Inducing Drugs: PB,PHT, CBZ: auto-induce their own metabolism > ↓ own concentration. Approx. 4 weeks;
  ↓ concentrations of other AEDs: PB, PHT, CBZ, LM, ZN, ESL, PMP,Cenobamate (3A4) (CBZ,LMT)
  ↓ concentration/efficacy of oral contraceptives
  Slow onset of induction effect: 3-4 weeks
- Hepatic Enzyme Inhibiting Drugs: VPA, FB, CBD, Cenobamate (2C19)
  ↑ concentrations of LM, CBZ
  CBD: 3x ↑ concentrations of clobazam/des-methyl clobazam (2C19, 2C9)
  CLB: 73% ↑ concentrations of 7-OH-CBD (2C19)

  Fast onset of action: days

CYP 450 Interactions Between AEDs



AED Drug-Drug Interaction involving UGT

- LM is metabolized by it
- OC/ gonadal steroids induce it
  ↓ LM levels with OC & during pregnancy Trimester 2-3, & at ovulation
  ↑ LM levels with OC withdrawal, perimenstrually, post-partum
- LEV: same effect in Pregnancy

AED Drug-Drug Interaction: Protein Binding

- Drugs that are highly protein-bound:

  PHT, CBZ, VPA, Tiagabine, (PMP: not)

AEDs Effect on Hormonal Contraceptives

- Increase OC Clearance

> Lowers Hormone Levels

- Phenobarbital
- Primidone
- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Topiramate (>200 mg/d)
- Felbamate
- PMP
- ESL
- CNB

- No Effect
- Ethosuximide
- Valproate
- Gabapentin
- Tiagabine
- Lamotrigine
- Levetiracetam
- Zonisamide
- Pregabalin
- Lacosamide
- Brivaracetam (≤ 200 mg/d)

Pharmacodynamic Interactions

Toxicity — dizziness, ataxia, diplopia, nausea:
PHT, CBZ, PB, LM, OXC, Lacosamide, cenobamate

Efficacy??

AED Serum Concentrations

- May have better relationship between AED effect/toxicity than drug dose and be used as a guide for evaluating the efficacy some AEDs
- PHT,PB,CBZ,VPA,LM have validated ranges
- For new AEDs there is no clearly defined "therapeutic range" for patient-to-population comparison
- Individual patients define their own "therapeutic" and "toxic" ranges

Patsalos PN, et al. Epilepsia. 2008 ;49

AED Serum Concentrations

- Useful to
  optimize AED therapy
  document positive or negative outcomes of AED therapy
  assess compliance
  tease out/monitor drug-drug PK interactions
  document concentration when a patient is well controlled
- In: pregnancy, renal & liver disease and the elderly
- May help in managing brand/generic switch

Patsalos PN, et al. Epilepsia. 2008 ;49

Use of AED Serum Concentrations

- Efficacy/toxicity monitoring of older AEDs: PB/PM, PHT, CBZ, VPA
- Protein-bound AEDs: PHT, CBZ, VPA
  when albumin level changes: hepatic and renal disease, elderly (↓), pregnancy
  Check total and free level for these AEDs/states
- Renally excreted AEDs: GBP, PGB, LMT, LEV,LCM
  levels ↑ in renal failure, elderly, ↓ in pregnancy:
- Hepatically metabolized AEDs: PB/PM, PHT, CBZ, CLB
  can be affected by liver disease, meds which affect liver metabolism/isozymes

Patsalos PN, et al. Epilepsia. 2008 ;49

Potential Target Range of AED Serum Concentration

AED	Concentration (µg/ml)	AED	Concentration (µg/ml)
Carbamazepine	4-12	Tiagabine	5-70
Ethosuximide	40-100	Zonisamide	7-40
Phenobarbital	20-40	Felbamate	40-100
Phenytoin	10-20	Lacosamide	10-20
Primidone	5-12	Rufinamide	?
Gabapentin	4-16	Clobazam	?
Lamotrigine	5-20	Ezogabine	?
Topiramate	4-25	Perampanel	180-980 ng/ml
Levetiracetam	7-60	Eslicarbazepine	?
Oxcarbazepine	12-25 (MHD)	Brivaracetam	?
Pregabalin	5-10	Cannabidiol	?
		Everolimus	?
		Cenobamate	?

AED ILAE Reference Range

TABLE 1. Antiepileptic Drugs and International League Against Epilepsy Recommended Reference Ranges[2,10]

Antiepileptic Drug	Reference Range
Brivaracetam	0.4–1.2mg/l
Lacosamide	10–20mg/l
Lamotrigine	2.5–15mg/l
Levetiracetam	12–46mg/l
Oxcarbazepine	3–35mg/l
Perampanel	180–980µg/l
Pregabalin	2.8–10mg/l
Topiramate	5–20mg/l
Zonisamide	10–40mg/l

AED SELECTION CRITERIA

- Epilepsy Type
- Mechanism of Action
- Efficacy
- Adverse Effects
- Co-morbidity
- Pharmacokinetics
- Interaction
- Ease of Use
- New Onset Seizures/Monotherapy
- Refractory Seizures/Polytherapy
- Special populations:
  women
  elderly

Ease of Use

- Iv ER initiation: PHT,PB,VPA, LEV,LCM, BRV
- Quick up-titration/early efficacy: PHT, PB, VPA, LEV, ZN, PGB, LCM, ESL, BRV
- Easy pharmacokinetics: LEV, OXC, PGB, LCM, BRV
- No drug-drug interaction: GBP, LEV, PGB, LCM, BRV
- QD administration: PHT, PB, ZN, PMP,ESL, CNB
  All XR/ER formulations: VPA, LM,TPM,LEV,OXC

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

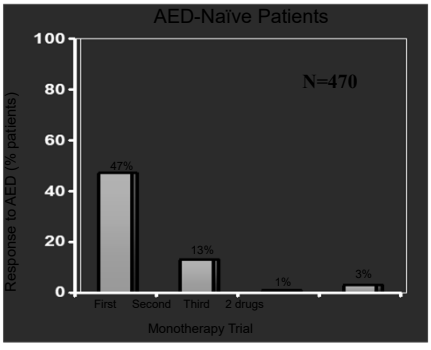
Principles of Management II

Pavel Klein, MD
Neurologist, Mid-Atlantic Epilepsy and Sleep Center

TALK OUTLINE: Part 2

- Pharmacoresistant Rx
- Generics
- Special populations: Elderly
- Special populations: Pregnancy
- Co-Morbidities: psychiatry
- SUDEP

Response to AED Therapy in Previously Untreated Patients with Epilepsy



1982-1997

Kwan P, et al. N Engl J Med. 2000;342:314-319

Response to 2nd AED

- 55% if 1st AED failed because of idiosyncratic reaction
- 41% if due to intolerable other side effects
- 11% If due to lack of efficacy

Kwan P, et al. N Engl J Med. 2000;342:314-319
Chen Z et al. JAMA Neurol 2018;75:279-286

Response to 2nd AED

- 55% if 1st AED failed because of idiosyncratic reaction
- 41% if due to intolerable other side effects
- 11% If due to lack of efficacy

Response to 3rd AED

4%

Response to 4th AED

1% for 4th, 5th

Kwan P, et al. N Engl J Med. 2000;342:314-319
Chen Z et al. JAMA Neurol 2018;75:279-286

Responder Rates of Patients with Newly Diagnosed Epilepsy: Impact of New AEDs

Recruitment Period	N	One AED (%)	Multiple AEDs (%)	Total (%)
1982-1997	470	61	3	64
1982-2006	1098	62	6.4	68.4
1982-2016	1795	62	2	64

Brodie MJ. Neurology 2012;78: 1548-1554

Drug Resistance 2018

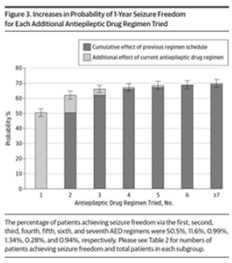


Table 2. Rates of 1-Year Seizure Freedom With Successive Antiepileptic Drug Regimens

Successive Antiepilepsy Drug Regimens	Total Patients Trying These Regimens, No.	Seizure Freedom			
		Total, No.	% of Patients Achieving Seizure Freedom With AED Regimen	% of the Total Achieving Seizure Freedom (n = 1144)	% of the Total Study Cohort (n = 1795)
First	1795	820	45.7	71.7	45.7
Second	742	208	28.0	18.2	11.6
Third	330	78	23.6	6.82	4.35
Fourth	140	21	15.0	1.84	1.17
Fifth	71	10	14.1	0.87	0.56
Sixth	43	6	14.0	0.52	0.33
Seventh	15	1	6.67	0.09	0.06
Eighth	9	0	0	0	0
Ninth	5	0	0	0	0
Tenth	2	0	0	0	0
Eleventh	1	0	0	0	0
Total	1795	1144	NA	100.04[a]	63.7

Chen et al., JAMA Neurol, 2018;75:279-286

Outcome at > 7 yrs of Newly Diagnosed Patients with Epilepsy

- 59% seizure free (37% from Rx initiation)
- 25% never seizure free for 1 year
- 16% fluctuated between periods of seizure freedom of ≥ 1 yr and relapse

Brodie MJ. Neurology 2012;78: 1548-1554

Definition of Drug Resistant Epilepsy

ILAE

- "failure of an adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom"

Kwan P et al. Epilepsia 2010;51:1069-1077

Predictors of Pharmacoresistance

Remission rates with treatment:

- Epi type: PGE: 66%
  FE : 57%
  Symptomatic (structural) and cryptogenic (unknown) FE epilepsy = same
- Etiology: CVA: 70 %
  Cortical dysplasia: 60%
  MTS: 50%
  Primary neoplasm: 52%
  TBI: 35%

Brodie MJ. Epilepsia 2012;54 (Suppl 2):S5-8.

Predictors of Pharmacoresistance (2)

- High pre-treatment seizure density (sz #/3-12 mo)
- Psychiatric comorbidity, especially depression
- High dose of 1st failed AED (≥ 50% standard)
- FH+
- FS in infancy
- EEG: not predictive

Brodie MJ. Epilepsia 2013;54 (Suppl 2):S5-8.

Treatment Options for Drug-Resistant Epilepsy

- More AEDS: n=33
- Still more AEDs: n=32
- Evaluate Diagnosis: EMU
- Presurgical evaluation for resection
- Treat Precipitants
- Neurostimulation
- Dietary
- Experimental/investigational

Seizure-free Rates with Successive AED Regimens in Patients with newly Diagnosed Epilepsy

AED	N	% total cohort seizure-free	% seizure free on regimen	Sz free on mono/poly-therapy
1st	1098	49.5	49.5	64
2nd	398	13.3	36.7	101/45
3rd	168	3.7	24.4	26/15
4th	68	1	16.2	6/5
5t	32	0.4	12.5	1/3
6th	16	0.2	12.5	1/1
7th	9	0.2	22.2	1/1
8th,9th	5	0	0	

Brodie MJ. Neurology 2012;78: 1548-1554

Seizure Freedom of New AEDs in Pivotal Studies

- Gabapentin 900 mg/d 4 %
- Lamotrigine 300 7
- Trileptal 1,200/2,400 10/22
- Topiramate 400 8
- Levetiracetam 3000 8
- Zonisamide 400 4
- Lacosamide 400/600 7
- Brivaracetam 100 5
- Cenobamate: 400 21%
- Placebo 0.5-2

Costa J et al. Epilepsia 2011; 52: 1280–91

Rational Polypharmacy

- Different Mechanisms of Action
- No data on human AED synergistic effect except possibly for VPA and LM

New AEDs: New MOA

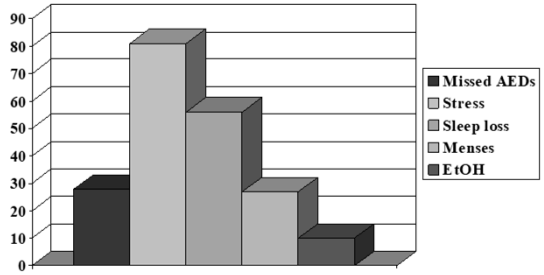
- Levetiracetam/BRV: SV2A protein
- Pregabalin: presynaptic Ca α-2δ receptor
- Lacosamide: slow inactivation of voltage-gated Na channel
- Ezogabine: K+ channel opener (M-type current)
- Perampanel: Glutamate AMPA receptor antagonist
- Cenobamate: Peristent NA current

Non-Drug Treatment

Avoidance/treatment of seizure triggers

- Sleep Deprivation
- Stress
- Fever
- Alcohol/recreational drugs
- Menses

% of Seizures Associated with Seizure Precipitants



Klein P. Epilepsia 2000, 41; (Suppl. 7):S112
Mattson RH. Adv Neurol 1991;55:453-60.

Other Seizure Precipitants

- Metabolic or electrolyte imbalance:
  Hypo > hyper-glycemia; ↓ Na, Ca, Mg
- Stimulants/recreational drugs:
- Medications: wellbutrin, antibiotics, antihistaminergics, decongestants, antitussives
- Concussion
- AED change: dose reduction
  Switch from brand to generic
  (Pharmacy/insurance company!)

Generics

- Bioequivalence = pharmacokinetic parameters Cmax and AUC fall within a specified range. Compares the brand to a single generic.
- Therapeutic equivalence = two products provide equal seizure control and tolerability. Rarely tested, but inferred by bioequivalence.
- Switchability = there is no change in therapeutic effect when one product is switched for another

Liow et al.Neurology 2007;68:1249-50

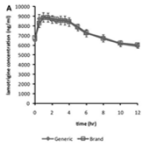
FDA Bioequivalence Requirements

- For both AUC and Cmax, 90% confidence intervals of the ratio of the generic to brand must fall within 80-125% range

Liow et al.Neurology 2007;68:1249-50

AES position statement on generic substitution of AEDs

- …[two] … prospective studies of generic AED substitution… demonstrated bioequivalence of generic[s].. in patients with epilepsy taking concomitant AEDs. …generic products of branded modified-release products (e.g., extended release) are bioequivalent and safely interchangeable.
- Results from these studies have shown no difference in bioequivalence when switching from a brand.. to a generic… or between multiple generic products.



LM brand and generic levels in 33 "AED brittle" patients[1]

[1]Ting T et al. Epilepsia 2015;56:1415—24
Vossler D et al. Epi Curr 2016;209-11
Privitera M et al;Lancet Neurol 2016:15:365-72
Johnson EL et al. Neurology 2016;86;1597-604

Epilepsy in the Elderly

- In 60% of new presentations cause can be identified
- Commonest causes: CVA, TBI, neurodegenerative diseases
- CVA = 30-40% of all new onset epilepsy in the elderly
  AD: 5-10X↑ risk of epilepsy, mainly in advanced stage
- 80% become seizure-free with medication
- Are more susceptible to adverse effects
- Avoid drugs with cognitive impairment and drug-drug interactions

Brodie M. BMJ.2005;331:1917-24

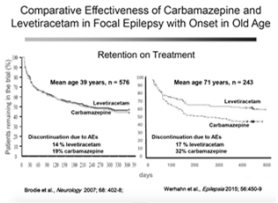
Efficacy and AEs may differ in the Elderly (2)

- Pharmacokinetics differ
- Ageing affects brain sensitivity to AEs of CNS active drugs
- Comorbidities and drug interactions may impact AED response

- Elderly generally achieve seizure control at lower doses c/w younger adults
- are more prone to develop AEs
- Differences in dose requirement are not completely explained by difference in pharmacokinetics

Brodie M. BMJ.2005;331:1917-24
Brodie et al/Lancet Nuerol 2009;8:1090-30
Ferlazzo et eal. Pharmacol Res 2016:06:21-6

Comparative Effectiveness of AEDs in the Elderly



VA Cooperative Studies #118 & #264

Mean Plasma Concentration in Patients With Adverse Effects (μg/mL)

Age	CBZ	VPA
<40	7.4	79.5
40-64	5.9	83.7
≥65	3.6	66.3

Ramsay R.E. Presented at the Annual AES Meeting, New Orleans, December 2-8, 1994

VA Cooperative Studies #118 & #264

Effective Mean Plasma Concentration at Study Termination (μg/mL)

Age	CBZ	VPA
<40	7.8	43.7
40-64	5.7	43.7
≥65	3.7	31.0

Ramsay R.E. Presented at the Annual AES Meeting, New Orleans, December 2-8, 1994

Epilepsy in the Elderly (4)

- Reduce dose of renally eliminated AEDs: LM,LEV,PGB, LCM, ESL
- Reduced albumin: increased free fraction of protein bound AEDs: PHT,CBZ, VPA
- Remember risk of: osteoporosis, hyponatremia, cognitive impairment, falls (balance). Avoid AEDs that could exacerbate these
- Lamotrigine and GBP: better tolerated than CBZ, as effective. LEV, LCM effective, well tolerated.

Brodie M. BMJ.2005;331:1917-24
Rowan AJ et al. Neurol 2005;64:1868-73
Ferrendelli JA. Epi Behav 2003;4:702-709

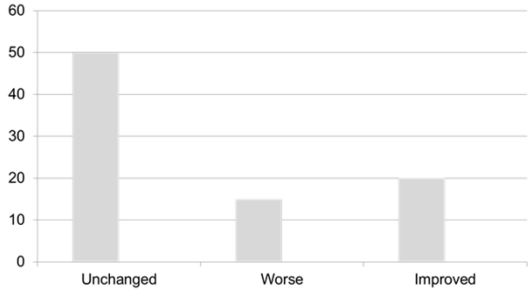
Challenges of Managing Epilepsy in the Elderly

- Changes in physiology/impact on drug pharmacokinetics
- Multiple other drugs used
  - Neurologic and non-neurologic comorbidities
    - Increased risk of adverse events
    - Increased risk of drug-drug interactions
- Problems with compliance
  - Difficulty following instructions
  - Economic challenges
- Psychosocial issues
  - Stigma of epilepsy

Pregnancy and Epilepsy: Issues

- The mother
  - Effect of pregnancy on seizures
  - Effect of seizures on Pregnancy
- The baby
  - Effect of epilepsy on the baby
  - Effect of seizures on the baby
  - Effect of AEDs on the baby
- Labor
- Breast feeding

Course of Seizures During Pregnancy



Major Malformations with AED Monotherapy

AED	% Major Malformations		
	North American APR	EURAP	
Valproate	9.3	10.3	
Phenobarbital	5.5	6.5	
Topiramate	4.2	3.9	Cleft defects 1.4
Carbamazepine	3	5.5	Spina Bifida Risk
Phenytoin	2.9	6.4	
Oxcarbazepine	2.2	3.0	
Levetiracetam	2.4	2.8	
Lamotrigine	1.9	2.9	Cleft palate

Hernández-Díaz S et al. Neurology 2012;78(21):1692-9
Tomson T et al. Lancet 2018;6:530-538

Teratogenic Risks of AEDs Increase with AED Polytherapy

- Major malformations risk with AED exposure:
  - No AED exposure: 0.8%
  - Single AED 3.1%
  - 2 AEDs 5.8%
  - 3 AEDs 8.3%

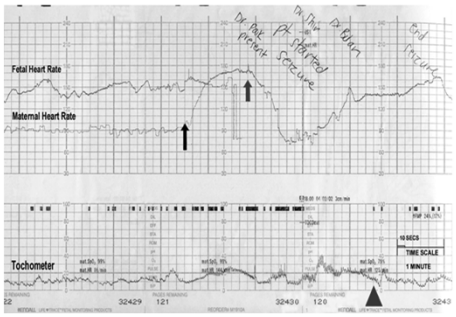
Kaaja E, et al. Neurology 2003;60:575

EURAP: Dose Dependent Effects on MCMs

Antiepileptic Drug	N	% Seizure Free	% Malformations
Cabamazepine			
<400 mg/d	148	64%	3.4%
400 to <1000 mg/d	1047	67%	5.3% *
≥1000 mg/d	207	62%	8.7% *
Lamotrigine			
<300 mg/d	836	67%	2.0%
≥300 mg/d	444	68%	4.5% *
Phenobarbital			
<150 mg/d	166	71%	5.4% *
≥150 mg/d	51	69%	13.7% *
Valproate			
<700 mg/d	431	71%	5.6% *
700 to <1500 mg/d	480	66%	10.4% *
≥1500 mg/d	99	61%	24.2% *

Tomson et al., Lancet Neurol 2011;10: 609-17 * More MCMs than LTG<300mg/d

Effect of Seizure on Fetus



Klein P. Arch Neurol 2005;62:1304-05

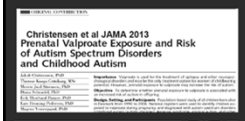
Cognitive Function at 3 & 6 years after Fetal Exposure to AEDs

	Mean IQs			
	VPA	CBZ	LTG	PHT
• Mean IQ, 3 years	92	98	101	99
• Mean IQ, 6 years	97	105	108	108

- VPA negative effect: Verbal>non-verbal

Meador K et al. NEJM 2009;360:1597-605
Meador et al. Lancet Neurology 2013;12:244-52.

Fetal Valproate: Autism, Autism Spectrum Disorder (ASD), & ADHD


Christensen et al JAMA 2013
Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Christensen et al, JAMA 2013.
Population-based Danish register study
ASD 4.4% (95% CI, 2.6%-7.5%) (HR 3.0)
Autism 2.5% (95% CI, 1.3%-4.8%) (HR = 4.9)


FULL-LENGTH ORIGINAL RESEARCH
Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy

Wood et al, Epilepsia 2015.
Small prospective study reporting increased scores in Childhood Autism Rating Scale at 6-8 years if exposed to VPA polytherapy (n=15)


Epilepsy & Behavior
Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years

Cohen et al, Epilepsy Behav 2013.
Prospective NEAD study at 6 years.
Children exposed to valproate had:
-Greater risk of diagnosis of ADHD
-Lower General Adaptive Composite scores

Lamotrigine & Lev Levels During Pregnancy

- LMT clearance increases and LMT levels decrease throughout pregnancy, with levels down by up to 50% of baseline.
- Clearance rapidly returns to preconception baseline at post-partum, with increase in LMT levels
- Changes in LMT clearance and levels are associated with seizure increase during pregnancy and toxicity during puerperium
- LMT levels should be checked monthly during pregnancy with appropriate dose adjustment
- LEV similar (less well documented)

Pennell PB. Neurology 2008;70:2130-26

Pregnancy, Vitamin K, and AEDs

- Enzyme inducing AEDs: phenytoin, carbamazepine, phenobarbital: lower vitamin K level >>
- ↑ risk of ante/perinatal intracranial hemorrhage in baby, and of parturition blood loss by mother – "inadequate evidence" [AAN Guidelines].
- Treatment: vitamin K (10 mg/kg/d, starting week 36; 1 mg im to the newborn)

AED Treatment in Pregnancy: Recommendations

- Careful planning of pregnancy
- AED Monotherapy wherever possible. Used in as low doses as clinically possible
- Use the AED best suited to patient's seizure control.
- There is little evidence of monotherapy teratogenicity for lamotrigine, levetiracetam or carbamazepine
- When considering switching a patient's AEDs because of planned pregnancy, do it 12 months before conception so as to establish response and optimal dose

Harden C et al. Neurology 2009;73:142-9

AED Treatment in Pregnancy: Recommendations (2)

- Folic acid supplementation before and throughout pregnancy 1 mg non-planning, 4m planning
- Prenatal screening for malformations
- Check AED levels monthly throughout pregnancy and soon after post-partum.
- For LM + LEV, adjust dose with levels
- With hepatic-enzyme inducing AEDs, give vitamin K – 1 month antenatally to mother, at birth to infant

Postpartum - Baby

- Breast feeding; yes
- AEDs excreted into breast milk: lamotrigine, levetiracetam
- Not excreted: protein bound: VPA, PHT,PB
- AED levels in the baby post-natally
- Potential effects on the baby: hypotonia, reduced feeding
- Treatment: check AED levels in baby;
  change AED or stop breast feeding
- PHT, CBZ, PB: pre/perinatal vitamin K
- PB/clonazepam/other benzodiazepines: possible risk of withdrawal seizures in the baby post-natally

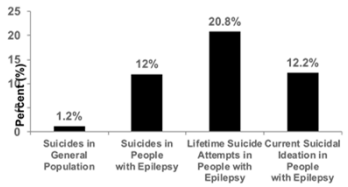
Prevalence of Psychiatric Disorders in Epilepsy

	In Epilepsy (Range)	General Population (Range)
Depression	11-60%	2-4%
Anxiety	19-45%	2.5-6.5%
Bipolar Affective Disorder	12.5-20%	2-7%
Psychosis	2-8%	0.5-0.7%
ADHD	25-30%	2-10%

Kanner, Epilepsia 2003;44(5):3-8.

Suicide

Suicide in the General Population and Among People With Epilepsy[9]



Jones JE et al.Epi Behav.2003;(Suppl 3):S31-38

Psychiatric Disease and Epilepsy: Bidirectional Relationship

- Patients with depression have 3-7x ↑ risk for developing epilepsy
- Epilepsy is associated with an increased onset of depression, anxiety and suicide 3 years before the diagnosis of epilepsy as well as after epilepsy diagnosis
- This suggests a possible common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicide.

Possible Suicide Risk with AEDs

FDA alert Jan 2008:
- Meta-analysis of 199 placebo-controlled add-on treatment trials (44,000 patients)
- Suicidality with adjunct AEDs vs. adjunct placebo:
  - 0.43% vs 0.22%
- Extra 2.1 patients per 1000 more patients will have suicidality
- 4 suicides with AEDs vs 0 with placebo
- "generally consistent across the 11 AEDs"

Data analysis is controversial and overall difference is very small

Further investigation is needed

Clinicians should be aware of potential risk and screen for depression/suicidality

www.fda.gov

AEDs for Psychiatric Indications

- VPA: bipolar affective disorder
- Lamotrigine: BAD
- Topiramate: BAD
- Pregabalin: anxiety
- Phenobarbital:?anxiety
- Clonazepam: anxiety
- Tranxene: anxiety
- (VNS: depression)

AEDs with Potential Psychiatric Side Effects

- Levetiracetam
- Topiramate
- Pregabalin
- Lacosamide
- Felbamate
- Perampanel

Treatment of Depression in Epilepsy

- Selective serotonin reuptake inhibitors
  - Es/Citalopram, fluoxetine, paroxetine, sertraline
- Norepinephrine/ serotonin reuptake inhibitors
  - Venlafaxine, duloxetine
- Tricyclics
  - Imipramine, nortriptyline
- MAO inhibitors
  - Only to be used by psychiatrists
- AEDs
  - As a prophylactic agent
  - LM,VPA,CBZ,OXC
- Lithium
  - Can worsen seizures
- Electroconvulsive therapy
  - Not contraindicated in seizure disorders
    - TMS ?

Kanner AM, et al. Epilepsy Behav. 2000;1:37-51.

Seizure Exacerbation or Trigger with Psychoactive Medications

- Antidepressants which ↑ Seizure Risk
  - Significant: high-dose bupropion
  - Moderate: some tricyclic antidepressants (clomipramine,maprotiline,amoxapine); and any tricyclic antidepressant at toxic serum concentrations
  - Low: SSRIs, trazodone, nefazodone
  - Inhibition of cytochrome P450 may lead to increased AED levels
- Antipsychotics which ↑ Seizure Risk
  - Significant: clozapine, chlorpromazine
  - Moderate: thioridazine, olanzapine, quetiapine
  - Low: haloperidol, risperidone

Kanner M. Epilepsia 2013;54 (Suppl 1)S3-12.

SUDEP: Definition

- Sudden
- Unexplained
- "sudden, unexpected, nontraumatic and non-drowning death in a patient with epilepsy where the postmortem examination does not reveal a toxicologic or anatomic cause of death, with or without evidence of a seizure and excluding status epilepticus."

Walczak TS et al. Neurology. 2001;56:519–25
Nashef L, Brown S. Lancet. 1996;348(9038):1324–1325

SUDEP: Incidence

Table e-2. Conclusions for SUDEP incidence

Population	SUDEP/1,000 patient-years (CI)	Confidence level
Overall	0.58 (0.31–1.08)	Low
Childhood	0.22 (0.16–0.31)	Moderate
Adulthood	1.2 (0.64–2.32)	Low

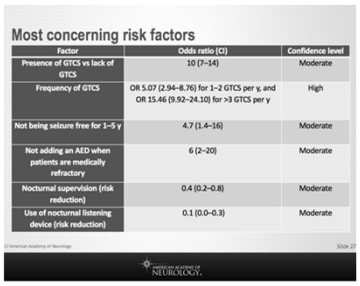
Children: 1/1000 ppy Keller AE Neurol 2018;91 e107-11 AAN/AES Guidelines, Neurology 2017

SUDEP: Epidemiology

- Risk of sudden death in epilepsy patients 24 x that of general population
- 2-18% of all deaths in all patients with epilepsy
- Incidence:
  1-2/1000 ppy in mixed epilepsy population
  9/1000 in surgical candidates
  15/1000 in surgery failures

Walczak TS et al. Neurology. 2001;56:519–25
Shorvon. Lancet. 2011.378:2028-2038

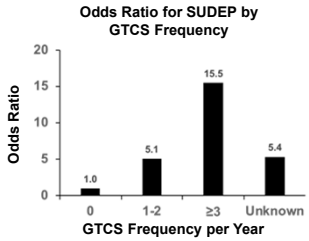
SUDEP: Risk Factors



- GTC occurrence increases SUDEP risk
- GTC frequency of > 3/year increases SUDEP risk 3-fold, c/w GTCS frequency of 1-2/y

AAN/AES Guidelines, Neurology 2017

Convulsive Seizures Increase Risk for SUDEP



Hesdorffer DC, et al. *Epilepsia*. 2011;52(6):1150-1159.

SUDEP: Risk Factors

- History of and number of GTCS (>3/month: 15↑ Risk)
- Uncontrolled seizures:
  frequent seizures
  AED polytherapy
  frequent AED changes
- Subtherapeutic AED levels
- Epilepsy:
  early onset
  symptomatic
  long duration
- Young adults
- IQ <70

Tomson et al. Epilepsia. 2005;46(Suppl 11):54–61
Hesdorfer et al. Epilepsia. 2011;52:1150-59

SUDEP: Causes?

- Common in bed
- 70-80% in prone position
- Respiratory: central or obstructive apnea/hypopnea
  ↑pCO_2 (av 19 mm)
  ↓ arousals
- Cardiac: ictal asystole, long QT syndrome,
  channelopathies (SCN1A, SCN5A, KCNH2)
- Biomarker: Prolonged post-ictal generalized EEG suppression
- Mechanism: ? Depressed pontine/medullary 5HT neuronal function (arousal, chemoreceptors, respiratory drive control)

Seyal,Bateman 2009;Epilepsia 50:2557-62
Richerson GB Epilepsia 2011;52 (Suppl 1):S28-38

SUDEP: Prevention?

- Identify patients at risk
- Treat epilepsy aggressively; but minimize polytherapy
- Someone present in the room of at risk patient at night/during sleep
- Actigraph-based alerting systems
- SSRIs?

Seyal,Bateman 2009;Epilepsia 50:2557-62
Richerson GB Epilepsia 2011;52 (Suppl 1):S28-38

END

Status Epilepticus

Pavel Klein, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

STATUS EPILEPTICUS

Pavel Klein, MD
Neurologist, Mid-Atlantic Epilepsy and Sleep Center

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **Consulting Fee (Member/Medical Advisory Board) - Alliance**
  - **Speaker Fee - Aquestive, Eisai, Sunovion;**
  - **Consulting/Speaker Fee - UCB Pharma**
- **Off-Label Usage**
  - **Treatment of epilepsy**

TALK OUTLINE

- Definition/Epidemiology
- Classification
- Etiology
- Evaluation
- Treatment
- Prognosis

Definition

- More than 30 minutes of continuous seizure activity

  or

- ≥ 2 sequential seizures spanning this period without full recovery between seizures

Epidemiology

- Incidence:
  41/100,000 (Richmond, VA)
  18/100,000 (Rochester, MN)
- Generalized SE 6.2/100,000
- More in children and elderly:
  Children 7.5/100,000
  Elderly 22/100,000
- Estimated 126,000-195,000 SE events with 22,200- 42,000 deaths/year in US

DeLorenzo RJ et al. Neurology 1996;46:1029-35

Classification

- Generalized: convulsive
  non-convulsive
- Partial/Focal: convulsive (epilepsia partialis continua)
  non-convulsive
- Non-epileptic seizure SE: "Pseudo-SE"

Classification of SE

I. NCSE occurring in the neonatal and infantile epilepsy syndromes
- 1a. Ohtahara syndrome
- 1b. West syndrome
- 1c. Severe myoclonic encephalopathy of infancy (SMEI; Dravet syndrome)
- 1d. NCSE in other forms of neonatal or infantile epilepsy

2. NCSE occurring only in childhood
- 2a. NCSE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
- 2b. NCSE in other forms of childhood epilepsie encephalopathies, syndromes, and etiologies (e.g., Ring chromosome 20, Angelman syndrome, Rett syndrome, myoclonic-astatic epilepsy, other childhood myoclonic encephalopathies)
- 2c. Electrical status epilepticus in slow wave sleep (ESES)
- 2d. Landau-Kleffner syndrome

3. Convulsive SE occurring only in childhood
- 3a. Febrile SE

4. NCSE occurring in both childhood and adult life with epileptic encephalopathy
- 4a. NCSE in the Lennox-Gastaut syndrome
  - i. Atypical absence SE
  - ii. Tonic SE
- 4b. Other forms of NCSE in patients with learning disability or disturbed cerebral development (cryptogenic or symptomatic) without epileptic encephalopathy
- 4c. Typical absence SE in idiopathic generalized epilepsy
- 4d. Complex partial SE:
  - i. Limbic
  - ii. Nonlimbic
- 4e. NCSE in the postictal phase of tonic–clonic seizures
- 4f. Subtle SE (myoclonic SE occurring in the late stage of convulsive SE)
- 4g. Aura continua [with: (i) sensory, (ii) special sensory, (iii) autonomic, (iv) cognitive symptoms]

5. Convulsive forms of SE occurring in childhood and adult life
- 5a. Tonic–clonic status epilepticus
- 5b. Epilepsia partialis continua (EPC; simple partial motor SE)
- 5c. Myoclonic SE

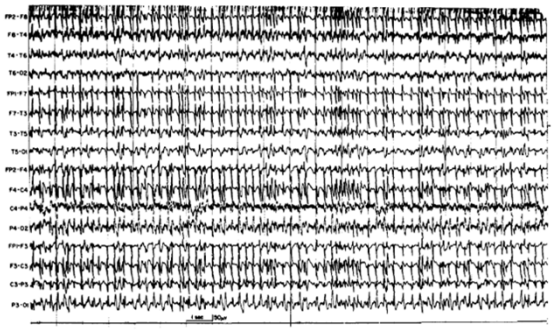
6. NCSE occurring in late adult life
- 6a. De novo absence SE of late onset

7. Boundary syndromes*
- 7a. Some cases of epileptic encephalopathy
- 7b. Some cases of coma due to acute brain injury with epileptiform EEG changes
- 7c. Some cases of epileptic behavioral disturbance or psychosis
- 7d. Some cases of drug induced or metabolic confusional state with epileptiform EEG changes

*Boundary syndromes are defined as cases in which it is not clear to what extent the continuous epileptiform electrographic abnormalities are contributing to the clinical impairment.

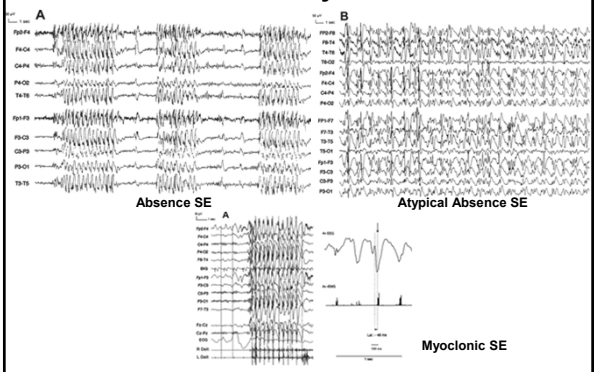
Task Force on SE of the ILAE Commission for European Affairs. Epilepsia 2008;49:1277-88

Generalized: Convulsive SE



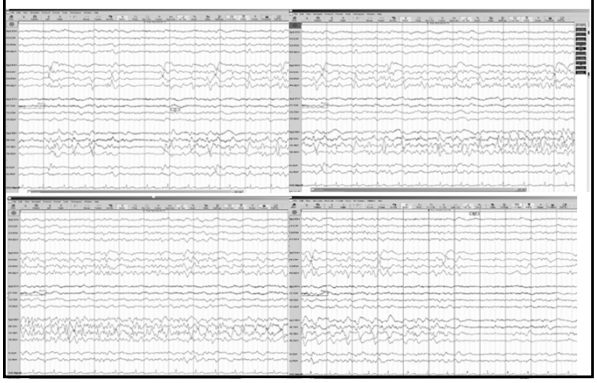
Treiman D.M. Epilepsia 1993;34(Suppl.1):S2-S11

Absence and Myoclonic SE

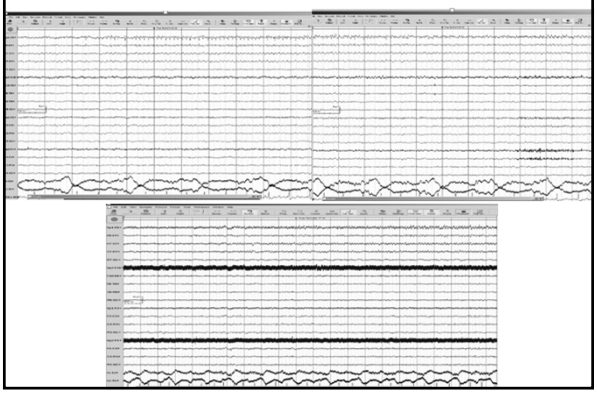


Thomas P et al. Brain 2006;129:1281-92

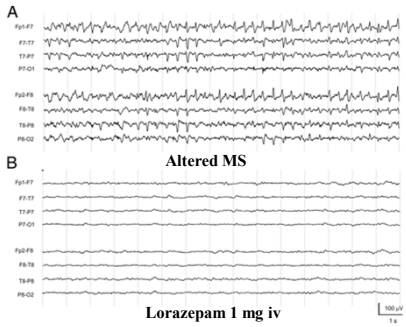
Non-Convulsive SE



NCSE

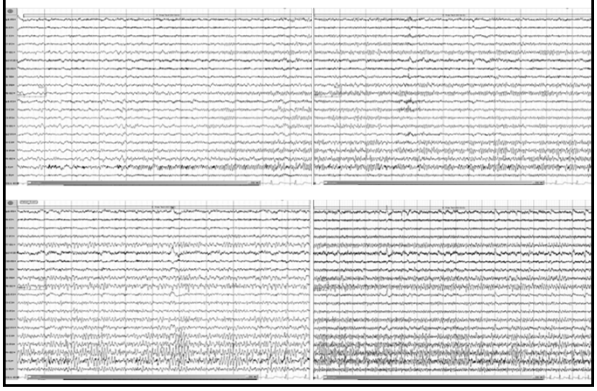


NCSE: diagnostic lorazepam



Friedman D et al. Anesth Analg 2009; 109: 506-523

Epilepsia Partialis Continua



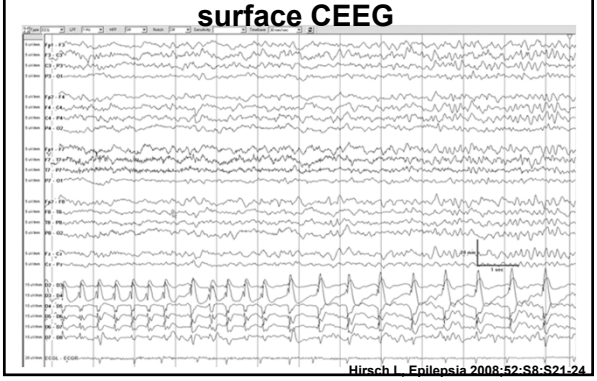
Prevalence of Non-convulsive SE in adult ICU

among 570 patients with CEEG monitoring for detection of subclinical seizures or evaluation of unexplained ↓ in LOC

	%
Overall	18
Unexplained altered MS	15
Epilepsy	31
CNS infection	26
Tumor	23
Neurosurgery	23
Traumatic brain injury	22
Toxic-metabolic	21
Stroke-SAH	18
Stroke-hemorrhagic	13
Stroke-ischemic	13
Hypoxia	10

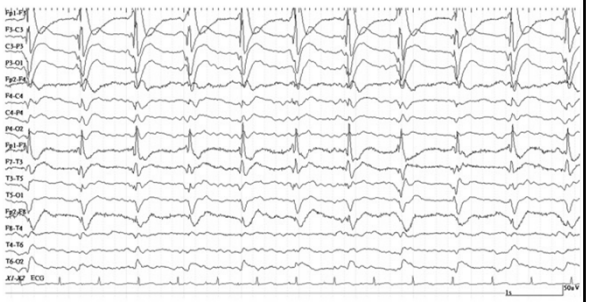
Claassen J.et al. Neurology 2004;62:1743-8

NCSE: Intracranial EEG in Acute Brain Injury showing focal SE, with normal surface CEEG



Hirsch L. Epilepsia 2008;52:S8:S21-24

PLEDS



Ictal-disputed
Post-ictal-yes

Etiology

- History of prior epilepsy: 44%
- Epilepsy type:
  Acute symptomatic: 50%
  Remote symptomatic: 20%
  Idiopathic:14%
  Other:17%
- Unknown: +/-9%

Shorvon S, Tan R.Epilepsia 2009; 50 (Supplement 12):S61-63

Etiology

Adult	%	Pediatric	%
CVA	25	Fever/infection	35
AED change	19		20
EtOH/recr. Drugs	12	Unknown	9
Anoxia	11	Metabolic	8
Metabolic	9	Congenital	7
Unknown	8	Anoxia	5
Fever/infection	5	CNS infection	5
TBI	5		4
Tumor	4	CVA	3
CNS infection	2	EtOH/recr. Drugs	2
Congenital	1	Tumor	1

DeLorenzo RJ et al.Epilepsia 1992;33 (S4):S15-25

Etiology:Uncommon causes

- Paraneoplastic: Hu, Ma2, CRMP-5 antibodies = intracellular antigens
- Autoimmune: Hashimoto's, voltage gated K channels, NMDAR, GABA-R,Rasmussen (Glu 3), SLE antibodies =extracellular antigens
- Chromosomal, genetic,dysplasic: Ring chromosome 20: inborn errors of metabolism; congenital dysplasia

Shorvon S, Tan R.Epilepsia 2009; 50 (Supplement 12):S61-63

Etiology: Epilepsia Partialis Continua

Fixed or progressive lesions involving the motor strip:

- Tumors
- Vascular: CVA, AVM
- Infection: abscess (esp.TB), encephalitis, HIV, subacute measles encephalopathy
- Autoimmune: Rasmussen, SLE, paraneoplastic
- Cortical dysplasia, Sturge-Weber
- TBI
- MS
- Gliomatosis cerebri
- PML

Guirrini R. Epilepsia 2009; 50 (Supplement 12):S7-9

Medications Causing SE

- Theophylline
- Lithium
- Isoniazid
- Cyclosporine, tacrolimus, ifosfamide
- Amoxapine, flumazenil
- AEDs: Tiagabine, vigabatrin

Riviello JJ. Neurology 2006;67:1542-1550

SE Stages: Clinical

- Prodromal: Confusion, myoclonus, increasing seizure frequency
- Stage 1 (early):
  Incipient (cont sz>5min): 5 min
  Early: 5-30 min
- Stage 2 (Established): 30-60 min
- Stage 3 (Refractory): ≥ 60 min
- Post-ictal

SE Stages: EEG

1.Discrete seizures with interictal slowing

2. Waxing/waning of ictal discharges

3. Continuous ictal discharge
   >Continuous ictal discharges interspersed by flat EEG

4. PLEDs/PEDs with flat background

Treiman M. Epi Res 1990;5;49-60

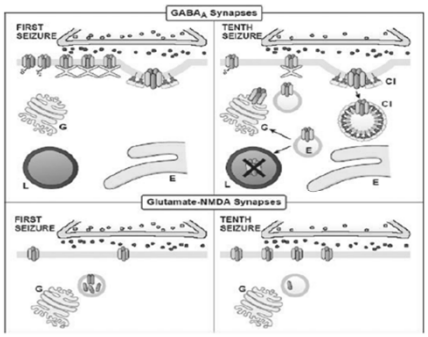
Pathophysiology of SE

Failure of seizure containment > transformation of isolated seizure to SE

- Msec/sec: neurotransmitter release, ion channel activation, receptor phosphorylation and desensitization
- Minutes-hour: receptor trafficking:
  $GABA_A$-R (β2-3, ϒ subunits): from synapse to cytosol > endocytosis & destruction >↓ $GABA_A$ receptor number at synapse
  AMPA/NMDA-R (NR1 subunits): ↑recruitment from cytosol to synapse
- Minutes/hours: depletion of inhibitory neuropeptides (galanin,somatostatin, NPY, dynorphin),
  ↑ in excitatory neuropeptides: Substance P, neurokinin B
- Hours/days: long term changes in gene expression, neuronal death, neuronal reorganization

Chen JWY, et al 2007;Acta Neurol Scand : 115 (Suppl. 186): 7–15.

Pathophysiology of SE



Chen JWY, et al 2007;Acta Neurol Scand : 115 (Suppl. 186): 7–15.

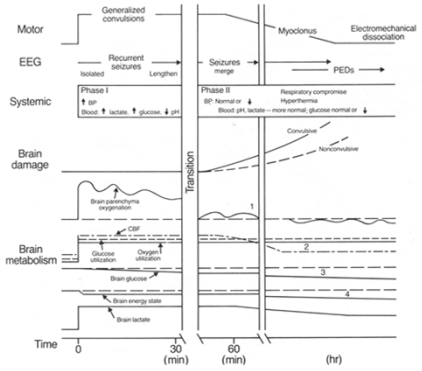
Epilepsia Partialis Continua: Pathophysiology

Poorly understood

- Cortical reflex myoclonus: originates from hypersynchronous discharges of neuronal aggregates in the cortex.
- ?long-loop reflexes generating cortical myoclonus, via ventrolateral posterior nucleus of the thalamus

Guirrini R.Epilepsia 2009;50 (Supplement 12):S7-9

SE: Metabolic Consequences



Lothman E. Neurology 1990;40 (suppl 2): S13-23

SE: Metabolic Consequence

- Acute:
  ↑ BP, lactate, +/-glucose levels
  Respiratory and (>) metabolic acidosis
  ↑CBF, O2 utilization
- Later:
  BP normal/slight fall, ↓glucose,
  Hyperthermia,
  ↓ respiration > ↓ O_2, ↑CO_2
  ↓brain oxygenation, ↓ CBF, ↓ brain glucose >>energy mismatch

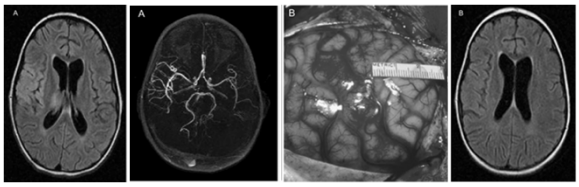
Privitera MD.Emerg Med Clin North America 1994;12:1089-1100

Complications of Tonic-clonic SE

Cerebral	**Hypoxic/metabolic damage**
	Excitotoxic damage
	Edema and ↑ ICP
	Venous thrombosis, infarction,hemorrhage
Cardiac	**Hypo/hypertension**
	Cardiac failure/shock
	Tachy/brady-arrhythmia, arrest
Respiratory	**Apnea, respiratory failure**
	Pulmonary edema, hypertension, pneumonia, aspiration, PE
Autonomic	**Hyperthermia, sweating**
Metabolic/systemic	**Hypoglycemia, ↓ Na, ↓ K, Acidosis Acute renal failure Acute hepatic failure DIC Rhabdomyolysis Infections Fractures**
Labs (other)	**Leukocytosis; CSF pleocytosis**

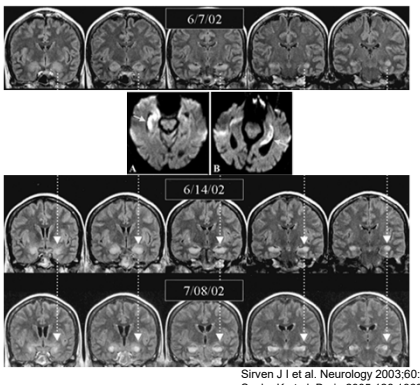
Fr.Task Force on SE of the ILAE Commission for European Affairs. Epilepsia 2008;49:1277-88

SE Periictal MRI: Local ↑



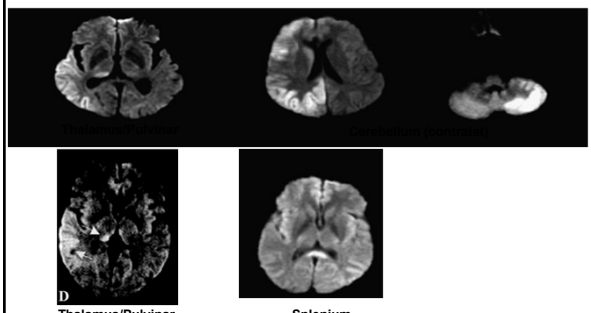
Cole AJ. Epilepsia 2004;45 (suppl 4): S72-77

MRI Changes:Hippocampus



Sirven J I et al. Neurology 2003;60:1866-66
Szabo K et al. Brain 2005;128:1369-76

Peri-ictal SE MRI: Remote Changes



Thalamus/Pulvinar

Splenium

Milligan TA et al. Seizure 2009;18:104-108
Szabo K et al. Brain 2005;128:1369-76

Peri-ictal SE Imaging Abnormalities

LOCAL		REMOTE
Local ↑ T2/DWI		**Uni/bilat diencephalic lesions**
Mass effect		**Cerebellar diaschisis**
Hippocampal swelling		**Splenium abnormalities**
Focal cortical lesions		**Reversible posterior leukoencephalopathy**
Migratory focal ↑ T2/DWI lesions		
BBB breakdown		
↑ Blood vessel caliber/flow		

Cole AJ. Epilepsia 2004;45 (suppl 4): S72-77

Management Timeline

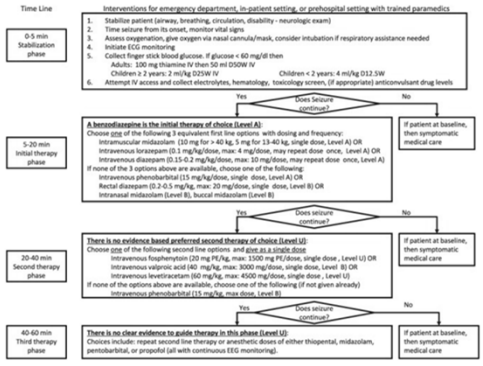
Time post onset	Treatment
0-5 min:	diagnose ABC: Airway, breathing, circulation Labs: BS, Chemistry, CBC, tox screen AED levels (if applicable) iv Glucose + thiamine 100 mg if applicable
4-5 min.	Lorazepam 4 mg (0.1 mg/kg), OR Midazolam 10 mg i.m, or Diazepam 10 mg (0.2 mg/kg) or rectal diazepam
7-8 min.	Phenytoin or **fosphenytoin 20 mg/**kg iv at ≤ 50 mg/min phenytoin or 150 mg/min fosphenytoin (≤ 0.75 mg/kg/min); **levetiracetam** (eg 60 mg/kg, maximum 4,500 mg), or **VPA** 40 mg/kg (maximum 3000 mg) Pyridoxine 100-200 mg IV in children under 18 mo

SE Treatment Timeline ctd.

Time post onset	Treatment
10 min	Repeat lorazepam or diazepam if seizures ongoing
30-60 min	EEG monitoring unless status ended and patient waking up
40 min	Second second line agent (incl. Phenobarbital 20 mg/kg at ≤ 5 mg per minute (0.75 mg/kg per minute)
60+ min	iv anesthesia: Pentobarbital 3-5 mg/kg load,1 mg/kg/hour infusion, **OR** Propofol 3-5 mcg/kg load, 5-10 mg/kg/hr initial infusion then 10-120 mcg/kg/min, as tolerated/needed **OR** Midazolam 0.2 mg/kg load, then .05-0.3 mg/kg/hr infusion
60+ min	CEEG, titrate medication to burst-suppression OR flat EEG

Lowenstein DH, Alldredge BK, Status Epilepticus. NEJM 1998; 338: 970-976.

AES Guidelines 2016: Treatment of Convulsive SE



Glauser T et al; Epi Curr 2016;16:48-61

Other Evaluations

- Neuroimaging: CT/MRI
- LP (after neuroimaging if ↑ ICP is a possibility): ↑ WBC without infection (BBB breakdown): up to 28 x 10^6
- EEG/CVEEG

Riviello JJ; Neurology 2006;67:1542-1550

Treatment of Early (Stage 1) Generalized Convulsive SE

	Route	Adult dose	Pediatric Dose
Lorazepam	iv	4 mg/0.07 mg/kg	0.1 mg/kg
Midazolam	im	5-10 mg	0.15-0.3 mg/kg
Diazepam	Iv (≤ 2-5 mg/min)	10-20 mg	0.25-0.5 mg/kg
	Rectal	10-20 mg	0.5-0.75 mg/kg
	Nasal	10-20 mg	0.5-0.75 mg/kg

Adapted Fr.Task Force on SE of the ILAE Commission for European Affairs. Epilepsia 2008;49:1277-88

Pre-Hospital Treatment of Generalized Convulsive SE

Response =	Seizure termination prior to arrival in ER without rescue Rx	
	Dose/route	Response %
Diazepam	10 mg iv	43
Placebo	im	21
Lorazepam	4 mg iv	59-63
Midazolam	10 mg im	73

Alldredge BK et al. NEJM.2001;345:631-637
Silbergleit R et al. NEJM 2012;366:591-600

Pre-hospital Treatment, ctd.

- At home: nasal midazolam, diazepam, diastat p.r. in patients with unstable pre-existing epilepsy
- In evaluation: intranasal clonazepam, im diazepam, buccal diazepam, inhaled alprazolam

AES Guidelines Alternative Treatments of Established (Stage 2) SE

	Evidence	Route	Adult dose	Pediatric Dose
Fos-phenytoin	Level U	iv Infusi rate	15-30 mg/kg 10-15 min	20-40 mg/kg 10-25 mg/kg neonates
Valproic Acid	Level B, 1 Class 2 study	iv Infusi rate	40 mg/kg (max 3,000 mg)	Not established
Levetiracetam	Level U	iv Infusi rate	60 mg/kg (max 4,500 mg) 5-15 min	Not established

Glauser T. Epi Curr 2016; 16:48-61

Comparison of 3 Treatments for Generalized SE: ESETT study

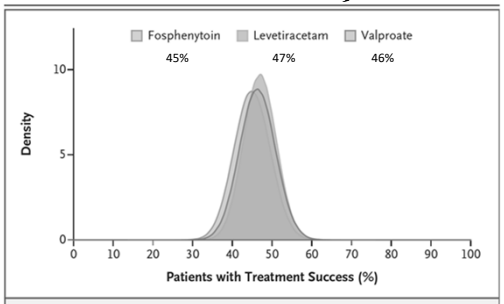


Figure 2. Posterior Probabilities of Success According to Treatment Group for the Primary Outcome of Cessation of Status Epilepticus at 60 Minutes.

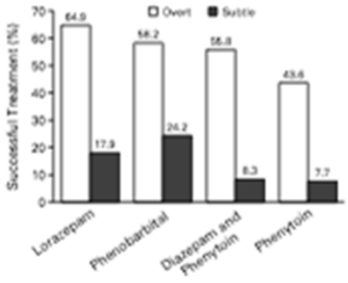
Kapur J et al.. NEJM 2019:381:2103-13

Treatment of Established (Stage 2) Generalized Convulsive SE

	Route	Adult dose	Pediatric Dose
Phenytoin/f-PHT	**iv** **Infusi rate**	**20 mg/kg,** **PHT ≤ 50 mg/min** **F-PHT ≤100 mg/min**	**same**
Phenobarbital	**iv** **Infusi rate**	**15-20 mg/kg** **≤100 mg/min**	**Same** **20 mg/min in neonates and infants**

Adapted Fr.Task Force on SE of the ILAE Commission for European Affairs. Epilepsia 2008;49:1277-88

Comparison of 4 Treatments for Generalized SE



Treiman D et al. NEJM 1998;339:792

Comparison of 4 Treatments for Generalized SE: Lorazepam, PB, PHT & PHT/DZP

	Response rate % (Sz end≤ 20 min)	Dose (mg/kg)	Maximal Admin Rate (mg/min)	Infusion Time (Min)
Lorazepam	**65**	**0.1**	**2**	**4.7**
Phenobarbital	**58**	**15**	**100**	**16.6**
Phenytoin + diazepam	**56**	**18** **0.15**	**50** **5**	**42**
Phenytoin	**44**	**18**	**50**	**33**

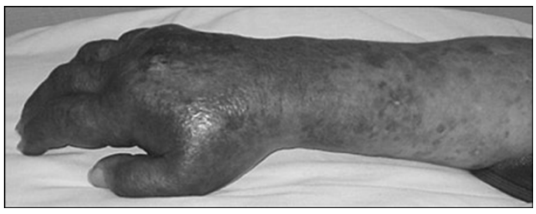
from Treiman DM et al. NEJM 1998;339:792-798

Phenytoin

- Phenytoin in NS (precipitates in dextrose): 20 mg/kg, (15 mg/kg in the elderly).
- Lack of sedation or respiratory depression.
- Infusion rate: children ≤ 25 mg/min, adults 50 mg/min, elderly 20 mg/min
- Monitor HR and BP. Reduce infusion rate if hypotension occurs
- Maintain therapeutic level 2 h after infusion to help with timing of maintenance treatment

Phenytoin iv: S/Es

- Hypotension
- Bradycardia
- Phenytoin is alkaline >> Skin irritation with extravasation: purple glove syndrome



fos-Phenytoin

- FosPhenytoin – phosphate ester prodrug of phenytoin
- >>given as phenytoin equivalent (PE), 20 mg/kg. Can be given in dextrose.
- Is water-soluble and can be given i.m.>paraesthesias and injection site pruritus.
- 100% bioavailability c/w PHT
- Conversion half life to PHT: 7-15 min

fos-Phenytoin (ctd)

- Check PHT levels 2 hours after infusion
- Is rapidly converted to PHT by serum and tissue alkaline phosphatases
- May be difficult to maintain therapeutic levels in infants

Lowenstein/Treiman NEJM
Leppik I, JAMA 1983;249:1452-1454

SE: PHT/fos-PHT

- Side effects: more likely in patients with hypoalbuminemia, renal and hepatic failures and in the elderly because of higher levels of free PHT.
- In these patients infusion rate should be reduced by 25-50%

Lowenstein/Treiman NEJM
Leppik I, JAMA 1983;249:1452-1454

Phenobarbital

- Efficacy is equivalent to PHT
- Respiratory depression and sedation, esp. when given with benzodiazepines or other respiratory depressants

Alldredge B et al. NEJM
Leppik I, JAMA 1983;249:1452-1454

Refractory (Stage 3) SE: Definition

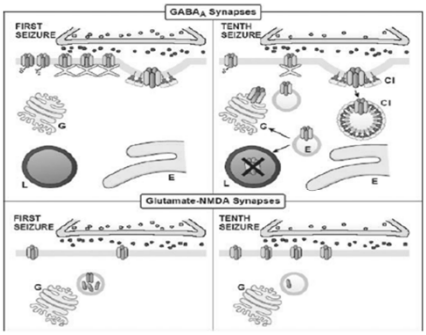
- SE lasting for > 1 (2) hours; and
- Has failed to respond to benzodiazepine + PHT or PB at adequate doses (levels)
- Ca. 35% of all SE

Lowenstein D. Epilepsia. 2006;47 Suppl 1:S35-40

Refractory (Stage 3) SE

- Convulsive SE evolves into NCSE: convulsions stop but mental status does not improve : 15% adults, 25% children

Pathophysiology of SE



Chen JWY, et al 2007;Acta Neurol Scand : 115 (Suppl. 186): 7–15.

Pathophysiology of Refractory SE

Pharmacoresistance develops during 30-45 min of seizure
After 30-45 min:

- Seizure-induced internalization of synaptic GABA-A receptor (subunits $\beta_{2,3}$, γ_2)
- Externalization of AMPA/NMDA receptors to the synapse

- 20x↓ of response to diazepam (experimental SSSE)
- NB: ↑ in extrasynaptic $GABA_AR$ (δ-subunit) and tonic currents

Wasterlain CG et al.Epilepsia 2009;50 (Suppl 12): S16-18

Refractory SE: Outcome

- Mortality: 39-48% adults
  16-44% children
- 32% children, 28% adults return to baseline
- Etiology is the most common determinant of responsive vs refractory SE and of refractory SE outcome
- Higher mortality among symptomatic patients

Classen J et al.Epilepsia 2002;43:146-153
Sahin M et al. Neurology 2003;61:398-401

Factors Determining Response vs Resistance to AEDs

Aetiology:
Rx resistance: acute structural lesions:
CVA, TBI, encephalitis in previously non-epileptic patients

Response: idiopathic in previously non-epileptic patients;
AED non-compliance in epileptic patients;

Duration: > 1 h

Lowenstein D. Epilepsia. 2006;47 Suppl 1:S35-40

Refractory SE: other

- Risk factors:
  infectious and inflammatory causes;
  paraneoplastic
- New Onset Refractory Status Epilepticus (NORSE):
  antecedent febrile illness
  prior good health, female, young
  CSF pleocytosis
- FIRES

Wilder-Smith EP et al. Ann Acad Med Singapore 2005;34:417-420

Refractory SE: Evaluation

- Monitor: continuous EEG monitoring to
  (a) diagnose;
  (b) monitor treatment response
- Goal: burst suppression or electrocerebral inactivity
- Degree of burst suppression is unclear:
  Duration of interburst interval: ?5 sec
- Persistent seizure control may be better with flat EEG than with burst suppression

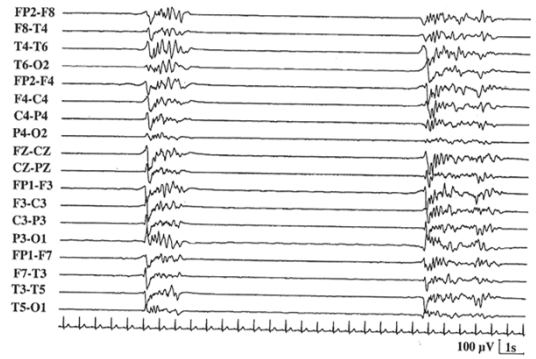
Krishnamurthy KB, Drislane FW. Epilepsia 1999;40:759-62

Monitoring Treatment Response

- Suppression of clinical and EEG seizures with burst suppression only if needed with iv midazolam/propofol infusion:
- Continuous EEG to monitor response and adjust iv anesthetic infusion rate/dose
- 18% acute treatment failure,
  56% breakthrough seizures
  68% post-treatment seizure recurrence
- Hypotension is more likely with burst suppression

Classen J et al.Epilepsia 2002;43:146-53

Burst-Suppression



Treatment of Refractory (Stage 3) SE: i.v. Anesthetics

Therapeutic coma

	Dose, bolus mg/kg	Followed by infusion mg/kg/h
Propofol	**1-2**	**5-10 mg/kg/h**
Midazolam	**0.1-0.3 (at 25 mg/min)**	**0.05-0.4 mg/kg/h**
Pentobarbital	**5-20**	**0.1-3**

Adapted Fr.Task Force on SE of the ILAE Commission for European Affairs. Epilepsia 2008;49:1277-88

Refractory SE: "Rational" Treatment

1. Stimulate remaining GABA-$_A$ receptors: Pentobarbital/phenobarbital (also block AMPA and kainate receptors),Midazolam, Lorazepam
2. Block NMDA/AMPA receptors: Ketamine(NMDA), ? Parampanel (AMPA)
3. Stimulate extrasynaptic d-subunit containing GABA$_A$-R Neurosteroids (allopregnanolone, ganaxolone)

Wasterlain CG et al. Epilepsia 2009;50 (Suppl 12): S16-18

Propofol

- 1-2 mg/kg load followed by infusion at 5-120 mcg/kg/min
- Rapid onset: sz control in 2.6 min vs 123 min with pentobarbital
- 64% efficacy vs 55% with pentobarbital
- Titrate up in increments of 10 mcg/kg/min per 5 min interval to EEG response/side effects
- Side effects: hypotension, metabolic acidosis
- Deaths: propofol infusion syndrome –cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure – with high dose long term (e.g., >4 mg/kg/h for > 24 h)
- Adults in RSE: 57% mortality with propofol treatment vs 17% with midazolam

Refractory SE: Other Rx

- Valproate
- Topiramate
- Levetiracetam
- Lacosamide
- Ketamine
- Iv lorazepam infusion
- Clonazepam

Treatment of RSE with non-anesthetic AEDs

All non-randomized, uncontrolled studies

	N treated	Efficacy % (mean)	Serious Adverse Events
Valproate	**172**	**79 (60-95)**	**Rare Pancreatitis/ Hepatitis**
Levetiracetam	**700**	**70**	**None**
Lacosamide	**136**	**56**	**Angioedema**
Topiramate	**6**	**100**	**Acidosis**

Cock et al. Epilepsia 2011;52:50-52
Trinka, Epilepsia 2011;52:1528-1167
Hoffler et al Epilepsia 2013;54:393-404
Towne et al.Neurology 2003;60:332-4

Refractory SE: Ancillary Treatment

- Ketamine
- Hypothermia
- Surgery
- Ketogenic diet
- Monitor electrolytes, ca, mg, acidosis, concurrent infection, fever, rhabdomyolysis/K, hypotension, bradycardia

Treatment Failure

- Continuous seizures
- Breakthrough seizures: clinical/EEG seizures >6 hours after seizure suppression
- Withdrawal seizures: seizures < 48 hours after stopping iv anesthesia
- 24-48 hours iv anesthetic >stop >evaluate >re-start if necessary
- Up to 11 months

Prognosis: mortalilty

- Children: 3-6%
- Young adults: 14%
- Elderly: 31-38% vs 7% non-elderly

Age
SE duration
Etiology

- 3% with duration of 30-60 min
  32% with duration > 60 min
- Higher with an acute precipitant/ symptomatic, elderly, & duration >24 h
- By etiology: High with anoxia
  Low with alcohol and AED withdrawal

De Lorenzo RJ et al. Neurology 1996;46:1029-35
Trinka E 2017, Seizure 2017.44:65-73

Prognosis: Children

Convulsive SE

- Mortality: 0-43%;
  short term: 3-5%
  long term: further 3%
  determining factor: etiology: symptomatic CSE
- Subsequent epilepsy: 25-40%: highest in acute symptomatic CSE
- Cognitive behavioral disorders: 0-83%
- 35% children with SE >30 min had neuroevelopmental decline

Scott R. 2009;Epilepsia 50:(Suppl 12):S32-33
Barnard C, Wirrell E. J Child Neurol 1999;14:787-94

END

Epilepsy Surgery

Gholam Motamedi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

EPILEPSY SURGERY

Gholam Motamedi, MD
Professor, Department of Neurology
Principal Investigator, Epilepsy Research
Director, Comprehensive Epilepsy Center
Georgetown University Hospital

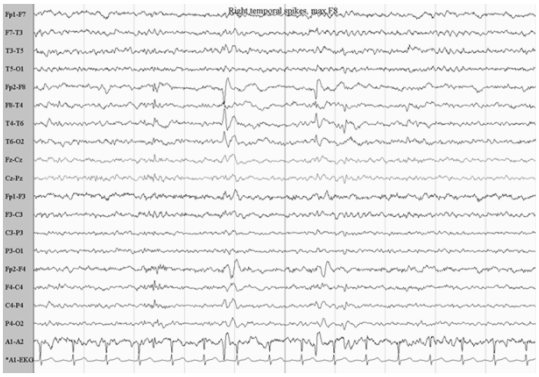
2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

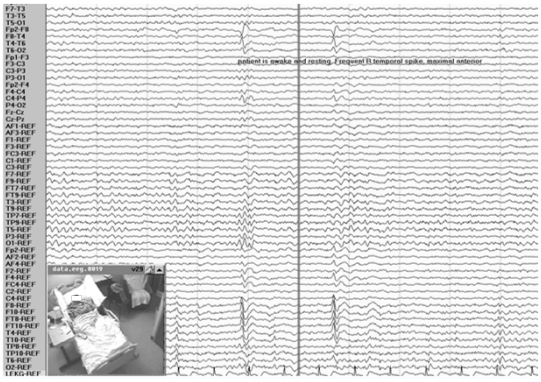
- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Case # 1

- A 28 year old female with seizures since age 9; "staring, left hand clenching before convulsion" (2/week)
- Multiple prior ASDs without much improvement
- Gave up college and previous jobs (unable to "focus", or drive)
- Tremor, memory and concentration problems
- High serum levels of phenytoin and valproate
- EEG and brain MRI obtained

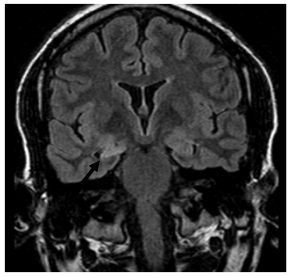


Right anterior-mid temporal spikes; 10-20 electrode system



Right anterior-mid temporal spikes; 10-10 electrode system

Mesial Temporal Sclerosis (MTS)



High resolution MRI detects MTS in 80-90% of cases

Drug Resistant (Refractory) Epilepsy

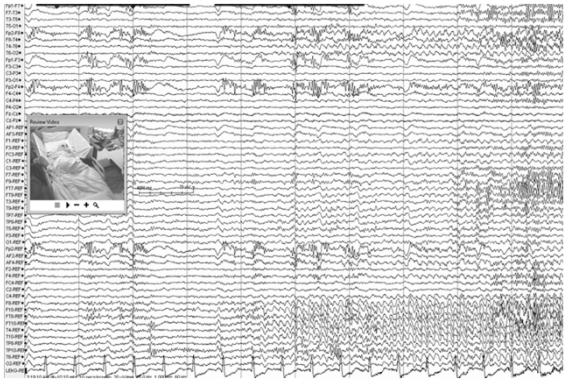
- **Failure of "adequate" trials of:**
  - 2 AEDs (ASDs), as mono- or combination therapy, to control seizures
  (Kwan et al. Epilepsia, 2009; Tellez-Zenteno et al. Epilepsia, 2014)
- **Adequate trial**:
  - Right medication
  - Max tolerated dose (no severe SE)
  - Sustained seizure freedom (A period 3X the longest inter-seizure interval, or 1 year, whichever longer)
- **Dx of refractory epilepsy should not take >1-2 yrs (often ~20 yrs)** (NIH Consensus Statement 1990)

Refractory Epilepsy – Treatment

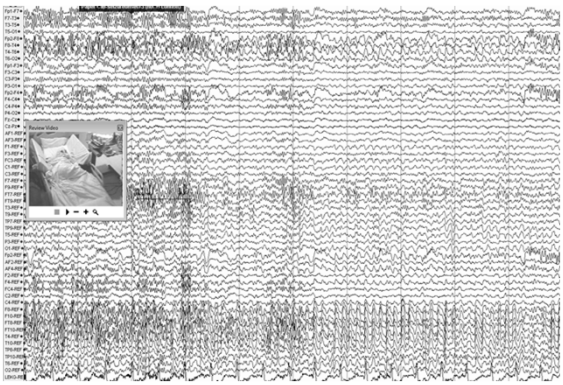
- **Surgical resection of the seizure focus**
- **Surgical "non-resection" options**
  - *VNS, RNS, DBS*
  - *Multiple subpial transections*
  - *Investigational options (TMS, TGNS, external VNS, tDCS)*
- **Ketogenic diet (pediatric)**
- **Future AEDs**
- **Novel potential therapies** (hypothermia, gene therapy, cell transplantation, vaccination)

Presurgical Evaluation

- **Localization**
  - *Video-EEG Monitoring*
  - *Imaging / Source localization (MRI, MRS, PET, SPECT, MEG, etc.)*
- **Neuropsychology**
- **Intracarotid amobarbital procedure (Wada test)**
- **Invasive recording & Cortical mapping**
- **Appropriate surgical procedure**

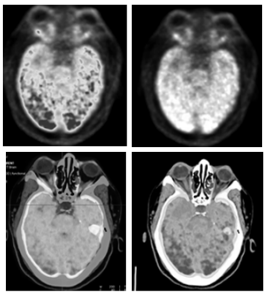


Buildup of rhythmic sharp discharges, Rt anterior-mid temporal

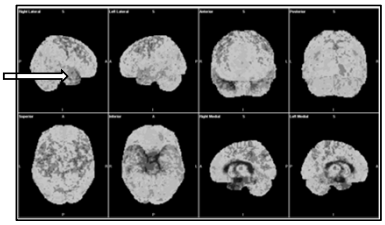


Continued – Ictal onset; Rt anterior-mid temporal

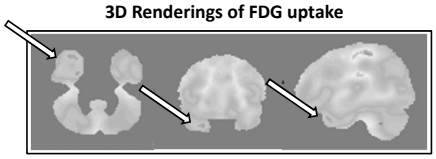
FDG PET Scan



Decreased glucose uptake in the Rt temporal area



3D Renderings of FDG uptake



Statistical maps (blue indicates less activity, 5 SDs)

Neuropsychology

What parts of the brain are impaired?

- Higher cognitive functioning
- Verbal and visual memory
- Language
- Establish a baseline

What are the potential post-surgical deficits?

- **Best predictor of postoperative adequacy:**
  - Preoperative cognitive and psychosocial status: *"The lower the pre-op cognitive / psychosocial status, the lower the risk for decline."*

Meador et al. 2001; Loring et al. 2008

Neuropsychology - 2

- **Lt language dominance**
  - 90-95% Rt-handed individuals
  - 70% Lt-handed individuals
- **Lt temporal / hemisphere**
  - Verbal and Narrative Memory, Language, Verbal Fluency
- **Rt temporal / hemisphere**
  - Visual Memory, Perceptual Reasoning

Intracarotid Amytal Procedure (Wada Test)

- Imitates surgery: Temporarily removing some brain functions by using a drug
- Lateralization of language dominance
- Assessment of memory dominance/function:
  - Ipsilateral memory "Adequacy" & Contralateral "Reserve"

Is the non-epileptic side capable of handling memory by itself?

- Assists with determining the seizure onset side

Case # 1 – 1st Wada Injection

1- 125mg sodium amobarbital -> Rt ICA

2- Lt hemiparesis (0-1/5 motor Lt arm, Lt facial weakness)

3- Dysarthria (No aphasia); could follow commands

4- EEG: Rt-hemispheric delta slowing

5- Quick initial language and attention evaluation, then at 50s post-injection, 8 target objects shown, one at a time

6- Language, motor, and EEG tested in more details *(naming, reading, comprehension, color and shape recognition, using printed material)* till full recovery at 4:52, 5:54, and 7 min, respectively

Case # 1 – 1st Wada Injection

- **At 10 minutes post-injection:**
  - The 8 target objects mixed with 16 decoy objects (foils) were shown to the patient, one at a time
  - Patient recognized 7/8 and no false positives with the decoy items
  - Total memory score for Lt temporal (Rt injection): 7

Case # 1 – 2nd Wada Injection

1- At 45 min a similar injection was given into the Lt ICA

2- Rt hemiparesis (0-1/5 motor Rt arm, Rt facial weakness)

3- Aphasic; unable to follow commands

4- EEG: Lt-hemispheric significant delta slowing with minimal involvement of the Rt

5- After the initial quick assessment, at 55s post-injection she was shown a new set of 8 target objects

6- Language recovery was slower, with full recovery at 10 min, motor at 8:10, and EEG at 8 min, respectively

Case # 1 – 2nd Wada Injection

- At 11 min. post-injection:
  - The 8 targets mixed with 16 decoys were shown
  - Patient recognized 3/8 correctly with 1 false positive (-0.5 point)
  - Total memory score for Rt temporal (Lt injection): 3 - 0.5= 2.5

Case # 1 – Final Wada Conclusions

- Language dominance lateralized to the Lt
- Memory showed a 4.5 point split (7-2.5) between the sides indicative of a significantly better memory function on the Lt

A memory split of ≥ 3 is preferred to establish functional adequacy of the side with higher score

- Difference not likely caused by sedation:
  - No drowsiness or behavioral changes
  - No excessive bilateral EEG changes
  - Stable mood and affect throughout the procedure with normal recovery process

Wada - Indications

- Original reason: language lateralization
- Modified after HM and other cases who became amnestic after unilateral anterior ATL
  - Memory component originally was to predict global amnesia
  - Later use:
    - To predict relative risk for memory loss
    - Left/right memory score used to predict post-op memory outcome and even seizure outcome

Wada – Indications 2

- **Currently, Wada indicated in patients**
  - At risk for significant memory loss (even if not global)
  - Unclear risk (e.g., concern over neuropsych results, primary language not English)
- **Risks for post ATL memory loss**
  - Language dominant hemisphere ATL
  - Older age of onset
  - Older age of surgery
  - No temporal lobe dysfunction (e.g., high pre-op verbal memory & naming; no ipsilateal PET hypometabolism)
  - Evidence of extra temporal lesion

fMRI has not been shown to be a reliable substitute for the Wada memory at this time

Wada – Indications 3

- **Not indicated in ALL left TLE cases**
- **Depends on VEEG, MRI, fMRI, neuropsych, +/- PET**
  - If all concordant, Wada may not add anything in prediction, on a group level, beyond these tests
- **Lt-handedness is not always an indication for Wada**
  - Language lateralization can be determined via fMRI, then depends on above findings
- **Extra temporal lesion is to be considered a risk factor for memory in an ATL candidate**
  - ? an indication of more widespread cerebral dysfunction reducing the potential for rewiring after surgery

Drane D et al. Epilepsia, 2015

Wada – Indications 4

- **Pt with Lt TLE**
  - MRI: Left MTS
  - fMRI: left language
  - PET: ipsilateral hypometabolism
  - Neuropsych: verbal memory & naming deficits

Wada Not indicated (esp. in laser surgery)

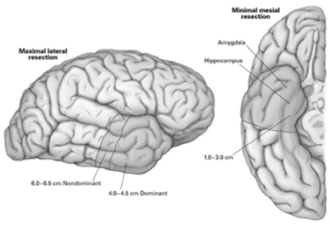
- MRI: no lesion
- PET: Normal
- Neuropsych: normal verbal memory & naming

Wada Indicated (even in laser surgery)

Case # 1 - Outcome

- Presurgical evaluation indicated candidacy for a Rt Anterioro-Mesial Temporal Lobectomy (ATML)
- Started on levetiracetam
- Lamotrigine added, phenytoin & valproate tapered off
- Better cognitive function & less frequent seizures on dual therapy
- Seizure free after Rt anterior temporal lobectomy, currently on minimal dose of monotherapy (F/U >8 years)

Anterior Temporal Lobectomy (En Bloc Resection)



Wiebe et al. N Engl J Med 2001;345:311-8

Is Epilepsy Surgery Warranted?

- **80 patients with TLE randomly assigned to surgery (n=40), or continued AED therapy for one year (n=40):**
  - Primary outcome: Seizure-freedom
  - Secondary outcome: Seizure frequency & severity, quality of life (QoL), disability, death
- **At 1 year, cumulative proportion of seizure-free patients**
  - **Surgical group: %58**
  - **Medical group: %8 (*P<0.001*)**

Wiebe et al. N Engl J Med, 2001

Is Epilepsy Surgery Warranted? - 2

- **Surgical group**
  - Fewer CPS, and significantly better QoL (*P<0.001*) compared to the medical group
- **Surgical group:** 4 patients (%10) had adverse effects
- **Medical group:** 1 death

In TLE, surgery is superior to prolonged medical therapy

Wiebe et al. N Engl J Med, 2001

Early Randomized Surgical Epilepsy Trial (ERSET)

- **Years of active epilepsy predict cognitive impairment in children and adolescents**

Farwell et al. 1985; Bourgeois et al. 1983

- **Multicenter, parallel-group RCT: 38 patients (≥12 yrs) with MTS and refractory MTLE, within 2 consecutive years of adequate trials of 2 AEDs**
  - Continued AED (n=23), OR
  - AMTL plus AED therapy (n=15)

Engel et al. JAMA, 2012

Early Randomized Surgical Epilepsy Trial (ERSET) - 2

- **Seizure-freedom during year 2 of follow-up:**
  - ***11/15 vs. 0/23 (surgical vs. medical group) (P<.001)***
- **Improved QoL: Higher in surgical group (P=.01)**
- **Memory decline: 4 patients (36%) after surgery**
- **Adverse events:**
  - **Surgical group: 1 stroke**
  - **Medical group: 3 status epilepticus**

Engel et al. JAMA, 2012

Temporal Lobe Surgery - Methods

- **Anterior temporal lobectomy (ATL, AMTL)**
  - **Standard (en bloc resection):** 3-6 cm of anterior temporal neocortex & 1-3 cm of mesial structures (amygdala & hippocampus)
  - **Modified (Yale group):** limited neocortical resection (3.5 cm from temporal pole), sparing superior temporal gyrus, for language concerns

Spencer et al. Neurosurgery, 1984; Spencer, in: H Luders, Ed, Epilepsy Surgery 1991

Temporal Lobe Surgery – Methods - 2

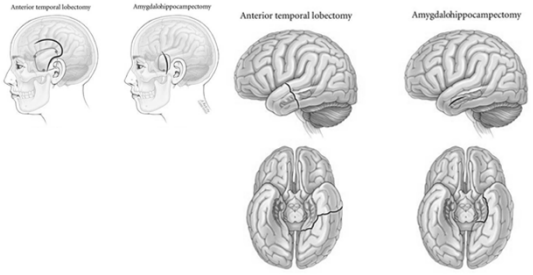
- **Selective Amygdalohippocampectomy (SAH)**

Niemeyer p, 1958

- **Lesionectomy / Super-selective surgery**
  - Resecting temporal pole & amygda, preserving hippocampus
- **Inferior temporal gyrus approach**
  - Resection of the parahippocampal gyrus, amygdala & uncus
- **Stereotactic radiosurgery**
- **Laser Interstitial Thermal Therapy (LiTT)**

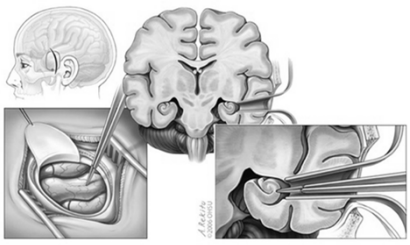
Cordeiro et al. Epileptic Disord, 2011; Vale et al. Neurosurg Focus, 2013; Quigg et al. Epilepsia, 2012

Selective Amygdalohippocampectomy (SAH)



Spencer & Burchiel. Epilepsy Res Treat, 2012

Transcortical Amygdalohippocampectomy



Spencer & Burchiel. Epilepsy Res Treat, 2012

Position of craniotomy, cortical incision, and surgical trajectory

Long-Term Surgical Outcome – MTLE & MTS

- **50 consecutive patients with MTS, S/P ATL**
- **Mean F/U:** 5.8 years (range 2-9.2)
- **Complete seizure free rate:**
  - 82% at 12 months
  - 76% at 24 months
  - 64% at 63 months

Better seizure outcome = Significantly better long-term QoL

Lowe et al. Epilepsia, 2004

- **Risk factor for seizure recurrence:**
  - Reduction in AED intake (5/17; 3 had first seizure within 24 months)

Long-Term Surgical Outcome – MTLE & MTS - 2

- **116 patients with MTS and MTLE**
- **S/P ATL-AH (AMTL)** (Anterior temporal lobectomy including amygdalohippocampectomy)
- **F/U:** 6.7 years
- **Complete seizure-freedom**
  - 103/116 (89%)
  - Engel Class I or II: 109/116 (94%)

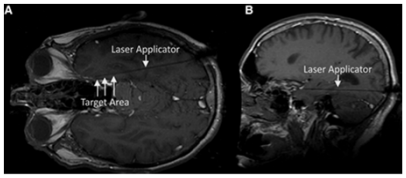
Elliott et al. J Neurosurg, 2013

Long-Term Surgical Outcome – MTLE & MTS - 3

- **Concordance (test consistent with the side of final surgery)**
  - Highest: Video-EEG (100%), PET (100%), MRI (99.0%), Wada (90.4%)
  - Lowest: SPECT (84.6%), Neuropsychological testing (82.5%)
- **Predictor of excellent long-term seizure control:**
  - Strong Wada memory lateralization
- **Predictor of persistent seizures:**
  - Less disparity in Wada memory between sides

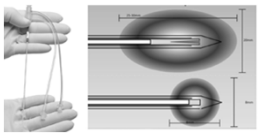
Elliott et al. J Neurosurg, 2013

Laser Interstitial Thermal Therapy (LiTT)



Laser probe. Trajectory planning for laser ablation of amygdala & hippocampus

Donos, Epilepsia. 2018



Visualase Cooled Laser Applicator System (vCLAS) with 10 mm (top) and 3 mm (bottom) diffuser tips and simulated ablation zones

LaRiviere and Gross, Frontiers. 2016

(LiTT)

- Likely lower seizure-free outcome in MTLE compared to temporal lobectomy
- Better outcome in TLE with MTS than non-MTS
- In dominant hemisphere: decline in verbal and narrative memory, but not in naming
- No differences in volumes ablated and seizure outcome
- No data on risk of post-surgical quadranopsia

Tao JX et a. JNNP, 2018; Donors et al. Epilepsia, 2018

Neurocognitive Outcome – ATL: Risk Factors

- **Cognitive impairment (very common in epilepsy):**
  - May be negatively or positively affected after surgery
- **Larger temporal lobe resections:**
  - Better seizure control
  - Worse cognitive outcome (resecting more functional tissues)
- **Individualized /tailored surgery preferred**

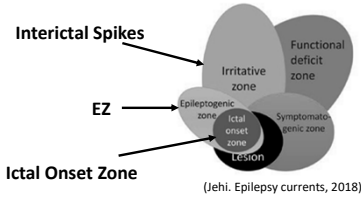
Helmstaedter. Epileptic Disord, 2013

Extra-temporal Surgical Methods

- Focal resection (limited / extensive)
- Lesionectomy
- Multiple subpial transections (MST)
- Corpus callosotomy
- Hemispherectomy

Epileptogenic Zone

- **Area of cortex necessary and sufficient for initiating seizures whose removal is necessary for complete abolishment of seizures** (Luders et al. 1993)



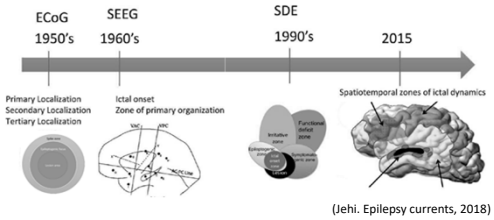
(Jehi. Epilepsy currents, 2018)

Epilepsy as a Network Disorder

- Surgical failure: when only one focus is removed
- High prevalence of comorbid neuropsychiatric disorders
- Functionally, anatomically, bilaterally, connected, cortical and subcortical brain regions
- Multiple foci in a circuit can act as independent seizure generators in an abnormal network
- The epileptogenic zone *is* the brain

(Spencer SS. Epilepsia, 2002; Phi and Cho, J Korean Neurosurg. 2019)

Network vs Focus



(Jehi. Epilepsy currents, 2018)

Broadly applied treatment (directed at any region of the network) **should be as effective as treatments directed at a specific seizure 'focus'**

Stereotactic Electroencephalography (sEEG)

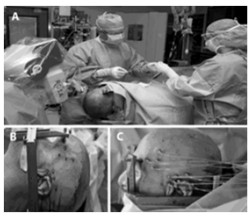
- **Electrodes' position as 3D reconstruction vs. 2D via grid electrodes**
- **Better depiction of epileptogenic network**
  - Simultaneous recording of multiple paths
  - Simultaneous sampling of both deeper, and distant areas of the network
  - Regional rather than focal resection
- **Less spatial resolution for cortical mapping, than grids**

Serletis D et al. J Neurosurg, 2014

sEEG - Robotic Assisted Electrode Placement

- No stereotactic frame
- Co-registering images, 3D image added to software
- Choosing entry point and a target
- Software pin points exact location and trajectory
- Multiple pinhole sized incisions

sEEG - Robotic Assistant Device



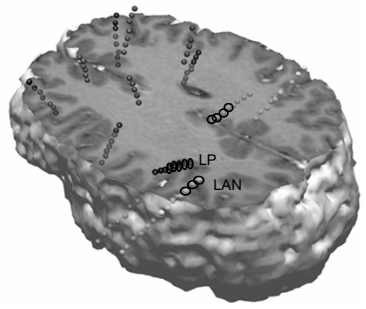
A. OR set up during a left frontal-temporal SEEG robotic implantation; robot device placed in the middle at the vertex

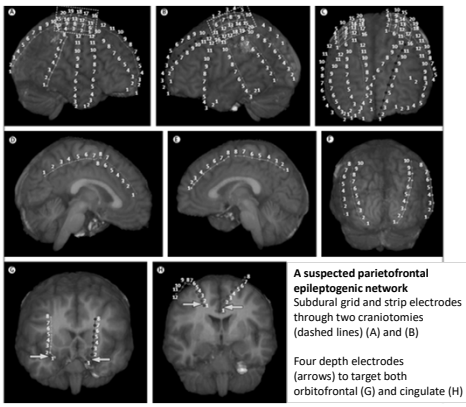
B. Implantation with the guiding bolts' final position

C. Final aspect

Alomar SA et al. Cleveland Clinic, 2016

- Interictal and ictal
  LP=Lt Parietal
  LAN=Lt Angular





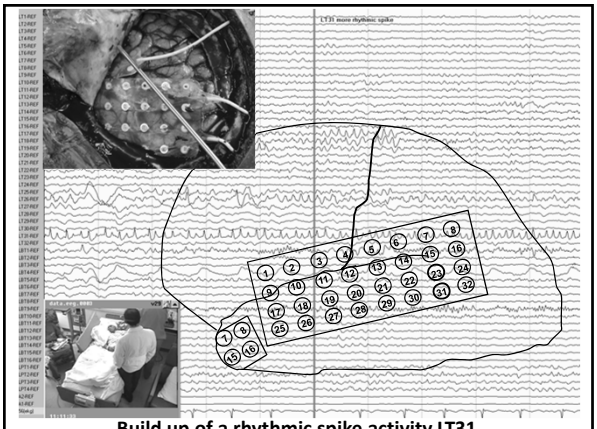
A suspected parietofrontal epileptogenic network
Subdural grid and strip electrodes through two craniotomies (dashed lines) (A) and (B)

Four depth electrodes (arrows) to target both orbitofrontal (G) and cingulate (H)

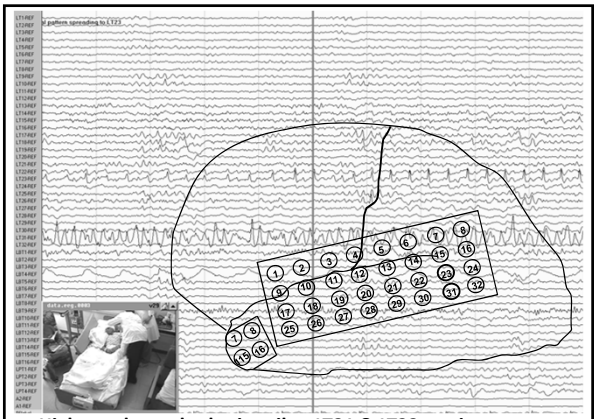
Spencer et al., Lancet Neur, 2018

Case # 2

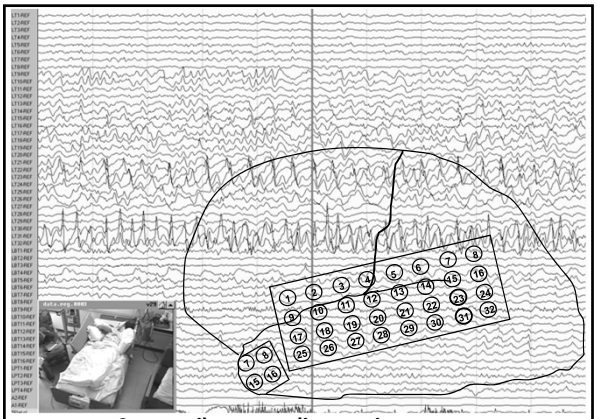
- A 43 year old man developed seizures two years after surviving a left temporal aneurysm rupture
- Aneurysm resected; did well until the seizures
- Multiple AEDs tried; continued having partial seizures with 2^{ndry} generalization (~ 2/month)
- Imaging: Lt lateral temporal encephalomalacia, no MTS
- Monitoring: seizure onset focus localized to the left posterior temporal area
- Admitted for subdural grid placement



Build up of a rhythmic spike activity LT31



Higher voltage rhythmic spikes LT31 & LT23; patient aware

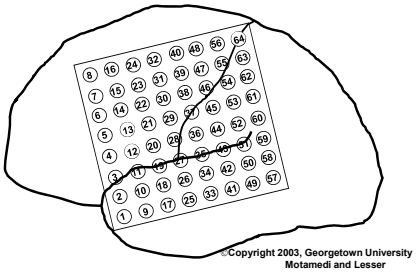


Same spikes spreading; patient aware

Cortical Stimulation Mapping

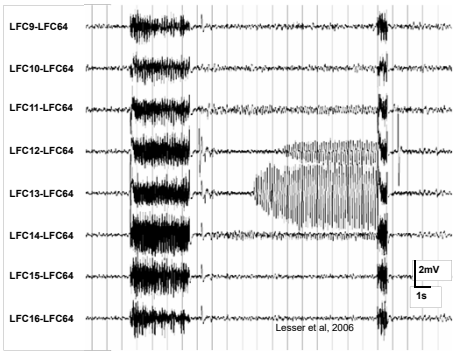
- 2.3-mm-diameter platinum-iridium electrodes embedded in a plastic sheet; 1cm center-to-center distances (Ad-Tech, Racine, Wisconsin)
- Alternating polarity square wave pulse pair stimulation (0.3 msec, 50 or 100 Hz), 3-5 seconds
- One electrode pair stimulated at a time starting at a low intensity (1 to 2 mA) titrated up by 0.5 to 1.0 mA at a time till a functional change occurs, or max current of 15-17.5 mA is reached, or ADs develop

Cortical Stimulation Mapping



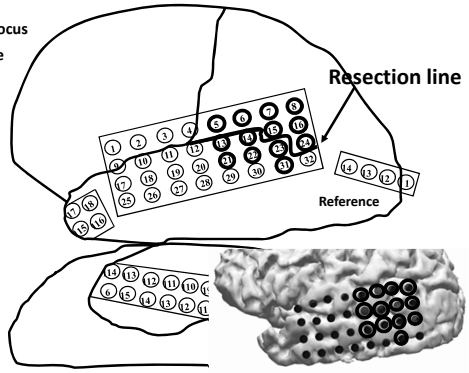
Left hemispheric subdural grid electrode; stimulated pair of electrodes (12 & 13) and reference (64)

Cortical Stimulation Mapping



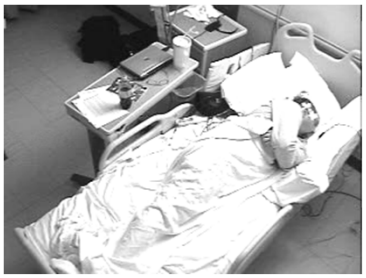
Cortical (Language) Mapping

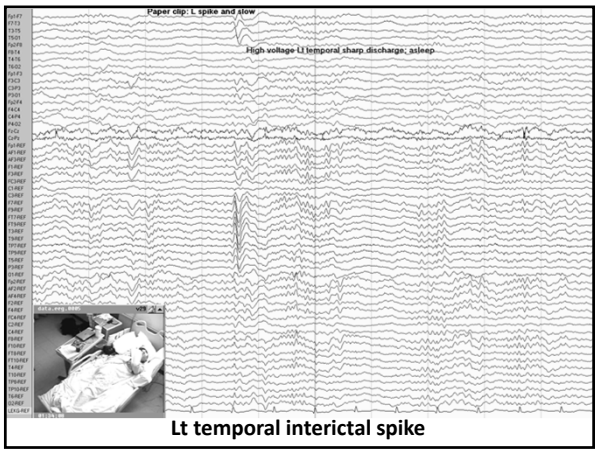
- Seizure focus
- Language
- Sensory
- "Clear"



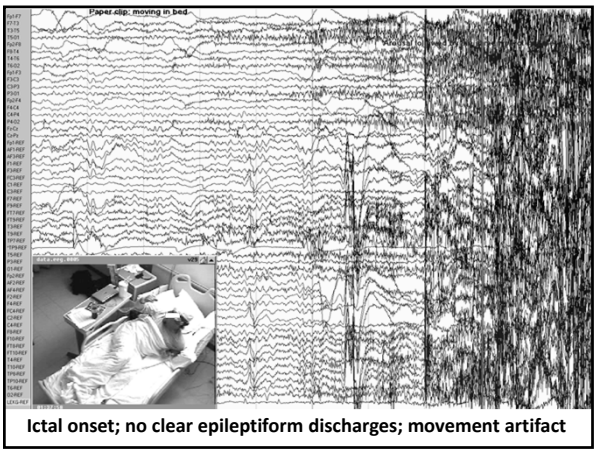
Case # 3

- A 45 year old male. For the past 20 years, he would wake up soon after falling asleep screaming and flailing his arms and legs for 30 seconds before full recovery
- Currently on 4 AEDs; has tried most available AEDs, Klonopin, and SSRIs, for seizures, sleep disorders, and "pseudoseizures"
- EEGs and PSG: always normal
- Current Sz frequency: 3-7/night
- Unemployed, no driving, wife sleeps in a separate room

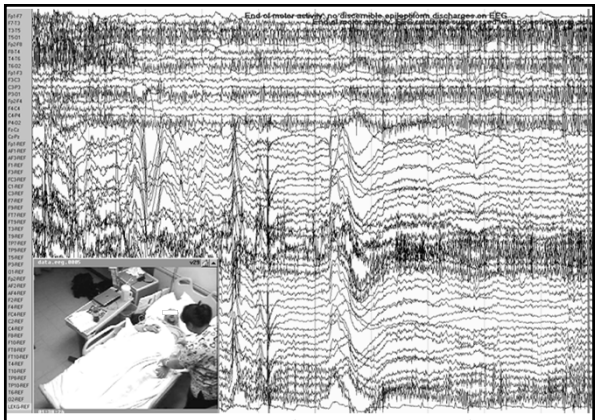




Lt temporal interictal spike

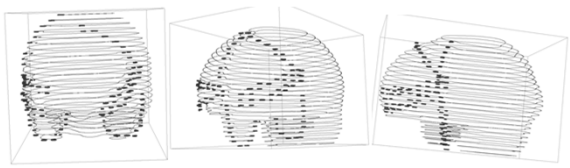


Ictal onset; no clear epileptiform discharges; movement artifact

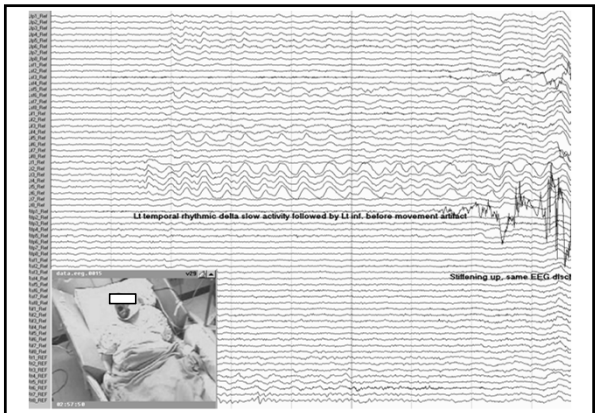


Postictal; no clear epileptiform discharges; artifactual

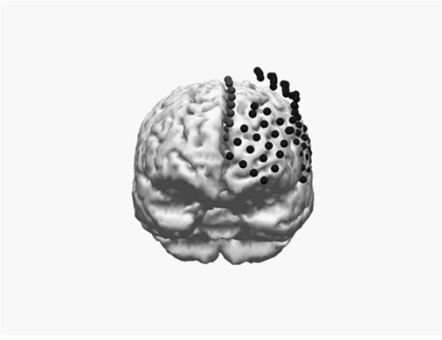
Subdural Strips – Lateralization (Phase 2a)

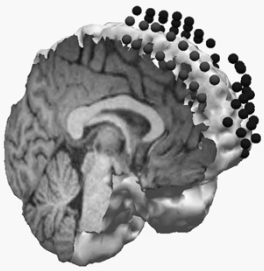


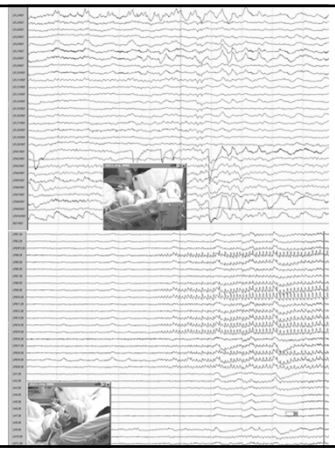
Frontal **Lt oblique** **Lt lateral**



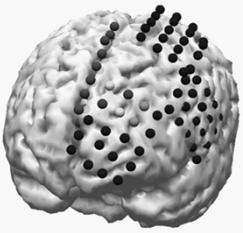
Lt temporal rhythmic delta discharges; 10 s from Sz onset







Very high frequency
Low voltage discharges
(ictal onset)
Lt fronto-polar
grid electrodes



Magneto-encephalogram- MEG

- In case of non-concordant findings, MEG may provide additional information in 35% (crucial to final decision making in 10%)

(Stefan et al. 2003; DeTiege et al., 2012)

- Seizure-free outcomes significantly improve if stereo-EEG evaluation sampled the entire MEG cluster of spikes (Murakami et al, 2016)

Outcome - Frontal Lobe Epilepsy Surgery

- FLE patients with identifiable focal lesion
  - More likely to achieve seizure-freedom (than those without)
- Meta-analysis of 21 studies (1199 patients) of FLE surgery; F/U ≥ 48 months
- Seizure-freedom (Engel Class I outcome): 45.1%
- Predictors of long-term seizure-freedom:
  - Lesional FLE
  - Localized resection (vs. extensive lobectomy)

Englot et al., J Neurosurg, 2012

Overall Seizure-Free Outcome

- Temporal lobectomy: 55-80%
- Frontal lobe resections: 5-18%
- Frontal lobectomy: 23-68%
- Parietal lobe resections: 45%
- Occipital resections: 46-88%
- Hemispherectomy: 60%

Corpus Callosotomy - Indications

- **Drop Attacks (Atonic seizures): most common**
- **West or Lennox-Gastaut syndrome (tonic, atonic, tonic-clonic)**
- **Recurrent episodes of status epilepticus with generalized seizures**
- **Partial seizures with rapid 2^{ndry} generalization:**
  - No obvious foci, multifocal, widespread frontal lobe lesions, 2^{ndry} generalization with normal MRI
- **Generalized tonic–clonic seizures**
- **Absence seizures**
  - Refractory idiopathic generalized epilepsy

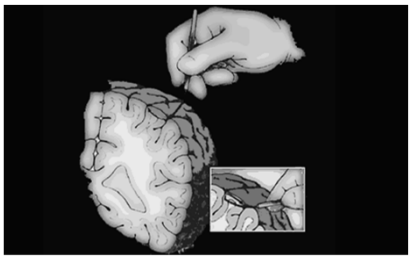
Asadi-Pooya et al., E & B, 2008

Hemispherectomy

- Introduced by McKenzie in 1938
- Indications:
  - Intractable seizures of infancy & early childhood
  - Arising diffusely from one hemisphere
  - Associated with unihemispheric insults
    - Hemimegalencephaly
    - Other multilobar cortical dysplasias
    - Perinatal strokes
    - Sturge-Weber syndrome
    - Rasmussen encephalitis

Wiebe and Berg, Neurology, 2013

Multiple Subpial Transection (MST)



Morrel F et al. J Neurosurg, 1989

Multiple Subpial Transection (MST)

- Some or all epileptogenic zone lying in eloquent cortex
- Epileptogenic discharges require side-to-side (horizontal) interaction of cortical neurons
- Major functional properties of cortical tissue depend upon the vertical fibers
- Severing of tangential intracortical fibers while preserving vertical fiber connections and blood vessels

Morrel F et al. J Neurosurg, 1989

Multiple Subpial Transection (MST)

- Intractable epilepsy arising from eloquent cortex (n=22)
- Resection + MST (n=16)
  - Seizure free: 9 (56%)
  - >95% seizure reduction: 6 (37%)
- MST alone (n=6)
  - Seizure free: None
  - >50% reduction: 4

Hufnagel et al. Epilepsia, 1997

Neuromodulation in Epilepsy (VNS, RNS, DBS)

Gholam Motamedi, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

NEUROMODULATION IN EPILEPSY (VNS, RNS, DBS)

Gholam Motamedi, MD
Professor, Department of Neurology
Principal Investigator, Epilepsy Research
Director, Comprehensive Epilepsy Center
Georgetown University Hospital

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

Primary Objective

Review indications & clinical/ technical aspects of
VNS
RNS
DBS
therapy in drug-resistant epilepsy

Outline

- Historical Aspect
- Indications
- Technical Aspects
- Clinical Trials
- Managing Stimulus Parameters
- Safety and Precautions

DRE- Definition

- **Failure of "adequate" trials of 2 AEDs as mono- or combination therapy, to control seizures**
- **Adequate trial**:
  - Right medication
  - Max tolerated dose (no severe SE)
  - Sustained seizure freedom (Time period 3 times the longest inter-seizure interval, OR 1 year, whichever longer.)

(Kwan et al., Epilepsia, 2009; Tellez-Zenteno et al., Epilepsia, 2014)

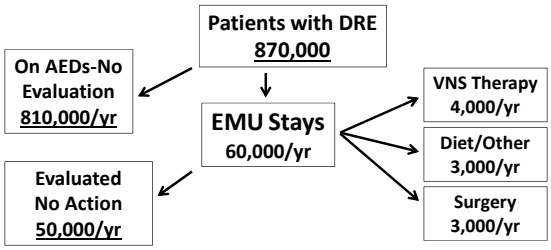
Drug Resistant (Refractory) Epilepsy

- **> 50% of patients with epilepsy have focal epilepsy**
- **AED success rate:**
  - **Focal epilepsy: ~ 50%**
  - **Primary generalized epilepsy: > 80%**

(Hauser et al., 1996; Sillanpää et al., 1998; Bergey, 2013)

DRE- Management

2.8 million patients in US with Epilepsy



Only 1-2% of DRE patients receive other treatments

Prevalence data based on CDC. Accessed June 2015

VNS- History

1985	First animal studies
1988	First human implant
1992	First randomized active control study (E03) completed
1994	European community approval
1996	Second randomized active control study (E05) completed
1997	U.S. Food and Drug Administration commercial approval in patients ≥ 12 years with refractory partial epilepsy
2005	U.S. Food and Drug Administration commercial approval in patients ≥ 18 years with chronic major depression refractory to adequate treatment with≥ 4 antidepressants
2018	>100,000 (>30,000 children) implants worldwide for both epilepsy and depression

Wheless JW, Wyllie's Treatment of Epilepsy: Principles and Practice, 2011
http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s050a.pdf

VNS- Approved Indications

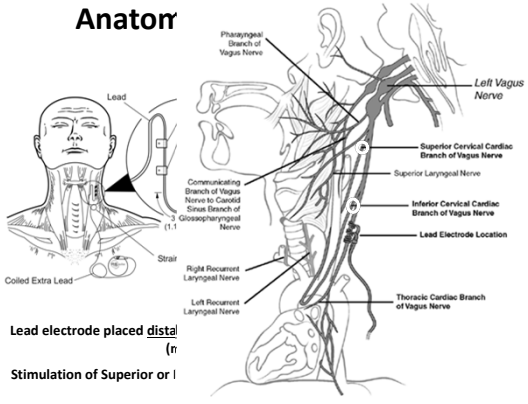
- **Adjunctive therapy in patients ≥ 12 years (≥ 4 years for SenTiva) with refractory (drug-resistant) focal onset epilepsy**
- **Adjunctive therapy in *patients ≥18 years with* chronic or *recurrent* major depressive episodes refractory to adequate response to ≥ 4 adequate antidepressants**

VNS- Clinical Indications

- **Patients with refractory focal epilepsy:**
  - **Not (resective) surgical candidates**
    - Multifocal epilepsy
    - Unclear focus
    - Overlapping eloquent cortex
  - **Opposed to brain surgery**
- **Patients with unsuccessful epilepsy surgery**
  - 18.75% had ≥50% reduction in seizure frequency, one had severe worsening
  - VNS may have a limited role in these patients but may have mood-stabilizing effects

(Koutroumanidis et al, 2003)

Anatom



Lead electrode placed distal
(r

Stimulation of Superior or I

Initial Clinical Trials- Overview

- **Purpose: Adjunctive VNS in DRE**
- **5 acute-phase clinical studies**
- **45 centers (40 US, 1 Canada, 4 EU)**
- **454 implanted with VNS**
- **Total patient exposure: 901 device-years**
- **Individual mean patient exposure: 24 months (8 days-7.4 years)**

Initial Clinical Trials- Overview

All patients implanted in all clinical studies, N=454						
Description of Patients						
	Longitudinal			Parallel		
Study	E01	E02	E04	E03	E05	Total
Number of patients implanted	11	5	124	115	199	454
Number of patients stimulated	10	5	123	115	198	451
Age in years (range)	32 (20–58)	33 (18–42)	24 (3–63)	33 (13–57)	33 (13–60)	32 (3–63)
Number of females (%)	4 (36%)	2 (40%)	57 (46%)	43 (37%)	104 (52%)	210 (46%)
Years with epilepsy (range)	22 (13-32)	20 (5-36)	17 (0.8-48)	21 (4-47)	23 (2-52)	21 (0.8-52)
Average number of AEDs	1.0	1.0	2.2	2.1	2.1	2.1
Median number of seizures per day at baseline	0.6	0.42	0.65	0.70 high/ 0.85 low	0.58high/ 0.51 low	-

Cyberonics.com, Physician's manual, 2008

Initial Clinical Trials- Design

1- Patients implanted (baseline period 12 wks)

2- VNS activated (2 weeks)

3- E03 & E05 (RCT, active control)
1. HIGH group (intense parameters)
2. LOW group (weaker; active control)

DeGiorgio et al., Epilepsia, 2000

4- Treatment period (14 weeks)

VNS Therapy- Parameters

	High	Low	Rapid cycling
VNS current (mA)	Up to 3.5	1.2 (0.25-2.75)	Up to 3.5
Frequency (Hz)	30 (20-50)	1 (to 2)	30
Pulse width (ms)	500	130	500
On time (s)	30 (to 90)	30	7
Off time (min)	5 (to 10)	180 (60-180)	0.2
Magnet current (mA)	Same as VNS	0	Same as VNS
On time (s)	30 (to 90)	30	30
Pulse width (μs)	500	130	500

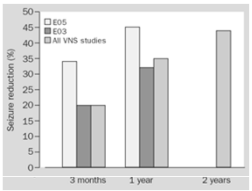
Values in red: most common settings from the E03 and E05 studies

(A randomized controlled trial of chronic VNS (E03), Neurology, 1995; Wheeler et al., Seizure, 2011)

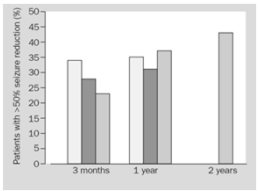
Clinical Trials- Efficacy and Safety

- **HIGH group: significant decrease in seizure frequency** (compared to baseline, and LOW group)
- **Mean seizure reduction:**
  - **HIGH group: 24.5%**
  - **LOW group: 6.1%** (p = 0.01)
- **≥50% seizure reduction:**
  - **HIGH group: 31%**
  - **LOW group: 13%** (p = 0.02)
- **Well tolerated; common adverse events**
  - Voice alteration, Dyspnea
  - %97 continued into long-term F/U phase

Clinical Trials- Efficacy



% Seizure reduction

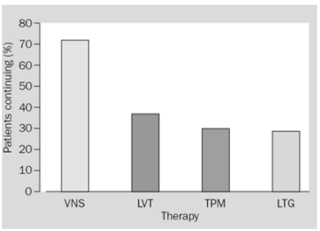


% of ≥50% seizure reduction

E03 (n=114), E05 (n=105) RCTs & all (E01-E05) combined (n=440)

(Ben-Menachem, Lancet Neurol. 2002)

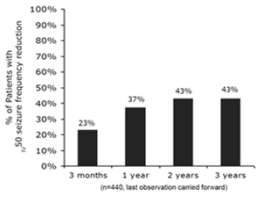
Clinical Trials- Adherence



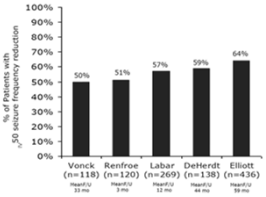
Comparison of long-term (3-year) continuation rates
VNS, levetiracetam (LVT), topiramate (TPM), lamotrigine (LTG)

Ben-Menachem, Lancet Neurol. 2002

Long-term Outcome Improvement



(Morris GL, et al. Neurology, 1999)



(Vonck et al. J Clin Neurophysiol, 2004; Renfroe and Wheless, Neurology, 2002; Labar, Seizure 2004; De Herdt et al. Eur J Paediatr Neurol. 2007; Elliott et al. Epilepsy Behav. 2011; From: Cyberonics , 2012)

Long-term Outcomes with Off-label Use

- 436 adults and children (1-76 years, mean: 29) with refractory partial and generalized epilepsy (1997 -2008)
- VNS duration: 10 days-11 years (mean: 4.9)
- Mean seizure reduction:
  - 55.8% (P<0.0001)
  - ≥90% in 22.5%, ≥75% in 40.5%, ≥50% in 63.75%
- Permanent vagus nerve injury: 2.8%

VNS can be an option for focal and generalized refractory epilepsy in adults and children

(Elliott et al., Epilepsy Behav, 2011)

Long-term Outcomes with Off-label Use

- 146 pediatric patients (age <18 years)
- Primary generalized epilepsy (68%), focal epilepsy (32%); F/U: 41 months
- Seizure frequency reduced (91%), seizure duration (50%), postictal period (49%), AED use (75%)
- No sig. difference between age ≥ & <12 years, in gender, seizure type or duration, frequency reduction, postictal period, AED use, or QOL improvement

Children with both types of epilepsy benefit from VNS

(Thompson et al., J Neurosurg Pediatr, 2012)

Stimulation & Safety

- **Stimulation therapy**
  - *Output current*
  - *Signal frequency*
  - *Pulse width*
  - *ON/OFF time*
- **Stimulation at high frequency (≥50 Hz) + ON time ≥ OFF time: degenerative nerve damage (in animals)**
  - *ON time ≥ OFF time can be induced by continuous or very frequent magnet activation (> 8 hrs)*

Initial Dosing Settings (suggested)

(Visit 1 ≥ 2 weeks post-op)

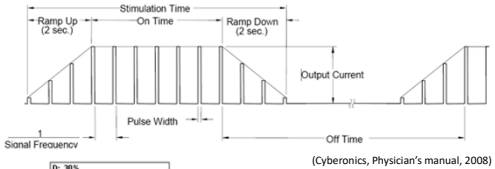
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
OUTPUT CURRENT	mA	0.25	0.5	0.75	1.0	1.25	1.5	1.5	1.5
SIGNAL FREQUENCY	Hz	20/30	20/30	20/30	20/30	20/30	20/30	20/30	20/30
PULSE WIDTH	µsec	250/500	250/500	250/500	250/500	250/500	250/500	250/500	250/500
SIGNAL ON TIME	seconds	30	30	30	30	30	30	30	30
SIGNAL OFF TIME	minutes	5	5	5	5	5	5	3	1.8
MAGNET CURRENT	mA	0.5	0.75	1.0	1.25	1.5	1.75	1.75	1.75
MAGNET ON TIME	seconds	60	60	60	60	60	60	60	60
MAGNET PULSE WIDTH	µsec	500	500	500	500	500	500	500	500

(Cyberonics, General Dosing Guidelines, 2012)

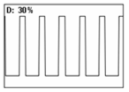
No AED changes for the first 3 months of VNS therapy

Give time to adapt before leaving office & before next increment

Duty Cycle



(Cyberonics, Physician's manual, 2008)



(From: Wikipedia)

30% Duty Cycle (pulse ON 30% & OFF 70% of the time)

Duty Cycle: % of time current is ON/Total time
(ON Time + 4 sec./ON Time + OFF Time)

Stimulation Parameters - Duty Cycle

Duty Cycles for Various ON and OFF Times

Duty Cycles (% ON Time)[1]

ON Time (sec)	OFF Time (min)								
	0.2	0.3	0.5	0.8	1.1	1.8	3	5	10
7	58%	44%	30%	20%	15%	10%	6%	4%	2%
14	69	56	41	29	23	15	9	6	3
21	76	64	49	36	29	19	12	8	4
30	81	71	57	44	35	25	16	10	5
60	89	82	71	59	51	38	27	18	10

[1]Duty Cycle = (ON Time + 4 seconds) / (ON Time + OFF Time), for which ON & OFF Time are measured in seconds.

Recommended

Not Recommended

(Cyberonics, General Dosing Guidelines, 2012)

Adverse Effects

- **Hoarseness**
  - *Device malfunction*
  - Nerve constriction (apparent within a few days)
  - Nerve fatigue (intense stimulation parameters): turn off for several days until hoarseness subsides
  - Persistent hoarseness *not associated with stimulation: ?* nerve irritation (immediate investigation)
- **Dysphagia and aspiration**
  - Higher risk with pre-existing swallowing difficulties
- **Dyspnea**
  - Higher risk with underlying COPD or asthma
- **Obstructive sleep apnea (OSA)**
  - Higher risk of apneic events during stimulation (lower stimulus frequency or longer "OFF" time recommended)
  - New onset OSA has been reported; consider prior evaluation

Adverse Effects

- **Nerve damage (device malfunction)**
  - Painful stimulation (tape magnet over the generator to stop stimulation if suspect a malfunction; possible surgical intervention)
- **Laryngeal irritation** (smokers)
- **Lead break**
  - May prevent stimulus delivery
  - Turn to 0mA output current (to prevent conductor material dissolution, pain, inflammation, vocal cord dysfunction)
- **Trauma to Vagus nerve**
  - During surgery (permanent dysfunction possible)
- **Manipulation of pulse generator & Lead by patients (Twiddler's Syndrome)**
  - May damage/disconnect Lead from generator

Adverse Effects- SUDEP

- Sudden unexpected death in epilepsy (SUDEP)
  - Incidence in **non-VNS** epilepsy patients
    - **1.3-3.5/1000**: Epilepsy population
    - **9.3/1000**: Surgical candidate population
  - ***40,443* VNS patients** in US (1988-2012)
    - ***277,661*** person-years of follow-up
    - ***3,689*** deaths
    - ***632*** SUDEP
    - Significant decrease in SUDEP over time
    - ***2.47/1000 (years 1-2), 1.68/1000 (years 3-10)***

Ryvlin P et al. Epilepsia, 2018

Precautions

- **Cardiac evaluation:** If FH, PMH, conduction problems
- **Serum electrolytes (K^+, Mg^{2+}, Ca^{2+})**
  - Document before implantation
- **Postoperative bradycardia**
  - History of cardiac arrhythmias
  - Post-implant EKG & Holter
- **Bradycardia (< 40 bpm), and/or asystole in OR**
  - Cardiac monitoring when activating in clinic

Impedance

High Lead impedance (≥5300 Ohms)

- **Not an indication of malfunction if:**
  - No other device-related complications
- **Patient not feeling even the max output stimulus:**
  - ? lead wire fracture/electrical discontinuity
- **Possible lead replacement if:**
  - High lead impedance
  - No sensation of max output
  - More seizures

Low Lead Impedance (≤600 Ohms)

- **Short-circuit in the lead; evaluate if:**
  - Sudden impedance drop
  - More seizures
  - Device-related complications (pain, no stimulation)

Optimizing Parameters

Increase charge density

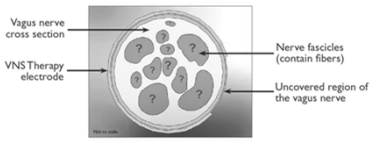
- Increase output current
- Modify ON/OFF times (duty cycle)

Managing side effects

- ***Decrease signal frequency (30Hz to 20Hz)***
- ***Decrease output current (by 0.25mA)***
  - Failed: lower pulse width (to 250μsec)
  - Failed: lower output current (by 0.25mA)

Response Variability

- Key fascicles vary among patients
- Position of fascicles
- Electrode may not fully encircle a large fascicle
  - Uncovered key fibers may require more current for activation



Krahl SE, et al. Epilepsia 2001

VNS Warnings - MRI

- MRI compatible (1.5T & 3T scanners)
- Head and extremity scans allowed using transmit and receive RF coil
- Program both (before entering MR room: risk of magnet mode activation):
  - Output Current (mA): 0.0
  - Magnet Current (mA): 0.0
- Post-MRI:
  - Turn the current back on to original
  - System diagnostics: impedance OK
  - Interrogate again

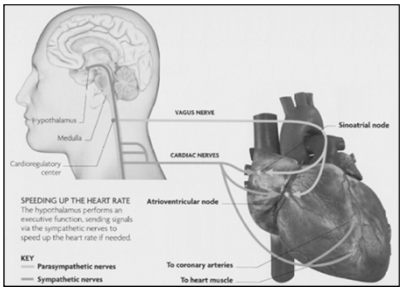
Cyberonics.com

VNS Warnings

- **Diathermy** (shortwave, microwave, ultrasound)
  - Should be avoided
- **Extracorporeal shockwave lithotripsy**
  - May damage the generator
  - Avoid positioning the area where the generator is implanted in the water bath
  - If positioning not possible, program the generator output to 0 mA
- **No MRI with lead breaks**
- **For more details contact Clinical Technical Support at 866-882-8804**

Cyberonics.com, Physician's manual

Stimulation Upon Tachycardia



82% of patients experience tachycardia during seizures

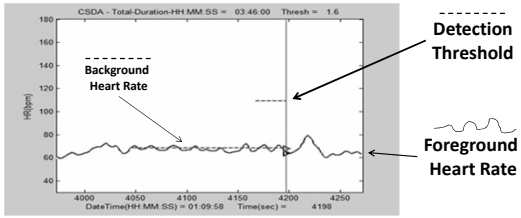
Adapted from Carter R et al. The Human Brain Book, 2009; Eggleston et al. 2014

AspireSR AutoStim

AspireSR Parameters	Description
Tachycardia Detection	**ON** or **OFF**
Threshold for AutoStim (% heart rate change)	**Range: 20-70 %**
Heartbeat Detection (sensitivity)	**Range: 1-5**
AutoStim Mode Settings	**Output current:** **0 mA-2.0 mA (0.125 mA increments)** **2.0 mA-3.5 mA (0.25 mA increments)** **Pulse Width: 130-1000** **Signal ON Time: 30/60 sec**

VNS Therapy Physician's Manual, Cyberonics

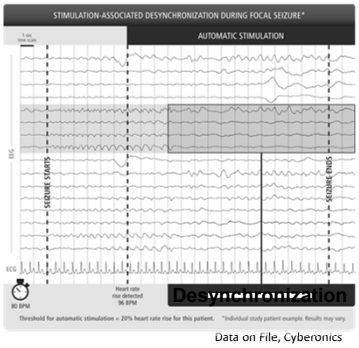
AspireSR- Detection Algorithm



VNS detects HR before- during- & after two ictal events
Floating Detection Threshold automatically adjusts to patient's underlying activity

Data on File, Cyberonics

Seizure Cessation via Auto Stim



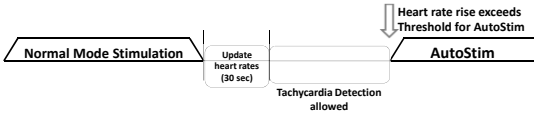
> 60% of seizures treated (n=46) ended during automatic stimulation

The closer the stimulation to seizure onset, the shorter the seizure duration

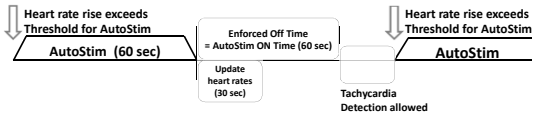
Data on File, Cyberonics

Post-Stimulus – AspireSR

A: After Normal Mode



B: After AutoStim



Data on File, Cyberonics

SenTiva

- **Indicated in children ≥ 4 years**
- **AutoStim**
  - HR dependent
- **Scheduled Programming**
  - Scheduled titration
- **Day & Night Programming**
  - Two independent sets of parameters

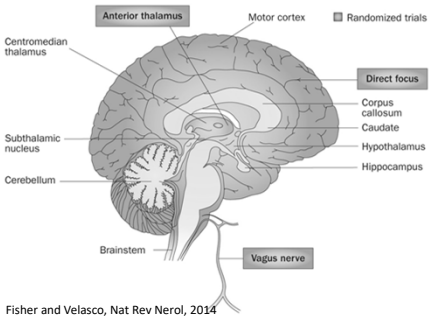
Mechanism of Action 1

- **Precise mechanism(s) unknown**
- **Animal models** (maximum electroshock, PTZ, alumina gel, strychnine, kindling)
  - **VNS prevented seizures or seizure spread** (except for alumina gel model)
- **VNS affects HR & RR**
- **Vagus-initiated activity localization in the brain**
  - use of *fos1* immunoreactivity
  - regional brain glucose metabolism (animals)
  - PET imaging (human)

Mechanism(s) of Action 2

- **PET scan evidence of increased CBF:**
  - Rostral medulla
  - Rt thalamus
  - Rt anterior parietal cortex
  - B/L hypothalamus
  - Anterior insula
  - Inferior cerebellum
- **Decreased CBF detected B/L:**
  - Hippocampus
  - Amygdala
  - Posterior cingulate gyrus

Neurostimulation



Fisher and Velasco, Nat Rev Nerol, 2014

Neurostimulation- Types

- **Open-loop**
  - Applying fixed preprogrammed stimulation without detecting an upcoming seizure (VNS)
- **Closed-loop**
  - Applying a tailored therapy in response to a detected seizure (RNS)

Sun & Morrell, 2014

Intracranial Neurostimulations

- Two pivotal trials of neurostimulation in patients with DRE
  - Closed-loop responsive neurostimulation (RNS) of intracranial structures (Morrell, 2011)
    - *FDA approved (Dec. 2013)*
  - Chronic programmed B/L stimulation of anterior thalamus (SANTE) (Fisher et al., 2010)
    - *FDA approved (May 2018)*

Responsive Neurostimulation (RNS)

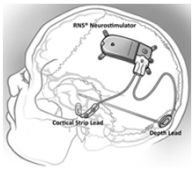
- NeuroPace RNS System
  - Adjunctive therapy in patients ≥ 18 years with intractable focal epilepsy with Both
    - 1 or 2 epileptogenic foci
    - Frequent disabling seizures

(FDA.gov, 2013; Heck et al., Epilepsia, 2014)

Responsive Neurostimulation (RNS)

Stimulator implanted in the skull

Leads implanted directly in the brain

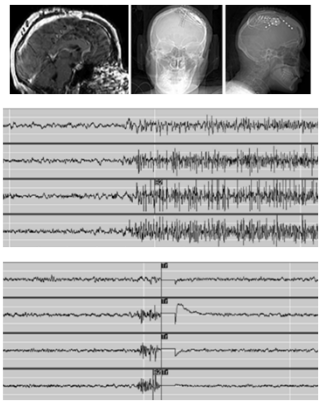


Implanted RNS Neurostimulator and NeuroPace depth & cortical strip lead

Heck et al., Epilepsia, 2014)

Patient Characteristics & Safety

1. Bergey, GK. Et al. Neurology. 2015
2. Data on file, as of Sept 2015. Presented at ANA annual meeting, 2015

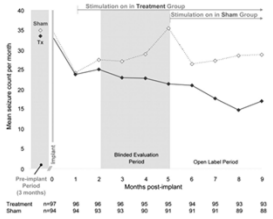


RNS- Pivotal Clinical Trial

- Multicenter, randomized double-blind (RDB)
- 191 patients with partial epilepsy (≥3 seizures/ month, 1 or 2 seizure foci)
- RNS detecting ictal EEG connected to depth or subdural leads placed at 1 or 2 seizure foci
  - 1 month post implant, subjects randomized 1:1 to Active or Sham stimulation
  - 12-week blinded phase
  - Then all received unblinded stimulation (open label)
- Median % seizure reduction at 84-week F/U:
  - 37.9% reduction in stimulated group vs. sham (17.3%) (p = 0.012)

(Morrell and RNS System in Epilepsy Study Group, 2011)

RNS- Pivotal Clinical Trial



- Open-label: seizure reduction sustained in Tx group (reduced in sham group when stimulation began)
- Overall QoL: Significant improvements (p < 0.02)
- Mood/Neuropsychological function: No deterioration

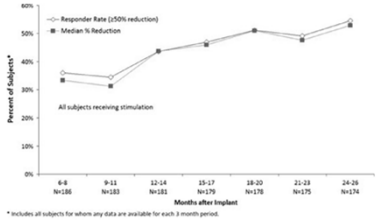
(Morrell and RNS System in Epilepsy Study Group, 2011)

RNS Pivotal Trial- Open Label

- 2-year F/U:
  - Seizure reduction in adults with focal DRE on RNS
- Median % seizure reduction:
  - 44% (at 1 year)
  - 53% (at 2 years)
- Adverse event:
  - No difference, active vs sham groups
  - Known risks of implanted medical device, seizures, and treatments
  - No adverse neuropsychological or mood effects
- Improving seizure reduction over time (p<0.0001), well tolerated, acceptable safety

(Heck et al., 2014)

RNS Pivotal Trial- Open Label

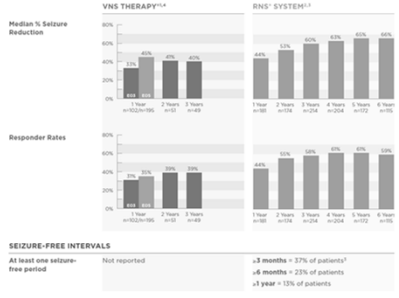


Heck et al., Epilepsia, 2014)

Median % seizure reduction
- 44% (1 year)
- 53% (2 years)

Improving seizure reduction over time

VNS vs. RNS- Seizure Reduction



1. Cyberonics. Vagus Nerve Stimulation System Manual. EO3 & EO5 Studies
2. Heck, CN. Epilepsia. 2014 Mar;55(3):432-41
3. Bergey GK. Neurology. 2015 Feb 24;84(8):810-7
4. DeGiorgio CM. Epilepsia. 2000 Sep;41(9):1195-200

VNS vs. RNS- Tolerability & Safety

	VNS THERAPY®	RNS® SYSTEM
Average Stimulation Duration	> 4.3 hours/day[1]	< 6 min/day[2]
Stimulation Related Side Effects Assessed at 1 Year	**Mostly persistent events[4]** • Voice alteration (55%) • Increased cough (15%) • Paresthesia (15%) • Dyspnea (13%) • Pharyngitis (10%)	**Mostly single events[5]** • Dysesthesia (4%) • Photopsia (4%) • Paresthesia (1%) • Muscle twitching (0.5%)

1. Cyberonics. Vagus Nerve Stimulation System Manual. EO3 & EO5 Studies.
2. Heck, CN. Epilepsia. 2014 Mar;55(3):432-41
3. Bergey GK. Neurology. 2015 Feb 24;84(8):810-7
4. DeGiorgio CM. Epilepsia. 2000 Sep;41(9):1195-200
5. Morrell MJ. Neurology. 2011 Sep 27;77(13):1295-304

RNS- Long-Term Safety

SUDEP rate (probable or definite) was 2.3 per 1,000 patient stimulation years (CI 0.9–6.1).[6]

3.5% infection rate per neurostimulator procedure. All infections were superficial soft tissue infections. There were no meningitis or parenchymal infections, and no chronic neurologic or medical consequences.[3, 7]

2.7% intracranial hemorrhage rate with no persistent, clinically significant neurologic sequelae.[3, 8]

3. Bergey GK. Neurology. 2015 Feb 24;84(8):810-7
4. DeGiorgio CM. Epilepsia. 2000 Sep;41(9):1195-200 5. Morrell MJ. Neurology. 2011 Sep 27;77(13):1295-304
6. Data on file, as of Sept 2015. Presented at American Neurological Association Annual Meeting, Chicago 2015.
7. Device-related serious adverse events not due to seizure-related head trauma.
8. Serious adverse events, not seizure related.

RNS - Neuropsychological Outcomes

- No cognitive decline (2 year follow up)
- Small beneficial effects
  - Naming (neocortical onsets)
- Modest improvements
  - Verbal learning (MTLE)

Modest cognitive benefits in some domains depending on the brain region involved

Loring et al, Epilepsia, 2015

Deep Brain Stimulation (DBS; Anterior Nucleus of Thalamus)

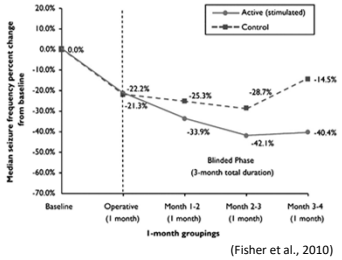
- Bilateral DBS of the ANT is an open-loop system
- Medtronic DBS (FDA approval May 2018)
  - Adjunctive therapy in patients ≥ 18 years with intractable focal epilepsy

Electrical Stimulation of the Anterior Nucleus of the Thalamus (SANTE Trial)

- Multicenter, double-blind, randomized
- 110 patients with partial epilepsy (baseline seizure frequency 19.5/month)
  - 3-month blinded phase: 50% received stimulation (5V), 50% no stimulation (turned off)
  - Then all received unblinded stimulation (5V)
- In the last month of blinded phase
  - Stimulated group had 29% greater seizure reduction compared to control (p=0.002)

(Fisher et al., 2010)

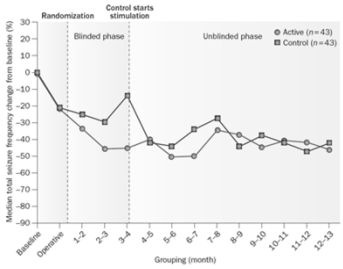
SANTE Trial- Blinded Phase



(Fisher et al., 2010)

Median % seizure reduction:
- 14.5% (Control group)
- 40.4% (Stimulated group)

SANTE Trial- Open Label Phase



Fisher and Velasco, 2014

Median seizure reduction: 56%
- ≥50% reduction in 54% (14 seizure-free for ≥ 6 months)
- No symptomatic bleed or brain infection

Mechanism(s) of Action 3

- High-frequency (> 45 Hz) stimulation of ANT desynchronizes both focal and the larger epileptic networks
- Reciprocal effective connectivity exists between the anterior nucleus of the thalamus and the hippocampus

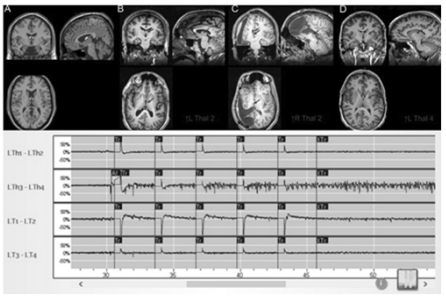
Yu et al. Brain 2018

RNS on Anterior Nucleus of Thalamus

- 3 patients with multifocal DRE implanted with RNS including unilateral stimulation of ANT
- >33 months follow-up
  - No SE on mood, memory or behavior
  - 2 patients ≥50% reduction in disabling seizures
  - 1 patient 50% reduction compared to baseline
- Modest reduction in seizure frequency
- RNS of the ANT is feasible, safe, and well-tolerated

Elder et al. Epilepsia Open. 2019

RNS targeting the anterior nucleus of thalamus



Localization of thalamic electrodes and electrocorticography of seizure detection in thalamic electrodes. Top Panel: (A) Location of ANT based on a standard subcortical MRI atlas (Ewert et al, 2017) superimposed on an Montreal Neurological Institute (MNI) template MRI. Location of select thalamic RNS electrodes (green) obtained from postimplant computed tomography (CT) coregistered to the preimplant MRI for Patient 1 (B), Patient 2 (C), and Patient 3 (D). Contact number identified by the red arrow is indicated in the text box. Bottom Panel: ECoG recording of ictal onset in Patient 1 with initial electrographic changes seen in thalamic electrodes. (LTh, Left thalamic electrode; LT, Left temporal electrode)

Genetic Analysis

John M. Schreiber, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

GENETIC ANALYSIS IN EPILEPSY

John M. Schreiber, MD
Pediatric Neurologist
Children's National Health System

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **Off-label uses of some medications**

Objectives

- Discuss the rationale and clinical indications for genetic testing in Epilepsy
- Review test methodology and limitations for genetic tests including chromosome microarray and next generation sequencing
- Understand how to interpret test results in context
- Provide examples of specific disorders where a positive result may influence treatment
- Recognize the impact of genetics on response to medications

Early Approaches

Genetic Basis of Epilepsy

- Risk for epilepsy is increased 2-4 times in first degree relatives of people with epilepsy of unknown cause
  - Annegers et al., 1982; Ottman et al., 1996
- Higher concordance in monozygotic than dizygotic pairs
  - Corey et al., 1991; Berkovic et al., 1998; Kjekdsen et al., 2003; Vadlamudi et al., 2004

Early approaches to Epilepsy Genetics

- Linkage analysis and positional cloning
  - Primarily identified genes encoding subunits of ion channels in families with epilepsy exhibiting Mendelian (usually autosomal dominant) inheritance patterns
- Genome-wide association studies (GWAS)
  - Intended to detect genetic variants (usually SNPs) more common in people with "complex genetic" epilepsy where patients usually have no affected relatives
  - "Common disease, common variant"
  - Effects of variants have been modest and causal variants are difficult to identify
  - Largely failed, possibly because variants are rare, but not very rare
- Copy Number Variants (CNVs)
  - Array CGH (comparative genomic hybridization)
  - SNP array

Epilepsy gene discovery

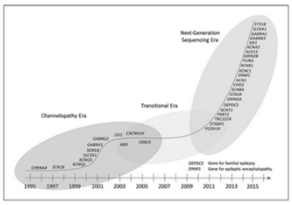
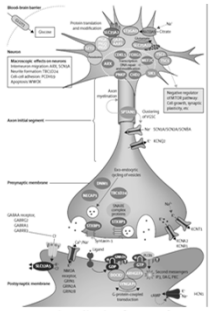


Fig. 2. Timeline of gene discovery in human epilepsies.

Mol Syndromol 2016;7:172–181



Lancet Neurol 2016; 15: 304-16

Impact of Minor Alleles

Pharmacogenomics

HLA-B* 1502

- Chung WH, et al., *Nature*, 2004 - strong association in Han Chinese between HLA-B*1502, and Stevens-Johnson syndrome induced by carbamazepine
- Tangamornsuksan W, et al. (2013) – meta analysis; **OR ~80** in Han Chinese, Thais, and Malaysians (not detected in individuals of white or Japanese ethnicity/ race)
- This may also be associated with phenytoin (Cheung YK, et al. *Epilepsia,* 2013) and lamotrigine (Zeng T, et al., 2015)
- HLA-A*3101 allele (2-5% prevalence in Northern Europeans) associated with carbamazepine-induced hypersensitivity (risk increased from 5% to 26*) (McCormack M, et al., *NEJM,* 2011)

HLA-B*1502 allele frequency

Continent	Population/ethnicity	Allele frequency (%)	n
North America	Asian	5.1	396
	African	0.2	251
	European	0	287
	Hispanic	0	240
	Native American	0	235
Asia	Korean	0.5	200
	Han Chinese	10.2	572
	Singapore	11.6	86
	Malay	8.4	101
	Thai	6.1	99
	Filipino	5.3	94
	India Mumbai Marathas	1	72
	India North Hindi	2	91
	India Khandesh Pawra	6	50

[102] Middleton D. Allele Frequencies in Worldwide Populations www.allelefrequencies.net
[103] International Histocompatibility Working Group www.ihwg.org

FDA

- FDA ALERT [12/12/2007]: Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. **Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine.** If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502. This new safety information will be reflected in updated product labeling

Review article

Pharmacogenomics in epilepsy

Simona Balestrini [a,b], Sanjay M. Sisodiya [a,*]

[a] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, and Epilepsy Society, Chalfont-St.-Peter, Bucks, United Kingdom
[b] Neuroscience Department, Polytechnic University of Marche, Ancona, Italy

Table 1
Influence of genetic factors on response and adverse reactions to AEDs through various mediators: summary of existing findings.

Response		
Mediator	Genetic factor	Effect [references]
Pharmacokinetics and pharmacodynamics	Variation in *CYP2C9* gene	Risk of developing concentration-dependent neurotoxicity from phenytoin [12,13]- established evidence
	Variation in *CYP2C19* gene	Association with the serum concentration of N-desmethylclobazam and with its clinical efficacy, indicating a gene-dose effect [17–21]
	Variation in *CYP2C19* gene	Ethnic differences in the tolerability profile of phenobarbital [22]
	UGT1A1 variants	Altered clearance of lamotrigine [25]
	Variation in *CYP2C19* gene	Risk of adverse reactions from zonisamide [28]
	Variation in *SCN1A, ABCC2, UGT2B7* genes	Association with oxcarbazepine maintenance doses [36]
	Variation in *CYP1A1* gene	Association with response to first-line antiepileptic drugs in Indian women [37,38]
	ABCB1 gene (encoding P-glycoprotein, P-gp, multidrug transporter) variants	Drug-resistant epilepsy [40–45]
	Variation in genes coding for AED targets	No significant association with drug response [49–53]
Adverse reactions	*HLA-B*15:02*	Stevens-Johnson syndrome and toxic epidermal necrolysis induced by carbamazepine and other aromatic AEDs in patients from Han Chinese and other South Asian ethnic groups [165–170]- established evidence
	*HLA-A*31:01*	Increased risk of carbamazepine-induced hypersensitivity reactions in patients of European ancestry and in the Japanese population [172,173]- established evidence
	T1405 polymorphism of the *CPS1* gene	Increased risk of valproate-induced hyperammonaemia in Caucasian patients [176]
	Val16Ala polymorphism of the *SOD2* gene	Elevated serum level of γ-glutamyltransferase induced by valproate in Japanese patients [179]
	Polymorphic *LEPR* and *ANKK1* genes	Weight gain on valproate in Han Chinese patients [180]
	Variation in *CYP2C9* and *CYP2A6* genes	Risk of toxicity from valproate [181,182]

Copy Number Variants

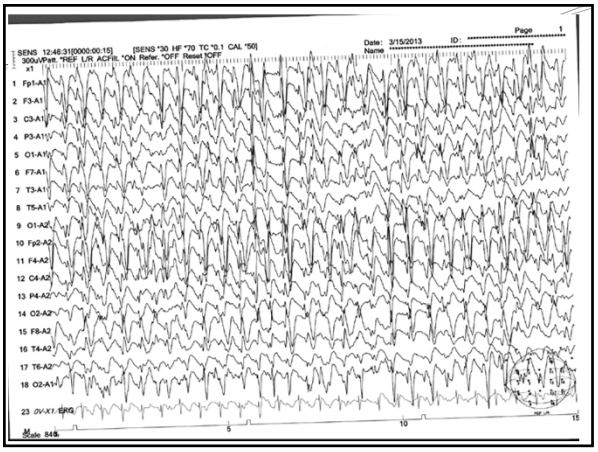
Chromosome Microarray

Copy Number Variants

- Criteria determining significance:
  - Size
  - Gene content
  - Presence or absence in control population
  - Inheritance
- Contribution to disease and phenotypic variability
  - Haploinsufficiency
  - Imprinting
  - Unmasking a recessive allelic mutation
  - Other background genomic variation

Copy Number Variants and Epilepsy

- Epileptic Encephalopathies – Mefford et al., 2011
  - Oligonucleotide array in 315 with EE
  - 25/315 (7.9%) had rare CNVs
  - > ½ clearly or likely pathogenic
- Infantile Spasms – Paciorkowski et al., 2011
  - Analyzed gene content of non-recurrent CNVs and deletion 1p36 in new and published IS subjects
  - Found gene content enriched for networks involved in ventral forebrain development, synaptic function, and GABAergic neurotransmission
- GGE ± ID – Mullen et al., 2013
  - Screened for recurrent microdeletions at 15q13.3, 15q11.2, and 16p13.11
  - Detected in 11/359 probands with genetic generalized epilepsy (GGE) and **6/60 with GGE and intellectual disability** (and another 13/60 rare CNVs [6 were also found in an unaffected parent])



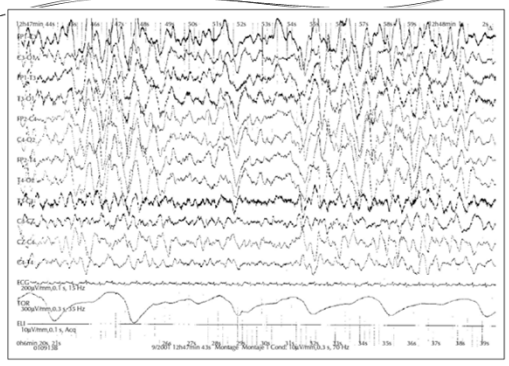


Figure 1. Typical EEG with high amplitude rhythmic 2-3/s activity in a 3-year-old boy with AS.

Laan LA, et al., 1999

Angelman Syndrome

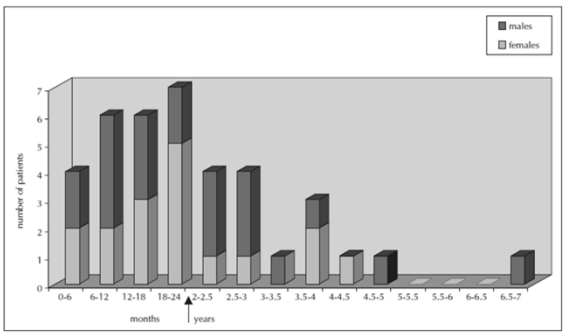
- 1:12,000-20,000
- Newborns typically have a normal phenotype
- Developmental delays are first noted at around age 6 months, but many of unique features of AS do not manifest until > 1 year
- MRI or CT is usually normal, although mild cortical atrophy or dysmyelination may be observed
- *UBE3A* gene encodes ubiquitin-protein ligase – targets proteins for degradation (only maternally inherited copy is normally active in the brain due to paternal imprinting)

Table 1 Main clinical characteristics of AS

Consistent (100%)	Frequent (more than 80%)	Associated (20–80%)
Severe developmental delay Speech impairment, no or minimal use of words; receptive and non-verbal communication skills higher than verbal ones Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs Behavioural uniqueness†: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behaviour; short attention span	Delayed, disproportionate growth in head circumference, usually resulting in microcephaly by age 2 Seizures, onset usually <3 years of age Characteristic EEG with large amplitude slow spike waves and triphasic waves	Flat occiput Occipital groove* Protruding tongue Tongue thrusting; suck/swallowing disorders Feeding problems during infancy Prognathia Wide mouth, widely spaced teeth Frequent drooling Excessive chewing/mouthing behaviours Strabismus Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases Hyperactive lower limb deep tendon reflexes Uplifted, flexed arm position especially during ambulation Increased sensitivity to heat Sleep disturbance Attraction to/fascination with water

Adapted from Williams CA, *et al*. Angelman syndrome: consensus for diagnostic criteria. *Am J Med Genet* 1995;**56**:237–8.
*Although emphasised particularly in Harry Angelman's first description, we have not found this to be a particularly useful sign.
†The characteristic behavioural phenotype has been shown to be perhaps the most useful diagnostic marker for AS.

Table 1. Age at onset of epilepsy in Angelman syndrome (n=35).



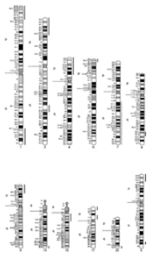
Other Select Chromosomal Disorders

- Wolf-Hirschorn (4p16.3 del)
  - Seizures in 70-100%
  - "greek helmet" profile
  - Low BW, growth retardation, MR, microcephaly, closure defects
- Ring chromosome 20 (very rare)
  - Mild-moderate MR
  - Behavioral disorder
  - No dysmorphisms
  - Epilepsy with frequent atypical abence or nonconvulsive status
- Trisomy 21
- [Fragile X syndrome]
  - 1/6000 males
  - CGG expansion of FMR1 (>200; normal <50)
- Many others

Top chromosomal disorders implicated in epilepsy:

- dup15q
- Angelman (deletion 15q11-q13)
- deletion 1p36
- trisomy 21
- ring chromosome 14
- ring chromosome 20
- deletion 4p (Wolf-Hirschhorn)
- Miller-Dieker (deletion 17p13.3)
- deletion 1q (deletion 1qter->q42 or q43)
- deletion 2p (deletion 2p24->pter and deletion 2p23->p25)
- deletion 15q13.3
- deletion 16p13.11
- deletion 15q11.2
- deletion 18q
- tetrasomy 12p (Pallister-Killian)
- Klinefelter syndrome (XXY)
- Phelan McDermid, deletion 22q13.3

Chromosomal Abnormalities and Epilepsy: A Review for Clinicians and Gene Hunters



Epilepsia, Volume: 43, Issue: 2, Pages: 127-140, First published: 19 March 2002, DOI: (10.1046/j.1528-1157.2002.19498.x)

Next Generation Sequencing

Gene panels
Whole exome sequencing

Epilepsy Gene Panel – Children's National

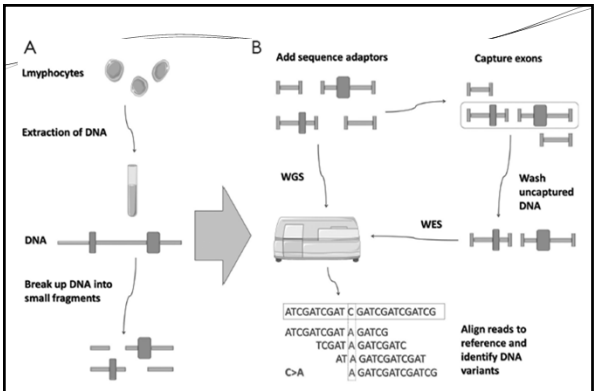
- ADSL
- ALDH7A1
- AMT
- ARHGEF9
- ARX
- ATP1A2
- ATP6AP2
- CACNB4
- CDKL5
- CHRNA2, 4, 7
- CHRNB2
- CLN3, 5, 6, 8
- CNTNAP2
- CSTB
- CTSD
- DNAJC5
- EFHC1
- EPM2A
- FOLR1
- FOXG1
- GABRA1
- GABRB3
- GABRG2
- GAMT
- GATM
- GCSH
- GLDC
- GOSR2
- GPHN
- GRIN2A/B
- KANSL1
- KCNJ10
- KCNQ2, 3
- KCTD7
- LGI1
- LIAS
- MAGI2
- MBD5
- MECP2
- MEF2C
- MFSD8
- MOCS1, 2
- NHLRC1
- NRXN1
- PCDH19
- PLCB1
- PNKP
- PNPO
- POLG
- PPT1
- PRICKLE1
- PRICKLE2
- PRRT2
- SCARB2
- SCN1A/B
- SCN2A
- SCN8A
- SCN9A
- SLC25A22
- SLC2A1
- SLC9A6
- SPTAN1
- SRPX2
- ST3GAL3
- STXBP1
- SUOX
- SYN1
- TBC1D24
- TCF4
- TPP1
- TSC1
- TSC2
- UBE3A
- ZEB2

Whole Exome Sequencing

Rationale
Methods
Applications

Some more recently reported genes associated with non-syndromic epilepsy

- ALG13
- ATP6V1B2
- CHD2
- CUX2
- DNM1
- **DEPDC5**
- EEF1A2
- FGF12
- GABBR1/2
- GABRB2
- GNAO1
- GRIN1
- HCN1
- KCNB1
- KCND2
- KCNT1
- KCTD7
- KIAA2022
- KPTN
- NGLY1
- PACS2
- PIGA
- SCN3A
- SLC6A1
- SLC35A2
- SCL25A12
- SPATA5
- STX1B
- SYNGAP1
- SZT2
- WDR45
- Many more. . .



Jiang et al., 2014

Interpretation (VUS ≠ mutation)

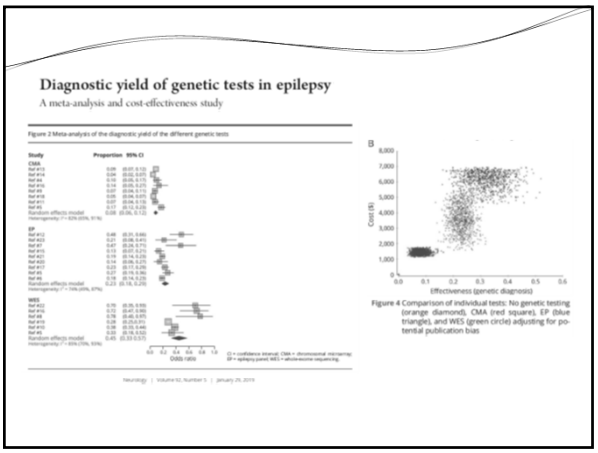
- Confirm with direct sequencing
- Known mutation/ known gene
- **Clinical Interpretation – epilepsy phenotype**
- Unknown mutation/ unknown gene
  - Population frequency – compare to SNP databases (1000 Genomes Project, NHLBI Exome Sequencing Project, ExAC browser, gnomAD, others)
  - Mutation type, comparative sequence analysis (conserved across species?)
  - Protein function (PolyPhen scores, SIFT, others)
  - Gene-specific tolerance to mutation
  - Evaluate trios and inheritance pattern (e.g. recessive vs dominant)
  - Variant-phenotype databases (ClinVar, DECIPHER), genematcher, etc
  - Functional assays

Epilepsy Syndromes

- Neonatal/ Infancy:
  - benign familial neonatal epilepsy, benign neonatal epilepsy, early myoclonic epilepsy, early infantile epileptic encephalopathy, epilepsy of infancy with migrating focal seizures, West syndrome, benign myoclonic epilepsy in infancy, severe myoclonic epilepsy in infancy (Dravet), benign familial infantile convulsions, familial infantile convulsions and paroxysmal choreoathetosis
- Childhood:
  - febrile seizures, febrile seizures plus, astatic-myoclonic epilepsy of Doose, Lennox-Gastaut syndrome, benign epilepsy with centrotemporal spikes, childhood absence epilepsy, Panayiotopoulos syndrome, late onset childhood occipital epilepsy (Gastaut type), Landau Kleffner syndrome, epileptic encephalopathy with continuous spike wave of sleep
- Adolescence:
  - juvenile absence epilepsy, juvenile myoclonic epilepsy
- Other syndromes:
  - autosomal dominant nocturnal frontal lobe epilepsy, autosomal dominant epilepsy with auditory features, idiopathic (genetic) generalized epilepsy, progressive myoclonic epilepsy, familial focal epilepsy with variable foci, gelastic seizures with hypothalamic hamartoma, reflex epilepsy, Rasmussen syndrome,
- Focal or multifocal epilepsy (right/ left, frontal/ temporal/ parietal/ occipital, with/ without known structural lesion)

WES: Limitations

- Coverage in certain areas
- Structural variants (e.g. translocations and inversions)
- Triplet repeat disorders
- Intronic mutations
- Uniparental disomy
- Gene-gene interactions
- Epigenetic changes (e.g. methylation)
- Data processing
- Deletions and duplications
  - Deletions or duplications account for 8-27% of Dravet syndrome



Diagnostic yield of genetic tests in epilepsy

A meta-analysis and cost-effectiveness study

Figure 2 Meta-analysis of the diagnostic yield of the different genetic tests

Figure 4 Comparison of individual tests: No genetic testing (orange diamond), CMA (red square), EP (blue triangle), and WES (green circle) adjusting for potential publication bias

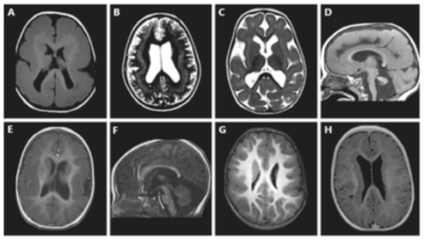
Specific Genes/ Conditions

Inborn errors of metabolism
Malformations of Cortical Development
Infantile Spasms
Monogenic Epilepsies

IEM with seizures as a prominent feature

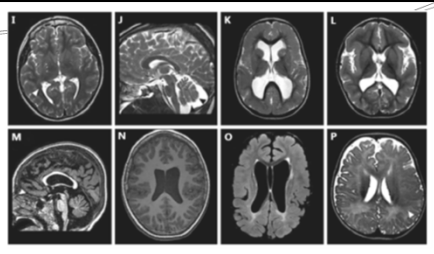
- Amino acid and organic acid disorders
- Glucose transport/ regulation disorders – GLUT1, HI/HA, DEND
- Hyperhomocysteinemia – cobalamin deficiencies, homocysteinuria, MTHFR deficiency
- Urea cycle disorders
- Fatty acid oxidation disorders
- Creatine synthesis/ transport disorders
- Neurotransmission – biopterin deficiencies, SSADH-D
- Sulfite oxidase deficiency
- Vitamins/ co-factors: biotinidase, cerebral folate, holocarboxylase, molybdenum cofactor, pyridoxine, thiamine
- Mitochondria – Co-Q10 deficiency, MELAS, PDH complex deficiency
- Metals - Menkes
- Lysosomal and peroxisomal disorders

MCD



Mol Syndromol 2016;7:220–233
DOI: 10.1159/000448639

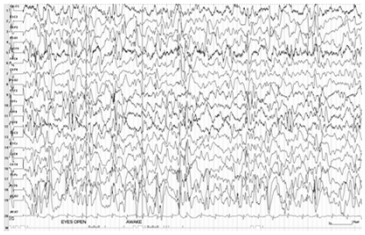
Fig. 1. Brain MRI of patients with different malformations of the cerebral cortex. **A** T1-weighted axial section. Posterior to anterior pachygyria in a boy with *LIS1* mutation. **B** T2-weighted axial section. Diffuse SBH in a girl with *DCX* mutation. **C**, **D** T2-weighted axial section and T1-weighted sagittal section. Lissencephaly and cerebellar hypoplasia in a girl with *RELN* mutation. **E**, **F** T1-weighted axial section and T1-weighted sagittal section. Thickened cortex with simplified gyral pattern and cerebellar hypoplasia in a girl with *TUBA1A* mutation. **G** T1-weighted axial section. Diffuse simplified gyral pattern with prominent thickening and infolding of the sylvian fissures in a boy with *TUBB2B* mutation. **H** T1-weighted axial section. Typical, classical bilateral PNH in a girl with an *FLNA* mutation. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls.



MCD categories
- Lissencephaly
- Periventricular Nodular Heterotopia
- Polymicrogyria
- Megalencephaly-polymicrogyria, dysplastic megalencephaly, focal cortical dysplasias

I, **J** T2-weighted axial section showing mild colpocephaly with unilateral PNH (white arrowhead) and T2-weighted sagittal section through the midline, showing cerebellar vermis hypoplasia (black arrowhead) with mega cisterna magna in a patient carrying a deletion in the 6q27 chromosomal region. **K** T2-weighted axial section. Bilateral frontoparietal polymicrogyria in a boy with *GPR56* mutation. **L**, **M** T2-weighted axial section and T1-weighted coronal section. Pachygyria and perisylvian polymicrogyria in a girl with *DYNC1H1* mutation. **N** Axial T1-weighted section in a patient with a mosaic *EKC/KEL* mutation. **O**, **P** T1-weighted and T2-weighted axial images form patients carrying mosaic mutations in the *MTOR* gene with different percentages of mosaicism [**O**: p.Thr1977Ile, 20% of mosaicism in blood, **P**: p.Ser2215Phe, 5.5% of mosaicism in dysplastic brain tissue) showing bilateral cortical dysgyria (**O**) and focal cortical dysplasia (**P**, white arrowhead)].

Case 1



11 month old boy presents with clusters of flexor spasms and developmental regression

Question 1

- What test has the highest diagnostic yield in infantile spasms with a normal MRI brain and lack of physical exam features of tuberous sclerosis or trisomy 21?
  - CSF neurochemistry
  - MR spectroscopy
  - Karyotype
  - Chromosome microarray
  - Laboratory evaluation for inborn errors of metabolism

How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium

*Elaine C. Wirrell, †Renée A. Shellhaas, ‡Charuta Joshi, §Cynthia Keator, ¶Shilpi Kumar, #Wendy G. Mitchell, and Pediatric Epilepsy Research Consortium (PERC)[]

Epilepsia, 56(4):617–625, 2015
doi: 10.1111/epi.12951

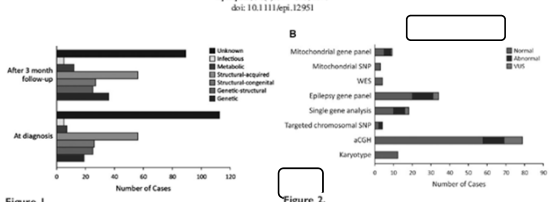


Figure 1.
Etiological Class at diagnosis, and after 3 months of follow-up.
Epilepsia © ILAE

Figure 2.
Yield of genetic testing. **(A)** Prior to diagnosis of spasms. **(B)** Entire cohort; within 3 months after diagnosis of spasms. **(C)** Children without obvious cause at diagnosis.

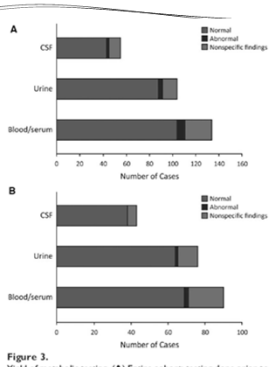


Figure 3.
Yield of metabolic testing. **(A)** Entire cohort; testing done prior to spasm onset or within first 3 months after diagnosis. **(B)** Children without obvious cause at diagnosis.

Recommendations for testing in newly diagnosed West syndrome (Wirrell et al, 2015)

- History and physical exam
- MRI brain
- If no obvious cause is identified:
  - Chromosome microarray
  - ⇩
  - Epilepsy gene panel, serum lactate, serum amino acids, urine organic acids
  - ⇩
  - Consider whole exome sequencing

Case 2

- 2 year old girl presents with staring spells, lasting approximately 10 seconds, multiple times throughout the day
- EEG shows generalized 3.5 Hz spike-wave discharges
- She fails treatment with adequate doses of ethosuximide, valproic acid, and lamotrigine

GLUT1 Deficiency Syndrome

Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency

*Todor Arsov, *†Saul A. Mullen, *John A. Damiano, *Kate M. Lawrence, ‡Linda L. Huh, §Melinda Nolan, ¶Helen Young, #Anaïs Thouin, *Hans-Henrik M. Dahl, *Samuel F. Berkovic, **Douglas E. Crompton, ††Lynette G. Sadleir, and *†‡‡Ingrid E. Scheffer

- 11/89 with early onset absence epilepsy (age < 4 yrs) had GLUT1 deficiency
- Early onset absence epilepsy defined as onset of absences before age 4 years, generalized spike waves > 2.5 Hz, no evidence of secondary cause, and absence of atonic-tonic seizures

Arsov et al. *Epilepsia* 2012.

GLUT1 Deficiency Syndrome

- Early-onset epilepsy (age < 3yrs)
- Diagnosis/ Clinical Aspects
  - Pure (n=111)
    - normal neurologic state and development, brief (4-20 s) and frequent (many per day) absence seizures with abrupt and severe impairment of consciousness, and EEG ictal discharges of generalized high-amplitude spike and slow wave complexes at 3-4 Hz with gradual/ regular slowdown
    - earlier initial seizure control and better seizure-free survival curve
  - Non-pure (n=77)
- Findings
  - Pure: no mutations in SLC2A1 or abnormal neuroimaging
  - Non-pure
    - 4 with SLC2A1 mutations and 21 with abnormal neuroimaging
    - in those receiving tritherapy, increased risk of structural brain abnormalities or SLC2A1 mutations, fewer myoclonic features and worse seizure-free survival curve

Agostinelli et al. *Epilepsia* 2013: 1761-1770.

Case 3

- 15 month old boy with a history of febrile status epilepticus and subsequent unprovoked hemiclonic seizures presents for a second opinion. He was started on oxcarbazepine initially and the dose has been increased, but seizures have been gradually worsening, now with frequent myoclonic jerks.

Question 2:

- For case 3, what is the most appropriate next medication?
  - Valproic acid
  - Lamotrigine
  - Phenobarbital
  - Lacosamide

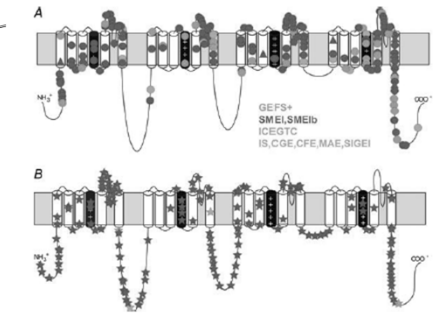


Figure 1. Mutations in $Na_v1.1$ channel patients with epilepsy
A, missense mutations (circles) and in-frame deletions (triangles). *B*, truncation mutations (stars). The clinical type of epilepsy is indicated by colour: GEFS+, generalized epilepsy with febrile seizures plus; SMEI, severe myoclonic epilepsy of infancy; SMEIb, borderline SMEI; ICEGTC, idiopathic childhood epilepsy with generalized tonic–clonic seizures; IS, infantile spasms; CGE, cryptogenic generalized epilepsy; CFE, cryptogenic focal epilepsy; MAE, myoclonic astatic epilepsy; SIGEI, severe idiopathic generalized epilepsy of infancy. Courtesy of M. Meisler and J. Kearney (Catterall *et al.* 2008).

J Physiol 588.11 (2010) pp 1849–1859

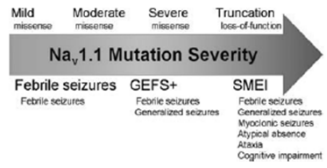


Figure 3. The unified loss-of-function hypothesis for $Na_v1.1$ genetic epilepsies
Increasing severity of loss-of-function mutations of $Na_v1.1$ channels, noted above the arrow, causes progressively more severe epilepsy syndromes from familial febrile seizures to GEFS+ and finally SMEI, noted below the arrow. Major symptoms of each syndrome are also listed.

J Physiol 588.11 (2010) pp 1849–1859

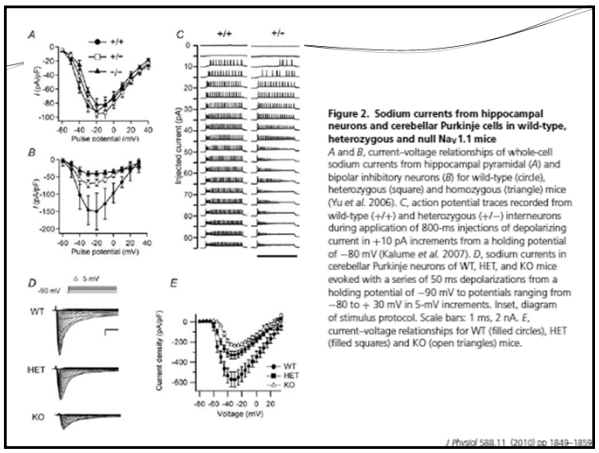


Figure 2. Sodium currents from hippocampal neurons and cerebellar Purkinje cells in wild-type, heterozygous and null $Na_V1.1$ mice
A and *B*, current–voltage relationships of whole-cell sodium currents from hippocampal pyramidal (*A*) and bipolar inhibitory neurons (*B*) for wild-type (circle), heterozygous (square) and homozygous (triangle) mice (Yu *et al.* 2006). *C*, action potential traces recorded from wild-type (+/+) and heterozygous (+/−) interneurons during application of 800-ms injections of depolarizing current in +10 pA increments from a holding potential of −80 mV (Kalume *et al.* 2007). *D*, sodium currents in cerebellar Purkinje neurons of WT, HET, and KO mice evoked with a series of 50 ms depolarizations from a holding potential of −90 mV to potentials ranging from −80 to + 30 mV in 5-mV increments. Inset, diagram of stimulus protocol. Scale bars: 1 ms, 2 nA. *E*, current–voltage relationships for WT (filled circles), HET (filled squares) and KO (open triangles) mice.

J Physiol 588.11 (2010) pp 1849–1859

Status Epilepticus and SCN1A

- Screened for SCN1A mutations and deletions in 71 children age 1 month – 16 years with status epilepticus
- 12 were detected, including 10 children with clinical Dravet syndrome and 2 with generalized epilepsy with febrile seizures plus (GEFS+)
- Among 26 children aged **≤ 18 months** at initial episode of status epilepticus, risk of SCN1A mutation was significantly increased for patients with **≥ 2 episodes** (56.3%), as compared with those who had only one episode (0.0%)

Le Gal, *Epilepsy Res.*, 2014

Malignant migrating partial seizures in infancy/ EIMFS

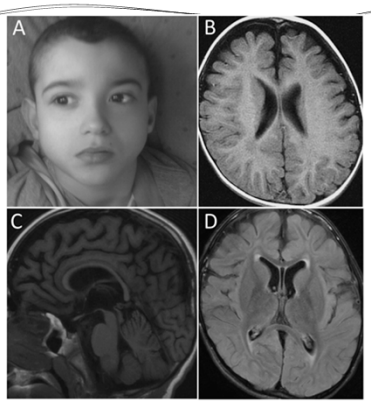
- Extremely rare and refractory form of epilepsy with intractable focal seizures
- Just over approximately 100 cases reported in the literature
- Vast majority have regression with severe developmental delay and microcephaly, in addition to severe and intractable seizures
- Significant risk for mortality in infancy and early childhood
- *KCNT1* (Barcia et al, 2012 in about ½), *SCN1A, SCN2A, SCN8A, TBC1D24, PNPO, KCNQ2, KCNQ3, STXBP1,PRRT2, etc*

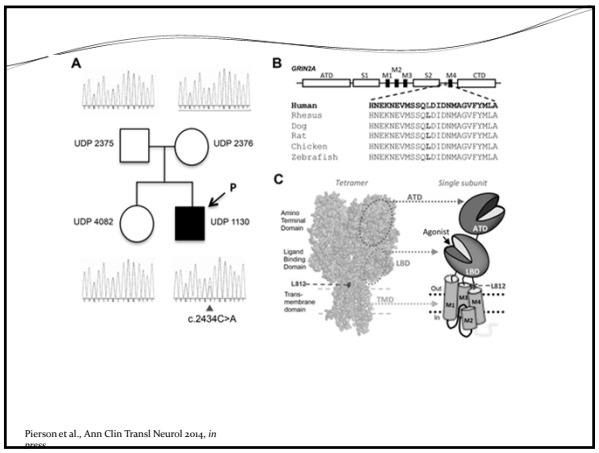
KCNT1

- Activating mutations have been identified in ADNFLE and EIMFS
- In the early onset epileptic encephalopathies, it is largely restricted to EIMFS (Ohba C, et al. Epilepsia, 2015)
- *KCNT1* encodes a weakly voltage dependent and intracellular sodium activated potassium channel
- Quinidine
  - Mikati MA, et al. *Ann Neurol* 2015 – treated one patient with EIMFS (improved) and one with ADNFLE (not improved)
  - Milligan CJ, et al. *Ann Neurol* 2014 – quinidine significantly reduces gain of function in all mutations studied
  - However, this has not been substantiated by additional study

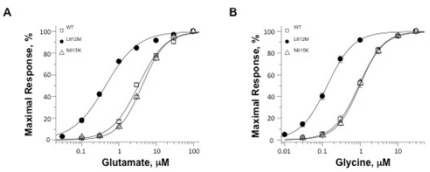
NMDA Receptors

- Ligand and voltage-gated ion channels
- Bind glutamate and glycine
- Comprised of ≥ 1 NR1 (GluN1) subunit and ≥ 1 NR2(A-D) (GluN2)subunits
- Opening results in depolarization and increase in intracellular Ca^{2+}
- *GRIN2A* (encodes GluN2A subunit)
  - Childhood-onset epilepsy syndromes (BECTS, LKS, CSWS) related to missense mutations or haploinsufficiency
  - Epileptic encephalopathies





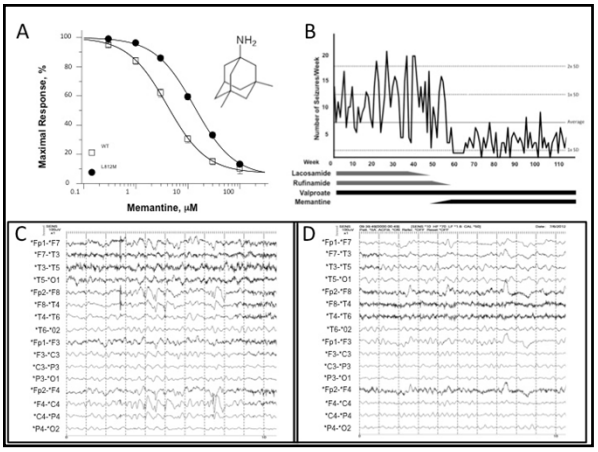
Pierson et al., Ann Clin Transl Neurol 2014, *in press*

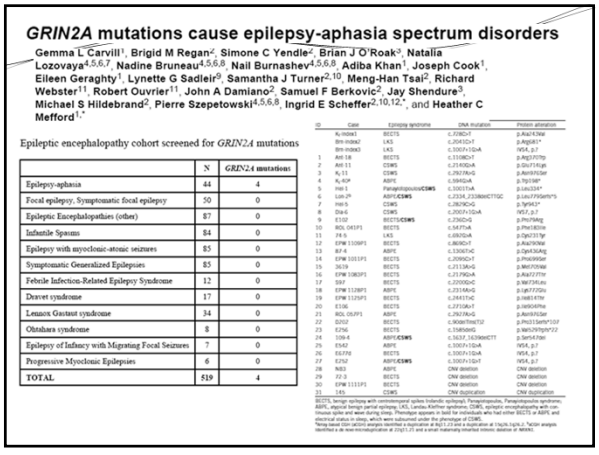


- Table 2 Screening FDA approved NMDAR antagonists

Name	Class	WT	L812M	N615K
Memantine	AD	4.6 ± 0.5 (15, 89%)	12 ± 0.8 (10, 87%)	43 ± 2.8 (16, 69%)
Amantadine	Antiviral	110 ± 11 (10, 94%)	113 ± 5.1 (8, 88%)	458 ± 25 (8, 76%)
Dextromethorphan	Antitussive	18 ± 2.4 (18, 88%)	33 ± 4.8 (10, 91%)	9.0 ± 1.3 (21, 92%)
Dextrorphan		1.9 ± 0.3 (18, 92%)	6.1 ± 1.3 (8, 85%)	0.34 ± 0.06 (11, 96%)

- IC_{50}, mM (n, max inhibition % at 100mM for memantine, at 1000 mM for amantadine, at 300 mM for dextromethorphan, at 30 mM for dextrorphan)



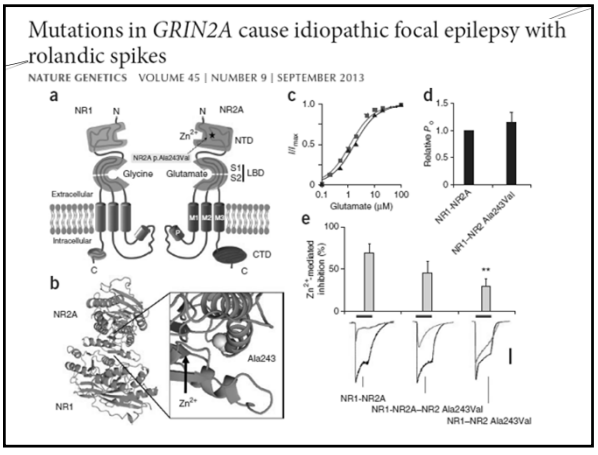


***GRIN2A* mutations cause epilepsy-aphasia spectrum disorders**

Gemma L Carvill[1], Brigid M Regan[2], Simone C Yendle[2], Brian J O'Roak[3], Natalia Lozovaya[4,5,6,7], Nadine Bruneau[4,5,6,8], Nail Burnashev[4,5,6,8], Adiba Khan[1], Joseph Cook[1], Eileen Geraghty[1], Lynette G Sadleir[9], Samantha J Turner[2,10], Meng-Han Tsai[2], Richard Webster[11], Robert Ouvrier[11], John A Damiano[2], Samuel F Berkovic[2], Jay Shendure[3], Michael S Hildebrand[2], Pierre Szepetowski[4,5,6,8], Ingrid E Scheffer[2,10,12,*], and Heather C Mefford[1,*]

Epileptic encephalopathy cohort screened for *GRIN2A* mutations

	N	*GRIN2A* mutations
Epilepsy-aphasia	44	4
Focal epilepsy, Symptomatic focal epilepsy	50	0
Epileptic Encephalopathies (other)	87	0
Infantile Spasms	84	0
Epilepsy with myoclonic-atonic seizures	85	0
Symptomatic Generalized Epilepsies	83	0
Febrile Infection-Related Epilepsy Syndrome	12	0
Dravet syndrome	17	0
Lennox Gastaut syndrome	34	0
Ohtahara syndrome	8	0
Epilepsy of Infancy with Migrating Focal Seizures	7	0
Progressive Myoclonic Epilepsies	6	0
TOTAL	519	4

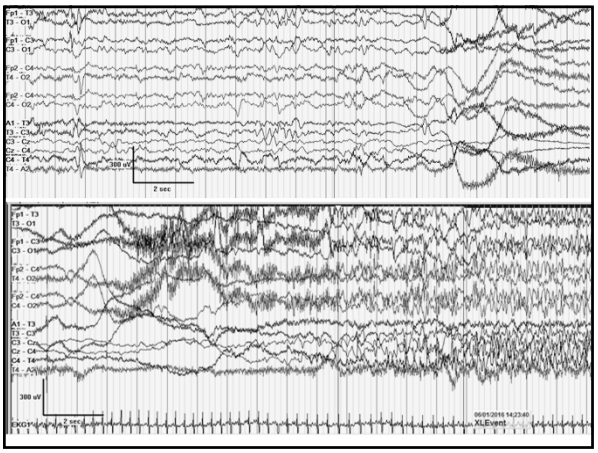


Mutations in *GRIN2A* cause idiopathic focal epilepsy with rolandic spikes

NATURE GENETICS VOLUME 45 | NUMBER 9 | SEPTEMBER 2013

Case 4

- 4 week old baby presents with increased seizures manifested by focal jerking on either side of the body and/or apnea
- History – born full term via normal pregnancy and delivery; started having seizures at 1 week of life that improved some with levetiracetam
- Normal development and exam in between seizures



Question 3:

- What is the most appropriate diagnostic test for the patient described?
  - Chromosome microarray
  - Sequencing of *SCN1A*
  - Sequencing of *KCNQ2*
  - Sequencing of *KCNT1*
  - Pyridoxine challenge

Benign Familial Neonatal Epilepsy

- "Fifth Day Fits"
- EEG background may be normal or abnormal
- Mutations in KCNQ2, or less commonly, KCNQ3
  - AD mutations, result in small reduction in current and less hyperpolarization
- Seizures - clonic, tonic, apneas, orofacial automatisms
- Benign idiopathic neonatal seizures
  - Almost always clonic seizures, mostly partial ± apnea

J Roger *et al.*, Epileptic Syndromes in Infancy, Childhood, and Adolescence

Potassium channels

- Important in determining resting membrane potential
- Reduce excitability
  - Delaying AP or reducing number of APs
- Enhance excitability
  - Hasten recovery of sodium channels from inactivation
- ~100 potassium channel subunits in the human genome, most expressed in brain

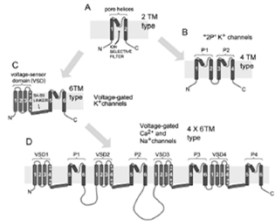


Figure 1. Structural features and evolutionary relationships among major groups of K^+, Na^+, and Ca^{2+} channels

(a) Structure of the simplest, ancestral K^+ channel, consisting of 2TM (transmembrane segments), a pore loop, and intracellular N-and C-terminals. This structure is found in a large group of human 2TM channels, including inward rectifier and G-protein coupled families. (b) Structure of the 4TM group, produced by tandem duplication and fusion of two 2TM channels. This structure is preserved in mammalian leak channels. (c) Structure of the 6TM K^+ channels, produced by fusion of a 4 transmembrane voltage sensor domain and a 2TM channel. The fourth transmembrane segment (S4) bears positively charged arginine residues, and moves in response to changes in the membrane potential. Movement of S4 is communicated to the pore, resulting in voltage-sensitive opening and closing of the transmembrane ion path. (d) The structure of human voltage-gated Na^+ and Ca^{2+} channels, produced by two duplications of a 6 TM channel. In addition, the ion selectivity of the pore has been altered through mutations.

Cooper EC, in *Jasper's Basic Mechanisms of the Epiilepsies, 4th Ed.* 2012

Potassium Channel Variants

- 2 transmembrane (2TM) – single pore; includes inward-rectifying, GIRK (in glia)
- 2 pore (4TM) – contribute to resting Vm
- Votage-gated (6TM) – KCNQ2, KCNQ3
- Non-pore forming accessory subunits – peptides that bind to specific K^+ channel pore subtypes

Cooper EC, in *Jasper's Basic Mechanisms of the Epiilepsies, 4th Ed.* 2012

KCNQ2/ KCNQ3

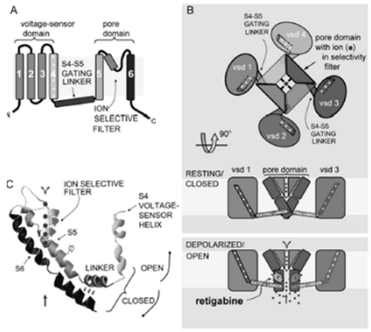
- Present at nodes of Ranvier (AP propagation) and at axonal initial segments in the CNS (AP initiation)
- Responsible for the M current
- Closely related K+ channels – *KCNQ4* and 5 in auditory hair cells and central auditory pathway; *KCNQ1* in GI tract, heart (mutations may cause long-QT syndrome), and cochlea
- In BFNS, the M-current is reduced/ altered
- In early-onset epileptic encephalopathy due to *KCNQ2* mutations, there may be a more severe M-current reduction, although seizures later subside

Retigabine

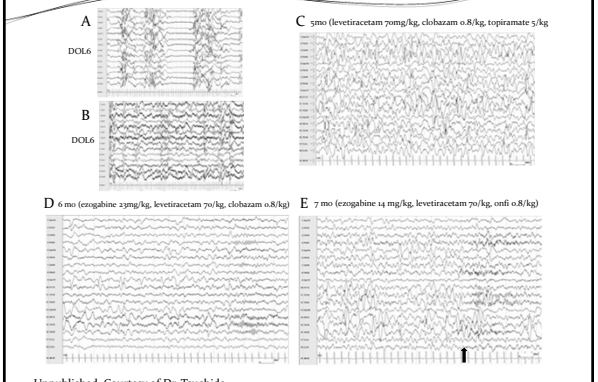
- Retigabine shifts voltage-dependence to hyperpolarized potentials, speeds activation in response to membrane depolarization, and slows deactivation
- Retigabine may be more effective in suppressing seizures in immature rats, and may be effective in preventing symptomatic neonatal seizures and status epilepticus

Cooper EC, in *Jasper's Basic Mechanisms of the Epiilepsies, 4th Ed.* 2012

Voltage-gated potassium channel



Cooper EC, in *Jasper's Basic Mechanisms of the Epiilepsies, 4th Ed.* 2012



Unpublished, Courtesy of Dr. Tsuchida

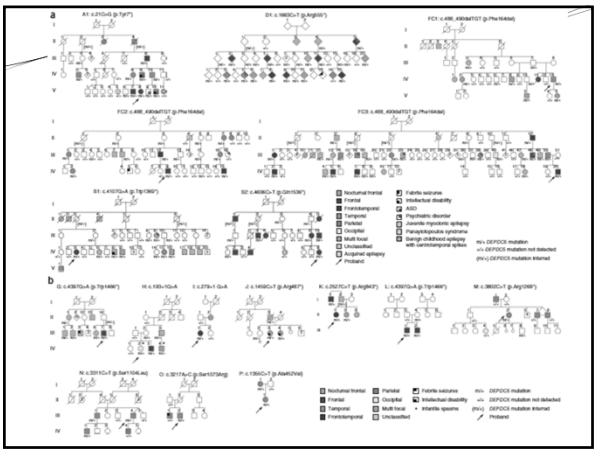
Case 5

- 14 year old boy with nonlesional focal epilepsy. Seizure onset was at age 11 manifested by head turn to the left with "figure of 4" posturing in arms with the left arm extended.
- Interictal and Ictal EEG shows bilateral frontal spike-wave discharges without clear laterality
- MRI brain and FDG-PET brain normal
- Family history notable for temporal lobe epilepsy in paternal grandmother and an ill-defined focal epilepsy in a paternal uncle

Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

Leanne M Dibbens[1,2,23], Boukje de Vries[3,23], Simona Donatello[4], Sarah E Heron[1,2], Bree L Hodgson[1], Satyan Chintawar[4], Douglas E Crompton[5,6], James N Hughes[7], Susannah T Bellows[6], Karl Martin Klein[6,8], Petra M C Callenbach[9], Mark A Corbett[10], Alison E Gardner[10], Sara Kivity[11], Xenia Iona[1], Brigid M Regan[6], Claudia M Weller[3], Denis Crimmins[12], Terence J O'Brien[13], Rosa Guerrero-López[14], John C Mulley[7,15,16], Francois Dubeau[17], Laura Licchetta[18], Francesca Bisulli[18], Patrick Cossette[19], Paul Q Thomas[7], Jozef Gecz[7,16], Jose Serratosa[14], Oebele F Brouwer[9], Frederick Andermann[17], Eva Andermann[17], Arn M J M van den Maagdenberg[3,20], Massimo Pandolfo[4], Samuel F Berkovic[6] & Ingrid E Scheffer[6,21,22]

NATURE GENETICS VOLUME 45 | NUMBER 5 | MAY 2013



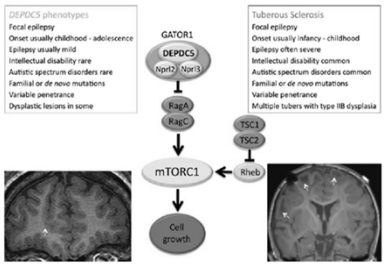


FIGURE 2: *DEPDC5* mutations and tuberous sclerosis show overlapping phenotypes and imaging abnormalities associated with activation of the mammalian target of rapamycin (mTOR) pathway.[11]

ANN NEUROL 2014;75:782–787

Question 4

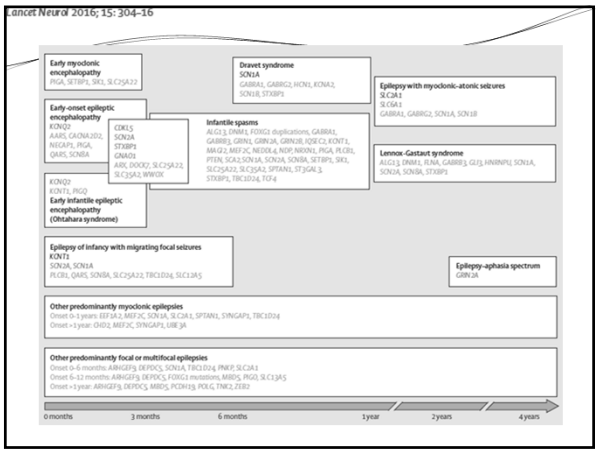
- A 10 year old boy presents for a consult due to worsening generalized tonic-clonic seizures. Examination reveals mild dysmorphic facies including large ears and a long face. Family history is notable for a mother with bipolar disorder, maternal grandmother with depression, and a maternal uncle with a learning disability. What is the most likely finding on genetic testing?
  - Missense mutation in *SCN2A*
  - 1.2 MB deletion of chromosome 4p
  - 14 kB duplication of chromosome 1p
  - 250 CGG repeats in the *FMR1* gene
  - Nonsense mutation in *SCN1B*

Summary

Epilepsy-Gene Associations
Genetic Epilepsies According to Age of Presentation
Precision Therapies

Select Epilepsy – Gene associations

- EIMFS – KCNT1 (nearly ½), SCN2A, SCN1A, others
- IS – STXBP1, SCN8A, SCN2A
- Ohtahara's – STXBP1, CDKL5, SCN2A
- FFEVF – DEPDC5
- Familial lateral temporal lobe epilepsy with auditory features – LGI1
- ADNFLE – CHRNA2, 4, 7; KCNT1
- Epilepsy-aphasia disorders – GRIN2A
- GEFS+ - SCN1A, SCN1B, SCN2A, GABRG2
- Dravet – SCN1A, PCDH19 (females)
- EPC – POLG1, MELAS
- Rett syndrome – MECP2
- For many epilepsy syndromes, there are multiple genetic causes
- Mutations in the same gene can result in vastly different epilepsy phenotypes



Treatment for specific genetic epilepsies

- Dravet syndrome due to SCN1A – stiripentol, cannabidiol, fenfluramine, valproate, clobazam, levetiracetam, topiramate, others; DO NOT use medications that block the voltage-gated sodium channel such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine
- SCN2A – medications that block the voltage-gated sodium channel
- SCN8A – medications that block the voltage-gated sodium channel; avoid levetiracetam
- POLG – DO NOT use valproate
- TSC1/TSC2 – vigabatrin, everolimus
- KCNQ2/ KCNQ3 – retigabine, medications that block the voltage-gated sodium channel
- SCL2A1 – ketogenic diet
- ALDH7A1 – pyridoxine
- PNPO – pyridoxine or pyridoxal-5'-phosphate
- GRIN2A – memantine (?)
- CLN2 – cerliponase alfa
- CACNA1A – acetazolamide
- Gene therapies

Objectives

- Discuss the rationale and clinical indications for genetic testing in Epilepsy
- Review test methodology and limitations for genetic tests including chromosome microarray and next generation sequencing
- Understand how to interpret test results in context
- Provide examples of specific disorders where a positive result may influence treatment
- Recognize the impact of genetics on epileptogenesis and response to medications

Diet Therapies, Hormonal Therapies, and Immunoglobulin

Nabil Azar, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DIETARY, HORMONAL AND IMMUNE THERAPIES IN EPILEPSY

NABIL J. AZAR, MD
Medical Director, Realtime Tele-Epilepsy Consultants

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

OUTLINE:

- **DIETARY THERAPIES:**
  - KETOGENIC.
  - MEDIUM CHAIN TRIGLYCERIDE (MCT).
  - MODIFIED ATKINS.
  - LOW GLYCEMIC-INDEX.
- **HORMONAL THERAPY.**
- **IMMUNOTHERAPY.**
- **QUESTIONS/ANSWERS.**

KETOGENIC DIET: HISTORICAL PRESPECTIVE

- ANCIENT AND BIBLICAL ANECDOTES
- 1920: EXPLORATION INTO THE EFFECT OF FASTING FOR SEIZURE MANAGEMENT
- 1990: SCIENTIFIC PROOF BY DR. FREEMAN AND COLLEAGUES
- 1994: *DATELINE NBC* REVIEW
- 1997: *DO NO HARM*, FILM STIMULATING INTEREST BY PARENTS
- 1998: FIRST PROSPECTIVE MULTICENTER STUDIES EMERGED DESCRIBING DIET EFFICACY WITH SEIZURE FREQUENCY (VINING ET AL., 1998)
- 2000: MEDICAL STATEMENT BASED ON POOL OF 11 REPORTS: "THE EVIDENCE IS SUFFICIENT TO DETERMINE THAT THE KETOGENIC DIET IS EFFICACIOUS IN REDUCING SEIZURE FREQUENCY IN CHILDREN WITH REFRACTORY EPILEPSY" (LEFEVRE AND ARONSON, 2000)
- 2008: RCT UNBLINDED IN MIXED GROUP OF CHILDREN WITH REFRACTORY EPILEPSY REVEALED SIGNIFICANT IMPROVEMENT IN SEIZURE CONTROL (NEAL ET AL., 2008)

KETOGENIC DIET: OVERVIEW

HIGH-FAT (LONG-CHAIN FA), LOW-PROTEIN, VERY LOW CARBOHYDRATE

3:1 OR 4:1 COMMON

- FATTY ACID OXIDATION IN MITOCHONDRIA → LARGE AMOUNTS OF ACETYL-COA GENERATED → HEPATIC SYNTHESIS OF KETONE BODIES Β-HYDROXYBUTYRATE, ACETOACETATE, AND ACETONE → UTILIZED AS AN ENERGY SOURCE IN EXTRAHEPATIC TISSUES, INCLUDING THE BRAIN.
- DIRECT EFFECT OF KETONE BODIES (**ACETONE** PROTECTIVE)
- DECREASE OF REACTIVE OXYGEN SPECIES (OXIDATIVE STRESSORS CONTRIBUTE TO DEVELOPMENT OF EPILEPSY)
- DECREASE OF GLUTAMATE
- INCREASE OF GABA (GABA LEVELS IN BRAIN UNCHANGED IN ANIMAL MODELS; INCREASED LEVELS IN CSF OF CHILDREN ON KD)
- NONMETABOLIZABLE GLUCOSE ANALOG 2-DEOXY-D-GLUCOSE INHIBIT KINDLING AND SUPPRESS SEIZURE-INDUCED INCREASE IN BRAIN-DERIVED NEUROTROPHIC FACTOR AND ITS RECEPTOR TRKB
- RESPONSE 1-65 DAYS; TYPICALLY 2 WEEKS BUT TRIAL FOR AT LEAST 3 MONTHS

KETOGENIC DIET: INDICATIONS AND USES

- **GLUT-1 DEFICIENCY (FIRST LINE THERAPY)**
- **PYRUVATE DEHYDROGENASE DEFICIENCY (FIRST LINE THERAPY)**
- LENNOX-GASTAUT SYNDROME
- DOOSE SYNDROME: MORE RESPONSIVE THAN OTHER EPILEPSIES, 50% SEIZURE FREEDOM, ALLOWING MEDICATION WITHDRAWAL AND ULTIMATELY DIET WITHDRAWAL
- SCN1A RELATED EPILEPSY AND DRAVET SYNDROME (SECOND LINE): REDUCTION IN SEIZURES, AND POSSIBLY IN SE.
- INFANTILE SPASMS (AFTER FAILURE OF FIRST LINE TREATMENTS): MODERATELY EFFECTIVE FOR REFRACTORY IS, GENERALLY SAFE AND TOLERABLE
- TUBEROUS SCLEROSIS COMPLEX
- RETT'S SYNDROME
- POSSIBLY BENEFICIAL IN LKS, LAFORA BODY DISEASE, SSPE, INTRACTABLE FCDS AND MEDICALLY INTRACTABLE EPILEPSY, PARTICULARLY GENERALIZED EPILEPSIES WITH MYOCLONIC COMPONENT

KETOGENIC DIET: CONTRAINDICATIONS

Absolute contraindications:

- Disorders of fatty acid metabolism
- Pyruvate decarboxylase deficiency
- Carnitine deficiency (primary)
- Carnitine palmitoyl transferase deficiency
- Carnitine translocase disorders
- Acute intermittent porphyria
- Targeted surgical candidacy

Relative contraindications:

- Failure to thrive
- Severe GERD
- History of liver disease, pancreatitis, renal disease

KETOGENIC DIET: EFFICACY

- ~50% of DRE patients have >50% seizure reduction, 25%–30% have >90% reduction, of whom half will be seizure-free
- Dravet syndrome: 25% w 50%-74% seizure reduction, 62.5% w 75–99 % reduction, 16% seizure free
- Doose syndrome: 15/26 (58%) free of myoclonic and atonic seizures, 9 w >50% reduction (better than ACTH, ESM, VPA)
- LGS: 51% w >50% reduction, 23% >90% reduction
- Infantile spasms: 104 infants after exposure to a mean of 3.6 AEDs, 64% had ≥50% reduction in seizures, 30 maintained spasm freedom.

KETOGENIC DIET: GENERAL PRINCIPLES

- Rigorous, requiring precision in preparation and administration
- Screening: CBC, CMP, Zinc, selenium, lipid profile, urinalysis, urine calcium/creatinine, acylcarnitine profile
- Pre-diet counseling and assessment of family's ability to adhere to regimen
- Initiation time to efficacy is delayed without fast, outcomes similar at 3 months
- Initiation monitoring for hypoglycemia, acidosis, dehydration
- Close monitoring of weight, height, lipids, CMP, CBC, carnitine, zinc, selenium, LFTs, urine calcium Q3mos, bone mineral density
- Medication switch to carb-free formulations
- Additional risk of acidosis with TPM and ZNS
- Supplementation with multivitamin, calcium/vit D, carnitine, laxatives, selenium, magnesium, zinc

KETOGENIC DIET: COMMON SIDE EFFECTS

ACUTE:

- Vomiting
- Dehydration
- Hypoglycemia
- Acidosis (concomitant use of carbonic anhydrase inhibitors)
- Constipation
- Acute pancreatitis

CHRONIC:

- Weight loss
- Dyslipidemia
- Osteopenia
- Prolonged QT
- Nephrolithiasis
- Thiamine deficiency (optic neuropathy)
- Anemia, leukopenia

MEDIUM CHAIN TRIGLYCERIDE (MCT) DIET

History: 1971 Peter Huttenlocher at University of Chicago

Utilizes MCT oil as source of medium chain fatty acids

Provides 60-70% calories from fat, through MCT diet (better absorption, direct delivery to liver, more efficient ketonic-state generation, allowing more carbohydrates and protein consumption).

Tolerability and efficacy, comparable to ketogenic diet

Side effects: diarrhea, vomiting, abdominal pain

MODIFIED ATKINS DIET

- Developed 2003. with a ratio of 0.9:1 (Fat: protein+carbs) with 65% calories from fat, 30% from protein. Initial carbohydrate =10g per day x1mo →15g →20-30g
- All carbohydrates are allowed, in contrast to LGI, fiber ignored
- Indications/ Effectiveness: comparable to KD; 43-65% w >50% reduction of seizures and 35% w >90%, 1 patient seizure-free
- Comments:
  - Can be initiated outpatient
  - Urine ketones twice per week
  - CBC, CMP and lipid profile monitoring
  - Weight loss, increase BUN
  - 25–50 mg/dl increase in total cholesterol

LOW GLYCEMIC-INDEX TREATMENT

Allows higher carbohydrate intake (40-60g) but limits to those with glycemic index <50 (larger particle size, less gelatinization, presence of fat, higher acidity and increased fiber).

Fat 60% of calories, protein 20-30%

- Indications/ Outcome: As an alternative to Ketogenic diet in DRE
- 60% with >50% seizure reduction and 38% with >90% generalized and focal seizures (MGH data).

Comments:

- Least restrictive and likely more acceptable
- Outpatient initiation

OVERALL COMPARISON OF DIET COMPOSITION

	FAT	CARBOHYDRATES	PROTEIN
Typical American Diet	20% to 35%	50% to 70%	15% to 20%
Classic KD (4:1 ratio)	90%	2% to 4%	6% to 8%
Modified Atkins Diet	60% to 65%	5% to 10%	25% to 35%
Low Glycemic Index Treatment	60% to 70%	10%	30%
Medium-Chain Triglyceride Oil Diet	60% to 75%	15%	10% to 20%

HORMONAL TREATMENTS IN EPILEPSY

•ACTH

-Corticotropin (ACTHar® gel) or Tetracosactin (Cortrosyn®, Cortrosyn-Z®) (Europe)

-Indications: Infantile spasms (first line), Ohtahara syndrome, LGS, LKS

•Corticosteroids

-Prednisone, Prednisolone, Methylprednisolone, Dexamethasone

•Indications: infantile spasms (first line), LGS, LKS

HORMONAL THERAPY OVERVIEW

Mechanism of action:
(proposed)

- direct neuropeptide action of ACTH
- down-regulation of corticotrophin-releasing hormone
- modulation of GABA-A receptors
- direct immunomodulation

Indications:

- Infantile spams of any etiology (first line)
- Landau Kleffner/CSWS
- Rasmussen
- Paraneoplastic disorders
- Seizures associated with autoimmune disorders
- Suspected immune-related epilepsy
- Ohtahara
- Lennox-Gastaut

HORMONAL THERAPY: EFFICACY

- Infantile spams- first line therapy
- AAP, AAN recommend the use of ACTH for IS
  - UKISS: prednisolone 70%, tetracosactide 76% parental report cessation of spasms
  - Knupp et al 2016, non blinded, non randomized: Clinical remission and resolution of hypsarrhythmia 55% ACTH compared to 39% oral corticosteroids, 36% for vigabatrin; ACTH highest percentage of mild or no developmental issues
- Corticosteroids: Seizure remission and resolution of hypsarrhythmia overall 31%. Parental reporting of seizure cessation 70%. Relapse rate 36%.
- CSWS: Improvement and even complete resolution
- Hydrocortisone 5 mg/kg/day x1mo, 4 mg/kg/day during x1mo, 3 mg/kg/day x1mo, and 2 mg/kg/day x9mos, slow withdrawal (total 21 months)
- 77.3% w reductions of seizures or neuropsychological improvement, long-term remission rate 45%

HORMONAL THERAPY IN INFANTILE SPAMS

Brief Communication

High-dose oral prednisolone for infantile spasms: An effective and less expensive alternative to ACTH

Eric H. Kossoff*, Adam L. Hartman, James E. Rubenstein, Eileen P.G. Vining

The Johns Hopkins Medical Institutions, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 9 January 2009
Revised 27 January 2009
Accepted 29 January 2009
Available online 4 February 2009

Keywords:
Prednisolone
Steroids
Infantile spasms
ACTH
Corticosteroids
Epilepsy

ABSTRACT

The ideal treatment of infantile spasms is unclear, but many studies advocate hormonal treatment. In the United States, intramuscular ACTH is most widely used, despite the problematic financial cost and side effect profile. Since September 2007, we have replaced ACTH with high-dose oral prednisolone (40–60 mg/day) according to the 2004 United Kingdom Infantile Spasms Study (UKISS). Ten of 15 (67%) infants with new-onset and previously treated infantile spasms became spasm free within 2 weeks; 4 later recurred. More children with an idiopathic etiology for infantile spasms were spasm free than were symptomatic cases (88% vs 43%, $P = 0.10$). Spasm freedom was equivalent to our most recent 15 infants receiving ACTH, with 13 (87%) responding, $P = 0.16$. Oral prednisolone had fewer adverse effects (53% vs 80%, $P = 0.10$) and was less expensive ($200 vs approximately $70,000) than ACTH. We now routinely recommend oral prednisolone to all families of children with infantile spasms.

HORMONAL THERAPY: SIDE EFFECTS

•Complications:

- Immunosuppression
- hypertension
- irritability
- Glucose intolerance
- Gastric Ulcers or GERD
- cataracts
- avascular bone necrosis
- electrolyte abnormalities
- psychosis
- skin breakdown,
- striae
- buffalo hump
- congestive heart failure
- cerebral atrophy

•Comments:

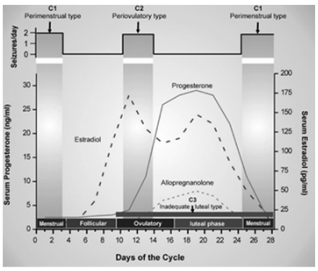
•Gastric protection

•TB exposure (may need PPD)

•Consider PCP prophylaxis

•Routine monitoring: BP, electrolytes, CBC, urine dipstick, stool blood

CATAMENIAL EPILEPSY- MENSTRUAL CYCLE



Estrogen: proconvulsant Progesterone: anticonvulsant

CATAMENIAL EPILEPSY: TREATMENT

- Progesterone 200 mgs tid on days 14-28 for C1 pattern
- Rescue benzodiazepines
- Transient increase in antiepileptic drug dosage
- Synthetic progestins
- Clomiphene citrate
- Ganaxolone (derivative of allopregnanolone):
  - catamenial epilepsy
  - infantile spams

IMMUNE THERAPY IN EPILEPSY

- Various findings indicate that the immune system might somehow be involved in the pathogenesis and evolution of several forms of childhood epilepsy:
- reduced serum levels of IgA and IgG subclasses
- elevated cerebrospinal fluid levels of IgG and IgM and cytokines
- Positive antinuclear antibodies, antimyelin, and anti- glutamate receptor antibodies in serum

- Inflammation in epilepsy:
- Rasmussen syndrome
- Autoimmune disease and paraneoplastic syndromes
- Febrile seizures
- Microglia, astrocytosis, cytokines in resected tissue from focal epilepsies

IVIG: OVERVIEW AND MECHANISM OF ACTION

- First used in treatment of childhood epilepsies in 1977
- Available IVIG commercial products (e.g., Gammunex, Gammagard, Phlebogam, Privigen)
- Proposed Mechanisms of action:
  - Interaction with subsets of B cells and T cells (including T regulatory cells)
  - modulation of cytokines
  - Reduction of complement complexes
  - blockage of idiotypic antibodies
  - alteration of gene expression associated with inflammation, fibrosis, and regeneration

IVIG: COMMON USES

- **Limbic encephalitis (any auto-immune epilepsy)**
- **Rasmussen encephalitis**
- Landau Kleffner syndrome / CSWS
- West syndrome
- Lennox-Gastaut syndrome

AUTO-IMMUNE EPILEPSIES: FEATURES

- Acute or subacute seizure onset
- Prior history of auto-immune conditions (patient, and first-degree relatives)
- Explosive onset of seizures
- Drug-resistant resistant seizures
- Multifocality on EEG
- Presence of extra-CNS neoplasm
- CSF evidence of inflammation
- Brain imaging evidence of inflammation
- Neuronal antibodies detection:
  - **Anti-LGI1 (anti-voltage-gated potassium channel complex antibodies)- Fasciobrachial dystonic seizures (ipsi arm/face, early sign)**
  - Anti-gad (glutamic acid decarboxylase)
  - Anti-thyroid antibodies
  - Anti-NMDA (seldom a pure epileptic syndrome, and often associated with other symptoms such as psychiatric)

TREATMENT OF AUTOIMMUNE EPILEPSY

- IV steroids (>oral): methylprednisolone 1000mgs for 3-5 days followed by weekly doses for 4-6 weeks
- IVIG: 0.4 g/kg/day for 3-5 days, followed by weekly dose for 4-6 weeks
- Plasmapheresis
- Chronic immunosuppression for confirmed and partially responsive autoimmune epilepsies:
  - Mycophenolate mofetil (cellcept)
  - Azathioprine (imuran)
  - Rituximab (Rituxan)

IVIG ADVERSE EFFECTS:

-Headache
-aseptic meningitis
-fluid shifts
-Hemodilution
-Thrombosis
-potential anaphylaxis in IgA deficiencies
-renal failure
-hemodilution
-Blood-born disease transmission

MCQ-1

Which of the following is true about catamenial epilepsy?

A. Seizure cluster around ovulation in C1 pattern
B. Seizure cluster before and during menses in C2 pattern
C. Seizure cluster in anovulatory cycles in C3 pattern
D. Estrogen is anticonvulsant
E. Progesterone is proconvulsant

ANSWER-1

Which of the following is true about catamenial epilepsy?

A. Seizure cluster around ovulation in C1 pattern
B. Seizure cluster before and during menses in C2 pattern
C. Seizure cluster in anovulatory cycles in C3 pattern
D. Estrogen is anticonvulsant
E. Progesterone is proconvulsant

In catamenial epilepsy, seizures tend to follow a cyclical pattern related to the menstrual cycle. There are three cyclical patterns of catamenial epilepsy: C1 pattern where seizures increase in frequency just before and during menses, C2 pattern where seizures increase around the time of ovulation, and C3 pattern where seizures occur with anovulatory cycles. Catamenial epilepsy is thought to be related to progesterone and estrogen fluctuations. Estrogen appears to be proconvulsant, and progesterone appears to be anticonvulsant

MCQ-2

For which of the following conditions is the ketogenic diet indicated for?

A. Primary carnitine deficiency
B. Pyruvate carboxylase deficiency
C. Pyruvate dehydrogenase deficiency
D. Porphyria
E. None of the above

ANSWER-2

For which of the following conditions is the ketogenic diet indicated?

A. Primary carnitine deficiency
B. Pyruvate carboxylase deficiency
C. Pyruvate dehydrogenase deficiency
D. Porphyria
E. None of the above

In pyruvate dehydrogenase deficiency, pyruvate cannot be metabolized into acetyl-coA. The ketogenic diet bypasses this step and provides ketones as an alternative fuel for the brain. All of the other choices are contraindications to the ketogenic diet. Long-chain fatty acids are transported across the mitochondrial membrane by carnitine (helped by CPT I and II and carnitine translocase); once in the mitochondrion, fatty acids are beta-oxidized to 2 carbon units of acetyl-CoA that can then enter the tricarboxylic acid cycle, to be used for energy production or ketone body production. A shift to use of fats as the primary energy source in disorders of fat metabolism would precipitate deterioration. Lack of carbohydrates would exacerbate acute intermittent porphyria.

MCQ-3

Screening for disorders of fatty acid metabolism should be performed prior to initiation of the ketogenic diet. Specifically, testing could include which of the following?

A. Complete blood count and complete metabolic panel including liver function tests and BUN and creatinine
B. Acylcarnitine profile, urine organic acids, and carnitine
C. CSF glucose, lactate, folate metabolites, amino acids, and neurotransmitters
D. Kidney ultrasound and nephrology consult

ANSWER-3

Screening for disorders of fatty acid metabolism should be performed prior to initiation of the ketogenic diet. Specifically, this testing could include which of the following?

A. Complete blood count and complete metabolic panel including liver function tests and BUN and creatinine
B. Acylcarnitine profile, urine organic acids, and carnitine
C. CSF glucose, lactate, folate metabolites, amino acids, and neurotransmitters
D. Kidney ultrasound and nephrology consult

This should adequately screen for disorders of fatty acid metabolism including carnitine deficiency, CPT I or II deficiency, carnitine translocase deficiency, and the beta-oxidation defects. The other choices are also reasonable considerations for preinitiation screening, but for other conditions.

MCQ-4

With rare exceptions, the ketogenic diet is initiated during an inpatient hospitalization. Complications during the initiation period could include all of the below, except:

A. Vomiting due to hypoglycemia, dehydration, excessive acidosis, constipation, or exacerbation of gastroesophageal reflux
B. Precipitation or deterioration in a patient with an undiagnosed disorder of fat metabolism
C. Excessive metabolic acidosis in a patient also treated with a carbonic anhydrase inhibitor
D. Deficiency of calcium and vitamin D, leading to loss of bone mineralization
E. Encephalopathy due to hypoglycemia, dehydration, and excessive acidosis

ANSWER-4

With rare exceptions, the ketogenic diet is initiated during an inpatient hospitalization. Complications during the initiation period could include all of the below, except:

A. Vomiting due to hypoglycemia, dehydration, excessive acidosis, constipation, or exacerbation of gastroesophageal reflux
B. Precipitation or deterioration in a patient with an undiagnosed disorder of fat metabolism
C. Excessive metabolic acidosis in a patient also treated with a carbonic anhydrase inhibitor
D. Deficiency of calcium and vitamin D, leading to loss of bone mineralization
E. Encephalopathy due to hypoglycemia, dehydration, and excessive acidosis

This would be a longer-term complication. Osteoporosis in the ketogenic diet is contributed to by calcium/vitamin D deficiency as well as acidosis.

MCQ-5

The literature supports the probable benefit of the ketogenic diet in which of the following conditions?

A. Benign myoclonus of infancy
B. Juvenile myoclonic epilepsy
C. Glucose transporter protein 1 deficiency
D. Pyruvate carboxylase deficiency

ANSWER-5

The literature supports the probable benefit of the ketogenic diet in which of the following conditions?

A. Benign myoclonus of infancy
B. Juvenile myoclonic epilepsy
C. Glucose transporter protein 1 deficiency
D. Pyruvate carboxylase deficiency

In GLUT1 deficiency syndrome, glucose transport across the blood-brain barrier is impaired. Since the ketogenic diet provides ketones that bypass the metabolic defect, serving as an alternative fuel to the brain, the ketogenic diet is the treatment of choice for this syndrome. Such epilepsy treatment is not necessary for benign myoclonus of infancy. Although the ketogenic diet may be particularly helpful for generalized epilepsies, there has not been data supporting its use in JME as of yet. The ketogenic diet is contraindicated for pyruvate carboxylase deficiency, which would impair tricarboxylic acid cycle function and energy production in the ketogenic diet.

MCQ-6

Which of the following statements accurately conveys the typical recommendations (by consensus) for discontinuation of the ketogenic diet?

A. Discontinue the ketogenic diet if it seems ineffective by 1 month following initiation
B. Wait for 3 months following initiation before deciding to discontinue the diet
C. Abrupt discontinuation is preferred over gradual weaning over 2-3 months
D. Wean after 1 year of seizure freedom

ANSWER-6

Which of the following statements accurately conveys the typical recommendations (by consensus) for discontinuation of the ketogenic diet?

A. Discontinue the ketogenic diet if it seems ineffective by 1 month following initiation
B. Wait for 3 months following initiation before deciding to discontinue the diet
C. Abrupt discontinuation is preferred over gradual weaning over 2-3 months
D. Wean after 1 year of seizure freedom

Although the benefit on seizure control can be seen within 2 weeks after initiation (in 75% of children in one study), it is recommended that the ketogenic diet be continued for 3 months before deciding to continue or discontinue. Gradual weaning rather than abrupt discontinuation is preferred and may assist with determining whether there has been benefit of the ketogenic diet on seizure control. The recommendation is to discontinue after 2 years of seizure freedom, similar to the time period used for anticonvulsant medications.

MCQ-7

Faciobrachial dystonic seizures are an early manifestation of:

A. Anti-NMDA antibody limbic encephalitis
B. Anti-LGI1 antibody limbic encephalitis
C. Anti-GAD antibody limbic encephalitis
D. Hashimoto's encephalitis
E. Landau-Kleffner syndrome

ANSWER-7

Faciobrachial dystonic seizures are an early manifestation of:

A. Anti-NMDA antibody limbic encephalitis
B. Anti-LGI1 antibody limbic encephalitis
C. Anti-GAD antibody limbic encephalitis
D. Hashimoto's encephalitis
E. Landau-Kleffner syndrome

Faciobrachial dystonic seizures are frequent brief dystonic seizures, typically affecting the ipsilateral arm and face found in association with LGI1 antibodies. Faciobrachial dystonic seizures often precede LGI1-antibody encephalitis. Recognition may lead to early diagnosis and early institution of immunotherapy, with improved outcome.

MCQ-8

Estrogen affects seizure control by:

A. Enhancing inhibition at GABA-A receptor
B. Increasing GABA synthesis
C. Accentuating the action of glutamate
D. Inhibiting synthesis of GABA
E. Estrogen is protective against seizures

ANSWER-8

Estrogen affects seizure control by:

A. Enhancing inhibition at GABAA receptor
B. Increasing GABA synthesis
C. Accentuating the action of glutamate
D. Inhibiting synthesis of GABA
E. Estrogen is protective against seizures

Estrogen may be proconvulsant as it may reduce inhibition at the GABAA receptor and also inhibits the synthesis of GABA. On the other hand, progesterone may be anticonvulsant as it enhances inhibition at the GABAA receptor and increases GABA synthesis.

MCQ-9

In addition to the traditional ketogenic diet, alternative dietary therapies have been developed for epilepsy treatment. Which of the following is an alternative dietary therapy for epilepsy treatment?

A. The low glycemic index treatment
B. The Atkins diet
C. The Paleo diet
D. The short-chain triglyceride diet

ANSWER-9

In addition to the traditional ketogenic diet, alternative dietary therapies have been developed for epilepsy treatment. Which of the following is an alternative dietary therapy for epilepsy treatment?

A. The low glycemic index treatment
B. The Atkins diet
C. The Paleo diet
D. The short-chain triglyceride diet

The *Modified* Atkins diet, the *medium*-chain triglyceride, and the low glycemic index treatment are alternative dietary therapies developed for epilepsy treatment.

MCQ-10

Which of the following is true regarding dietary therapy?

A. It is a natural therapy so should be tried any time a parent does not like medication
B. It should be considered in any patient with drug resistant epilepsy regardless of age or gender
C. It should be considered as a last resort because it has shown only anecdotal evidence of success
D. Dietary therapies use protein as the major source of calories
E. Dietary therapy is obsolete

ANSWER-10

Which of the following is true regarding dietary therapy?

A. It is a natural therapy so should be tried any time a parent does not like medication
B. **It should be considered in any patient with drug resistant epilepsy regardless of age or gender**
C. It should be considered as a last resort because it has shown only anecdotal evidence of success
D. Dietary therapies use protein as the major source of calories
E. Dietary therapy is obsolete

Dietary therapies should be considered after a patient has failed 2-3 appropriate AEDs in adequate doses and is not a surgical candidate. RCTs show that at least 38% patients will have >50% reduction in seizures although numbers are higher in other reports. Current dietary therapies for epilepsy use fat as the major source of calories.

MCQ-11

Which of the following is false regarding the ketogenic diet?

A. It has shown to be particularly effective in Doose syndrome and should be considered early in LGS, IS, Dravet syndrome.
B. It is first line in Pyruvate decarboxylase deficiency
C. It is the therapy of choice in Pyruvate dehydrogenase deficiency
D. Side effects include vomiting, dehydration, acidosis, constipation, osteopenia, dyslipidemia and risk of acute pancreatitis, prolonged QT and nephrolithiasis
E. Fasting and induction may decrease time to effectiveness but no significant difference in outcome is seen at 3mos following initiation.

ANSWER-11

WHICH OF THE FOLLOWING IS FALSE REGARDING THE KETOGENIC DIET?

A. IT HAS SHOWN TO BE PARTICULARLY EFFECTIVE IN DOOSE SYNDROME AND SHOULD BE CONSIDERED EARLY IN LGS, IS, DRAVET SYNDROME.
B. **IT IS FIRST LINE IN PYRUVATE DECARBOXYLASE DEFICIENCY**
C. IT IS THE THERAPY OF CHOICE IN PYRUVATE DEHYDROGENASE DEFICIENCY
D. SIDE EFFECTS INCLUDE VOMITING, DEHYDRATION, ACIDOSIS, CONSTIPATION, OSTEOPENIA, DYSLIPIDEMIA AND RISK OF ACUTE PANCREATITIS, PROLONGED QT AND NEPHROLITHIASIS
E. FASTING AND INDUCTION MAY DECREASE TIME TO EFFECTIVENESS BUT NO SIGNIFICANT DIFFERENCE IN OUTCOME IS SEEN AT 3MOS FOLLOWING INITIATION.

MCQ-12

WHICH OF THE FOLLOWING IS TRUE REGARDING THE MODIFIED ATKINS DIET?

A. IT HAS NO ROLE IN THE TREATMENT OF EPILEPSY AND SHOULD BE CONSIDERED PURELY FOR WEIGHT LOSS
B. ONLY CARBOHYDRATES WITH A GLYCEMIC INDEX <50 ARE ALLOWED
C. IT HAS BEEN SUCCESSFULLY USED IN THE TREATMENT OF DRUG RESISTANT EPILEPSY IN CHILDREN AND ADULTS
D. IT REQUIRES INITIATION IN THE INPATIENT SETTING
E. IT IS NATURAL AND HAS NO SIDE EFFECTS

ANSWER-12

WHICH OF THE FOLLOWING IS TRUE REGARDING THE MODIFIED ATKINS DIET?

A. IT HAS NO ROLE IN THE TREATMENT OF EPILEPSY AND SHOULD BE CONSIDERED PURELY FOR WEIGHT LOSS
B. ONLY CARBOHYDRATES WITH A GLYCEMIC INDEX <50 ARE ALLOWED
C. **IT HAS BEEN SUCCESSFULLY USED IN THE TREATMENT OF DRUG RESISTANT EPILEPSY IN CHILDREN AND ADULTS**
D. IT REQUIRES INITIATION IN THE INPATIENT SETTING
E. IT IS NATURAL AND HAS NO SIDE EFFECTS

MAD WAS CREATED AS A MORE PALATABLE AND LESS RESTRICTIVE DIETARY TREATMENT PRIMARILY FOR CHILDREN WITH BEHAVIORAL DIFFICULTIES AND ADOLESCENTS. MAD CAN BE INITIATED EFFICIENTLY IN AN OUTPATIENT CLINIC SETTING. MAD IS A MAINSTREAM THERAPY FOR CHILDREN AND ADULTS WITH INTRACTABLE EPILEPSY AND HAS SHOWN EFFECTIVENESS SIMILAR TO KD: 43-65% W >50% REDUCTION OF SEIZURES AND 35% W >90%. ALL CARBOHYDRATES ARE ALLOWED BUT IN RESTRICTED AMOUNTS. SIDE EFFECTS INCLUDE WEIGHT LOSS, DYSLIPIDEMIA, INCREASED BUN, ETC.

MCQ-13

WHICH OF THE FOLLOWING IS TRUE REGARDING IVIG?

A. IT HAS NO ROLE IN THE TREATMENT OF EPILEPSY
B. IT'S MECHANISM OF ACTION IN EPILEPSY HAS BEEN WELL ELUCIDATED
C. SIDE EFFECTS INCLUDE ASEPTIC MENINGITIS, THROMBOSIS, HEADACHE, RENAL FAILURE, ETC.
D. IT IS CONTRAINDICATED IN RASMUSSEN'S ENCEPHALITIS.
E. IT IS FIRST LINE IN THE TREATMENT OF IS

ANSWER-13

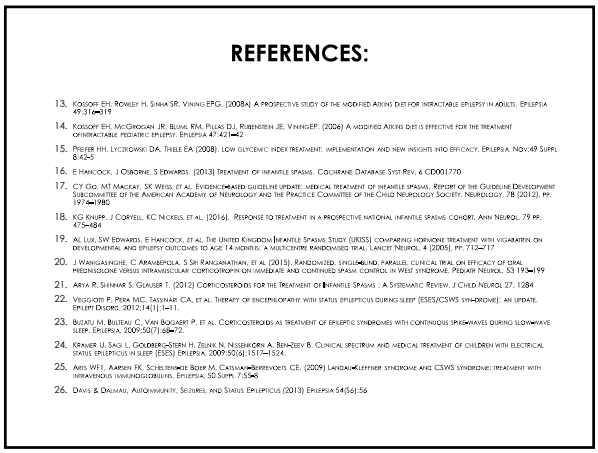
WHICH OF THE FOLLOWING IS TRUE REGARDING IVIG?

A. IT HAS NO ROLE IN THE TREATMENT OF EPILEPSY
B. IT'S MECHANISM OF ACTION IN EPILEPSY HAS BEEN WELL ELUCIDATED
C. **SIDE EFFECTS INCLUDE ASEPTIC MENINGITIS, THROMBOSIS, HEADACHE, RENAL FAILURE, ETC.**
D. IT IS CONTRAINDICATED IN RASMUSSEN'S ENCEPHALITIS.
E. IT IS FIRST LINE IN THE TREATMENT OF IS

IVIG HAS BEEN USED FOR MANAGEMENT OF EPILEPSY IN LGS, WEST SYNDROME, CSWS AND RASMUSSEN ENCEPHALITIS. INDIVIDUAL STUDIES DEMONSTRATE GOOD RESULTS BUT ROBUST STUDIES ARE LACKING. IN REPORTS, THERE WERE IMPROVEMENTS IN 33% WITH CSWS. IN RASMUSSEN'S ENCEPHALITIS IT HAS SHOWN INITIAL BENEFIT BUT LESS CLEAR CUT LONG-TERM EFFECT. SIDE EFFECTS ARE AS LISTED ABOVE.

REFERENCES:

1. NEAL EG, CHAFFE H, FITZSIMMONS G, ET AL. (2008) THE KETOGENIC DIET FOR THE TREATMENT OF CHILDHOOD EPILEPSY: A RANDOMISED CONTROLLED TRIAL. LANCET NEUROL. 7(6):500–6.
2. VINING, E.P. FREEMAN, J.M., BALLABAN- GIL, K ET AL.(1998). A MULTICENTER STUDY OF THE EFFICACY OF THE KETOGENIC DIET. ARCH NEUROL 55, 1433– 1437.
3. HEMINGWAY, C., FREEMAN, J.M., RIBBS, D.J., AND PYZIK, P.L. (2001). THE KETOGENIC DIET: A 3- 6 YEAR FOLLOW UP OF 150 CHILDREN PROSPECTIVELY ENROLLED. PEDIATRICS 108, 898– 905
4. LEFEVRE, F., AND ARONSON, N. (2000). KETOGENIC DIET FOR THE TREATMENT OF REFRACTORY EPILEPSY IN CHILDREN: A SYSTEMATIC REVIEW OF EFFICACY. PEDIATRICS 105, E46
5. HARTMAN AL, GASIOR M., VINING P ET AL. (2007). THE NEUROPHARMACOLOGY OF THE KETOGENIC DIET PEDIATR NEUROL. MAY; 36(5): 281– 292.
6. KOSSOFF, E.H., CARABALLO, R.H., DU TOIT, T., KIM, H.D.,MACKAY, M.T., NATHAN, J.K., AND PHILIP, S.G. (2012). DIETARY THERAPY: A WORLD WIDE PHENOMENON. EPILEPSY RES 100, 205– 209.
7. CARABALLO RH. (2011) NONPHARMACOLOGIC TREATMENTS OF DRAVET SYNDROME: FOCUS ON THE KETOGENIC DIET. EPILEPSIA. 52(SUPPL. 2):79–82
8. DRESSLER, A., TRIMMEL- SCHWAHOFER, P., REITHOFER, E ET AL (2015B). EFFICACY AND TOLERABILITY OF THE KETOGENIC DIET IN DRAVET SYNDROME: COMPARISON WITH VARIOUS STANDARD ANTIEPILEPTIC DRUG REGIMEN. EPILEPSY RES 109, 81– 89.
9. CARABALLO, R.H., CERSOSIMO, R.O., SAMIR, D ET AL. (2006). KETOGENIC DIET IN PATIENTS WITH MYOCLONIC- ASTATIC EPILEPSY. EPILEPTIC DISORD 8, 151– 155
10. LEMMON ME, TERAO NN, KOSSOFF EH, ET AL. (2012) EFFICACY OF THE KETOGENIC DIET IN LENNOX–GASTAUT SYNDROME: A RETROSPECTIVE REVIEW OF ONE INSTITUTION'S EXPERIENCE AND SUMMARY OF THE LITERATURE. DEV MED CHILD NEUROL. 54(5):464–8.
11. HONG, A.M., TURNER, Z, HAMDY, R.F., AND KOSSOFF, E.H. (2010). INFANTILE SPASMS TREATED WITH THE KETOGENIC DIET: PROSPECTIVE SINGLE-CENTER EXPERIENCE IN 104 CONSECUTIVE INFANTS. EPILEPSIA 51, 1403– 1407.
12. KOSSOFF EH, DORWARD JL. (2008) THE MODIFIED ATKINS DIET. EPILEPSIA 49 (SUPPL 8):37–41.



REFERENCES:

13. Kossoff EH, Rowley H, Sinha SR, Vining EPG. (2008a) A prospective study of the modified Atkins diet for intractable epilepsy in adults. Epilepsia 49:316–319

14. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, ViningEP. (2006) A modified Atkins diet is effective for the treatment ofintractable pediatric epilepsy. Epilepsia 47:421–2

15. Pfeifer HH, Lyczkowski DA, Thiele EA (2008). Low glycemic index treatment: implementation and new insights into efficacy. Epilepsia. Nov;49 Suppl 8:42-5

16. E Hancock, J Osborne, S Edwards. (2013) Treatment of infantile spasms. Cochrane Database Syst Rev. 6 CD001770

17. CY Go, MT Mackay, SK Weiss, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 78 (2012). pp. 1974–1980

18. KG Knupp, J Coryell, KC Nickels, et al. (2016). Response to treatment in a prospective national infantile spasms cohort. Ann Neurol. 79 pp. 475–484

19. AL Lux, SW Edwards, E Hancock, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: A multicentre randomised trial. Lancet Neurol. 4 (2005). pp. 712–717

20. J Wanigasinghe, C Arambepola, S Sri Ranganathan, et al. (2015). Randomized, single-blind, parallel, clinical trial on efficacy of oral prednisolone versus intravesicular corticotropin on immediate and continued spasm control in West syndrome. Pediatr Neurol. 53:193–199

21. Arya R, Shinnar S, Glauser T. (2012) Corticosteroids for the Treatment of Infantile Spasms : A Systematic Review. J Child Neurol. 27: 1284

22. Veggiotti P, Pera MC, Tassinari CA, et al. Therapy of encephalopathy with status epilepticus during sleep (ESES/CSWS syndrome): an update. Epilept Disord. 2012;14(1):1–11.

23. Buzatu M, Bulteau C, Van Bogaert P, et al. Corticosteroids as treatment of epileptic syndromes with continuous spike-waves during slow-wave sleep. Epilepsia. 2009;50(7):68–72.

24. Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES) Epilepsia. 2009;50(6):1517–1524.

25. Arts WF1, Aarsen FK, Scheltema-de Boer M, Catsman-Berrevoets CE. (2009) Landau-Kleffner syndrome and CSWS syndrome: treatment with intravenous immunoglobulins. Epilepsia. 50 Suppl 7:55-8

26. Davis & Dalmau, Autoimmunity, Seizures, and Status Epilepticus (2013) Epilepsia 54(56):56

Psychosocial Management and Systems-Based Practice Issues

Shubhi Agrawal, MD

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

PSYCHOSOCIAL MANAGEMENT AND SYSTEMS-BASED PRACTICE ISSUES

Shubhi Agrawal, MD
Neurologist, Berman Brain& Spine Institute

2020 EPILEPSY BOARD REVIEW AND BEST PRACTICES

DISCLOSURES

- **Disclosure of Financial Relationships**
  - **None**
- **Off-Label Usage**
  - **None**

Acknowledgement

Sara Inati, MD
Chief EEG Section
National Institute of Neurological Disorders and Stroke
Bethesda, Maryland

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
- School and work situations, Legal protections

Systems Based Practice Issues

- Community education and support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Importance of psychosocial issues

- US survey of major problems identified by people with epilepsy (Fisher 2000, Gilliam 2004)
  - Limitations of daily activities (driving, independence)
  - Stigma
  - Family concerns
  - Fear of the seizures
  - Work and education
  - Seizure medication side effects (cognitive problems, energy level, school performance, coordination, having children)

Negative Predictors of HRQOL

- Medication side effects
  - Medication side effects and depression were strongest predictors of HRQOL (Gilliam 2002)
  - Consider monotherapy over polytherapy to maximize HRQOL (can improve independently from seizure control)
  - Use of medication side effect questionnaire (AEP), led to significant improvements in side effects, seizure control and HRQOL (Baker 1994)
- Stigma
- Concerns about employment
- Depression
  - Present in 20-50% patients with epilepsy
  - Treatable (medications or psychotherapy)
  - Screen with NDDI-E (Neurological Disorders Depression Inventory for Epilepsy) (Gilliam 2006)
- Sleep disorders
- Migraine
  - High prevalence in patients with epilepsy, high overlap with depression; have poorer epilepsy prognosis
- Lack of social support
  - Epilepsy negatively impacts social functioning, particularly if seizures or comorbities are severe and there is little family support

Health-related quality of life (HRQOL): Positive Predictors

- Inconsistent findings regarding seizure frequency and QOL
  - This is usual goal of therapy
  - QOL improves mostly when patient becomes totally seizure free – then becomes similar to general population
- Surgery
  - Likely dependent on becoming seizure free
  - Other significant factors for improved QOL postoperatively: driving, mood, employment, AED cessation; NOT IQ status
- Exercise
  - McAuley 2001: no change in seizure activity, AED levels
    - Also improved mood

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
  - Seizure education
  - Drug information, compliance
  - Safety issues
  - Lifestyle – sleep, exercise, drugs and alcohol
  - Prognosis and additional concerns
- School and work situations, Legal protections

Systems Based Practice Issues

- Community Education and Support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Common Comorbidities

Psychiatric comorbidity	Prevalence	Proposed mechanisms and associated factors
Mood disorders	Depression ~23%, Mania ~12%, post-ictal symptoms only ~22% admitted to EMU (5-17% in general population)	Bidirectional relationship Dysfunction in temporal, orbitofrontal lobes, stigma, limitations at work and school, medication side effects
Anxiety disorders	~23% (5-7% in general pop)	GABAergic mechanisms, unpredictability of seizures, stigma, amygdalar atrophy
Psychosis	Interictal psychosis ~5- 7%, Postictal psychosis 2% (~1% in general pop)	Bidirectional relationship, abnormalities in dopamine receptor sensitivity, aberrant synaptic circuits in dentate-CA3-CA1 circuit, automine encephalitis
Suicide attempt or completed suicide	5-14% (Incidence)	Mood disorder, prior attempts
ADHD	12-37% (4-12 % in general pop)	

Jette, Intl Rev of Psychiatry 2017
LaFrance, Intl Rev of Neurobiology 2008

Depression in Epilepsy

- More common in temporal or frontal lobe epilepsy and in patients with poorly controlled seizures.
- Suicidality is 9-25 times higher than general population. One of the highest standardized mortality rate in epilepsy patients.
- Peri-ictal depression- Precital dysphoria may start 1-3 days before a seizure. Post-ictal depression reported in 43% in 1 study. Can last for several days. Some patients may have post-ictal suicidality. Ictal depression can be a type of experiential aura.
- Interictal depression can be identical to depressive disorders in non-epileptic population.
- Depression can be an adverse event of medication
- Mood lability is common in 6 weeks to 3 months after epilepsy surgery, esp anterior temporal lobectomy. Persistent depression has also been reported after ATL, esp in patients with pre-existing psychiatric comorbidities

Management of Depression in Epilepsy

- peri-ictal or interictal
- Related to initiation or discontinuation of AEDs
- Choosing anti-depressant-
  - Bupropion, amoxepine, clomipramine can increase seizures
  - TCAs – can increase risk of seizures at high doses, with rapid titration, in presence of other proconvulsants
  - One study with SSRI and SNRI showed lower incidence of seizures in depression patients on treatment. Typically 1st line in epilepsy patients. Citalopram, Escitalopram, Sertraline have minimal interaction with AEDs (esp important for AEDs affecting CYP enzymes).
- Psychotherapy
- Electroconvulsive therapy is not contraindicated in epilepsy and should be considered for refractory depression

Anxiety in Epilepsy

- 2nd most common psychiatric comorbidity. Includes generalized anxiety disorder, panic disorder, phobias, obsessive compulsive disorder, post traumatic stress ds
- Ictal fear or panic usually seen in mesial temporal onset seizures or with spread to cingulate gyrus
- Interictal symptoms can usually be treated with SSRIs* and/or psychotherapy
- Ictal or post-ictal symptoms usually don't respond to treatment
- Avoid using benzodiazepines for long term management. Short term use while initiating another medication may be helpful
- Psychotherapy, alternative approaches like meditation can also be very helpful

Psychosis in Epilepsy

- Postictal psychotic episodes- often start after a short delay from time of last seizure, last hours to a few weeks. Clustering of symptoms into delusional or affective-like psychosis. Respond well to low dose neuroleptic or benzodiazepine. Small percentage can progress to chronic psychosis. PIP correlates with bilateral independent ictal foci in several studies
- Ictal psychotic symptoms can be seen in non-convulsive status epilepticus, esp when associated with other ictal signs like automatisms
- Forced Normalization- emergence of psychosis when abnormal EEG patterns subside and EEG normalizes. Has been reported in temporal lobe epilepsy and in generalized epilepsies.
- Chronic or interictal psychosis of epilepsy that doesn't meet criteria for schizophrenia- typically less severe, has few or no negative symptoms, less common deterioration of patient's personality
- Iatrogenic psychosis- AED adverse event or post temporal lobectomy

Choosing antipsychotics

- For post-ictal psychosis, low dose benzodiazepine or atypical antipsychotic can be used as needed
- Conventional antipsychotics may have lower risk of provoking seizures but cause more extrapyramidal and anticholinergic side effects. Atypical antipsychotics often better tolerated
- For inter-ictal psychosis, atypical antipsychotics like quetiapine, risperidone, ziprasidone typically used as first line. Atypical antipsychotics can cause/worsen metabolic syndrome esp risperidone and olanzapine
- Clozapine and high dose chlorpromazine are associated with increased risk of seizures, should be avoided as far as possible

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
  - Seizure education
  - Drug information, compliance
  - Safety issues
  - Lifestyle – sleep, exercise, drugs and alcohol
  - Prognosis and additional concerns
- School and work situations, Legal protections

Systems Based Practice Issues

- Community Education and Support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Patient and Family Education: Seizures and Epilepsy

- Type of seizures and epilepsy syndrome
- Causes of epilepsy (risk factors, heritability)
- Use of seizure diaries for self-monitoring
- Recognition of seizure emergencies
  - Seizure clusters
  - Status epilepticus
  - Seizure related injuries
  - Have seizure action plan
- Know names, doses of medications
- Prevent, recognize, treat side effects
  - Recognition and management of allergic reactions
- Know possible interactions
  - Other medications, drugs, alcohol
- Afford treatments
- Manage refills
- Other treatment options
  - Surgery, devices, dietary therapies

Seizure First Aid

- Always stay with the person until the seizure is over
- Pay attention to the length of the seizure
  - Get help if longer than usual
  - Need rescue medication?
- Stay calm – most seizures only last a few minutes
- Prevent injury by moving nearby objects out of the way
  - Help them avoid dangerous situations if wandering or confused (traffic, trains, heights, sharp objects)
- Make the person as comfortable as possible
  - Help them sit down, help to the floor, support the head
- Keep onlookers away
- Do not forcibly hold the person down
  - Can lead to injuries, agitation
- Do not put anything in the person's mouth
- Make sure their breathing is OK
  - For GTCS, breathing will resume when seizure ends – rescue breathing not necessary
  - Turn on their side when possible; prevents saliva from blocking the airway
- Nothing by mouth until fully alert
- When to call for emergency help
  - Seizure lasting >=5 minutes
  - Seizure cluster without return to baseline or closer than usual for the person
  - Breathing problems, choking
  - Seizure in water
  - Injury
  - Person asks for medical help
- Be sensitive/supportive

From epilepsy.com

Compliance/adherence

- 50-80% of patients with epilepsy are adherent
  - Defined as taking the dose or at least having the medication available >=80% of the time (Faught 2012)
- Reasons for nonadherence:
  - Forgetting/memory problems
  - Complicated regimen
  - Not having the medication available
    - forgot, can't get to the pharmacy, $ or insurance problem
  - Side effects
  - Problem accepting the diagnosis
- Consequences of poor adherence:
  - Increased likelihood hospitalization/ED visit
  - Increased costs
  - Increased mortality
- Strategies:
  - Pill boxes
  - Using reminders and alarms
  - Modifying lifestyles to make medication taking easier
  - Keep 1 week emergency supply
  - Counseling to identify and work to overcome other barriers
  - Track changes in AED dose, schedule

Seizure Precautions

- Weighing safety against quality of life
- Driving restrictions per state and federal guidelines
- Avoiding activities with risk of serious injuries in the event of loss of consciousness- climbing to heights – like roofs, swimming in open water
- Supervision for activities with risk of significant injuries- like working with open flames, heavy knives
- Special situations- carrying firearms, use of heavy machinery etc

Minimizing risks at home

- Shield fire places/stoves, cover radiators or supervision while cooking
- Use microwave, induction cooking
- Temperature control device on hot water taps
- Prefer electric tea or coffeemakers vs hot water kettle
- Furniture without sharp edges
- Unbreakable glass on low windows/showers
- Use doors that can be opened from the outside
- Don't take a bath when alone; prefer showers
- If frequent falls out of bed, consider mattress on the floor

Sports / Activity Participation

- In general, encourage participation in activities
- American Medical Association Committee on Medical Aspects of Sports
  - 1968: opposed participation in collision and contact sports
  - 1983: Urged full participation in physical education programs and interscholastic athletics, aided by common sense and proper supervision
- Concerns:
  - Fear of physical injury, provocation of seizures
    - Rates and degrees of injuries during participation in contact sports are similar between people with and without epilepsy (Miele 2006)
    - Sports generally do not provoke more or more serious seizures
    - Very few seizures occur during active sports; often occur during rest periods afterward
  - Also hyperventilation, fatigue, changes in seizure medication metabolism, psychological stress, increased heart rate
- Advantages:
  - Psychosocial (mood, attention, depression)
  - Physiologic benefits (cardiovascular, bone health)
  - May reduce frequency and severity of seizures

Activities: Risk in Individuals with Epilepsy

Low Risk	Moderate Risk	High Risk
Baseball	Basketball	Boxing
Bowling	Biking	Downhill skiing
Cross-country skiing	Boating/sailing	Gymnastics (if high height)
Golf	Football	Hang gliding
Table Tennis	Gymnastics (floor)	Hockey
Track	Horseback riding	Motor sports
Walking	Karate	Rock climbing
Weight training (machines)	Skateboarding	Scuba diving
Yoga	Soccer	Swimming (long distance)
	Swimming/waterskiing	

From IOM 6 Quality of Life and Community Resources ." *Epilepsy Across the Spectrum: Promoting Health and Understanding* . Washington, DC: The National Academies Press, 2012 . Adapted from Drazkowski and Sirven 2011.

Sports, cont.

- Cycling:
  - If seizures are well controlled, just need to take normal precautions (helmet)
  - If active seizures, avoid busy roads, consider riding with someone
  - Properly managed cycling is better than covert unsupervised cycling
  - If frequent seizures, consider tandem or some 3 wheelers
- Swimming:
  - Most fatal accidents in epilepsy occur in water (60%), but few while swimming – mostly in bath, fishing, falling into water
  - If not seizure free, must have supervision, preferably a person with lifesaving skills
  - Avoid open water where first aid/rescue is more difficult
  - DON'T SWIM ALONE!

Sports: Recommendations

- Use normal safety precautions/protective equipment; in addition, special guards need to be available with sports in or around water
- Educate instructors and trainers what to do when a seizure occurs
- Have an initial neurological evaluation to establish a baseline and another after any injuries
  - Adhere to prescribed medication regimens

Driving and Epilepsy

- 5-27% people with epilepsy report having a seizure that led to a car accident
- In US: 0.2% of MVAs resulting in a fatality are attributed to seizures
- Risk of accident is about 2 times higher for patients with epilepsy compared to health people. It is not significantly higher than some other chronic diseases like diabetes, heart disease, or even teenage males
- Most car accidents involving patients with epilepsy are caused by driver errors than seizures

Driving Discussion Points

- Essential to educate patients about driving risks and relevant state laws
- Applicable legal requirements
  - Required seizure free interval if applicable
  - Reporting requirements
  - Consequences of driving illegally, besides injuries to self and others
    - Possible prosecution or litigation following an accident
    - Denial of insurance claims
- Explain risks associated with seizures, but also comorbidities, seizure medication side effects
- Factors increasing risks of driving illegally
  - Valid driver's license, being employed, no history of seizure-related accidents
- Local transportation services
- DOCUMENT – have a duty to warn patients not to drive if appropriate

Piloting regulations

"An established diagnosis of epilepsy, a transient loss of control of nervous system function(s), or a disturbance of consciousness is a basis for denial no matter how remote the history. Like all other conditions of aeromedical concern, the history surrounding the event is crucial. Certification is possible if a satisfactory explanation can be established."

www.faa.gov
Guide for Aviation Medical Examiners

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
  - Seizure education
  - Drug information, compliance
  - Safety issues
  - Lifestyle – sleep, exercise, drugs and alcohol
  - Prognosis and additional concerns
- School and work situations, Legal protections

Systems Based Practice Issues

- Community Education and Support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Sleep and epilepsy

- Increased incidence of drowsiness (2X) in people with epilepsy
  - Worsens quality of life, increases risk of accidents
- Causes of disrupted sleep in epilepsy:
  - Nocturnal seizures (~20% seizures occur during sleep, N2>N3>>REM)
  - Coincident sleep disorders
    - 1 series: 71% epilepsy patients referred for sleep study had obstructive sleep apnea (~30% of epilepsy patients)
    - Also insomnia, periodic limb movements, excessive daytime sleepiness
  - AEDs: sedating or alerting
  - Insufficient sleep, poor sleep hygiene
  - Mood disorders (depression, anxiety)
- Effects of sleep disruption:
  - Increased seizure frequency (particularly JME)
  - Worse short-term memory, concentration, mood
- Consider PSG if excessive daytime sleepiness, concern with memory, cognitive functioning – potentially correctable cause

Sleep Counseling

- Exercise regularly
- Use your bed for sleep and sex only
- Quiet and dark sleep environment
- Consistent sleep hours
- Don't exercise or eat just before bed
- Avoid caffeine 6 hours before bedtime
- Limit nighttime alcoholic drinks
- Relax before bedtime
  - Warm shower
  - Meditation
  - Stop working
  - Turn off electronics
- If can't sleep after 30 minutes, get out of bed, do relaxing quiet activity until tired, then return to bed; repeat
- If behavioral methods fail, can try melatonin, diphenhydramine
  - Don't use for more than 2-3 weeks

Regular Exercise

- Has benefit for overall physical and mental health
- Shown to improve anxiety, reduce stress, improve sleep
- Some animal studies have shown beneficial effects in delaying seizure onsets or reducing seizure duration
- Several studies have shown no increased risk of seizures with physical exercise. Some studies have shown seizure reduction with exercise
- Independent positive predictor of quality of life

Alcohol risks

- Drinking 1-2 alcoholic beverages usually causes no meaningful changes in blood levels of seizure medicines or in seizure control
  - Some syndromes (JME) may be sensitive to even limited alcohol intake
  - Ability to limit intake is often limited, particularly in teens
  - More may increase risk of seizures
- Alcohol-related seizures often related to withdrawal, binge drinking
  - Also missed sleep or missed medication doses
  - Alcohol abuse may worsen seizure control
- Combination of seizure medicines and alcohol or other drugs can have strong sedative effect, lower tolerance/rapid intoxication
  - Makes driving especially dangerous

Recreational Drug Use Risks

- Cocaine:
  - Can cause seizures even in those who don't have epilepsy; might increase seizures in people with epilepsy
- Amphetamines:
  - Generally safe in doses used for ADHD. Can cause seizures in overdose, esp in combination with antidepressants or other proconvulsants
- Heroin / narcotics:
  - Uncommon, but can cause seizures on withdrawal. Some case reports of seizures with high doses. Risk of excessive sedation in combination with AEDs
- Other illicit drugs:
  - Often not studied in epilepsy, but can lead to missed medication doses or poor sleep, also some lead to withdrawal seizures

Management of Seizure Triggers

- Sleep hygiene / avoiding sleep deprivation
- Stress management
- Medication compliance
- Drug and alcohol
- Other triggers:
  - Time of day
  - Illnesses
  - Visual triggers (flashing lights or patterns)
    - Rare- only ~3% people with epilepsy, children>adults, JME
  - Medications
  - Hormonal changes

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
  - Seizure education
  - Drug information, compliance
  - Safety issues
  - Lifestyle – sleep, exercise, drugs and alcohol
  - Prognosis and additional concerns
- School and work situations, Legal protections

Systems Based Practice Issues

- Community Education and Support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Prognosis

- Seizure outcome (remission, refractoriness)
- Mortality/Morbidity
  - SUDEP
  - Suicide
  - Status epilepticus / prolonged seizures
  - Seizure-related injuries / accidents

Prognosis, cont.

- After 1st unprovoked seizure:
  - ~50% recurrence risk after 1st seizure (23-71%)
  - 73% recurrence risk after 2 unprovoked seizures
  - Treatment reduces risk of short-term relapse but no effect on long-term seizure remission (FIRST and MESS study)
- 55-70% of people with epilepsy will achieve remission (Annegers 1979, Kwan and Brodie 2000)
  - Less likely if no response to 1st seizure medication, numerous seizures before beginning a medication, structural or metabolic etiology
- After surgery for refractory epilepsy: 66% experienced >=2 seizure free years, 25% relapsed (Spencer 2005)

Prognosis by syndrome

Excellent (20-30%): high probability spontaneous remission	**Good (30-40%): easy Rx control, possible spontaneous remission**	**AED-dependent (10-20%): may respond to AEDS, likely relapse with withdrawal**	**Guarded (20%): likely refractory**
Benign neonatal seizures	childhood absence	JME	Assoc with congenital neurologic defects
Benign partial epilepsies	GTCS 2 specific conditions	Most partial epilepsies	Assoc with progressive neurologic disorders
Benign myoclonic epilepsy in infancy			Some symptomatic/ cryptogenic
Reflex epilepsies			

Mortality

- Mortality rate higher in people with epilepsy (2-3X) (Forsgren 2005, Gaitatzis 2004)
  - 10 years of life lost with known cause of seizures (2.2-6.5 X increase) – usually due to the cause
  - 2 years of life lost with unknown cause of seizures (1.1-1.8 X increase)
  - 3-12 X increase with epilepsy and neurological deficit
- Epilepsy-Related Causes of Death:
  - Due to seizures:
    - Accidents, injuries
      - 6-20% of all deaths of people with epilepsy
      - Most often in water (60% bathtubs) > burns, trauma
      - 2X the general population
    - Status epilepticus
    - Pneumonia
  - Suicide
    - 1.6-9.1% deaths in cohort with epilepsy
    - 3.5-5.8 X general population risk
  - SUDEP
    - 1 in 10,000 of newly diagnosed
    - 9 of 1,000 candidates for epilepsy surgery
  - Risk factors for seizures
    - Brain tumors, strokes, traumatic brain injuries, infections

Nonfatal Accidents and Injuries

- Higher accidents and injuries in people with epilepsy vs matched controls (27% vs 17% at 24 months)
  - Higher injury rates in people with poorly controlled epilepsy (>1 seizure/month), GTCS
    - Particularly burns/scalding, head injury, dental injury, fractures (Asadi-Pooya 2012)
- Most common: wounds, abrasions, concussions, burns
- More serious: head trauma, fractures, choking, drowning
- Other:
  - Complications related to other conditions (diabetes, pregnancy)
  - Late complications: pneumonia, head injury

Traveling

- Using public transport is generally possible. Some patients need to be warned to stay towards the middle of a train platform, away from the curb on pavements if they have h/o ictal or post-ictal wandering behavior
- Seizures in a train or plane are not more dangerous than seizures at home
- Bring medications- preferably 2 sets- one checked and one carry-on
- Bring letter from doctor explaining the diagnosis and the medications (especially useful at customs)
- Have appropriate travel insurance
- May be useful to have an epilepsy "passport" – contains information on epilepsy in many languages

Dating/Social Interactions

- Good idea to discuss epilepsy with dates/friends, but best to do it in person, wait until relationship feels comfortable
- Fear of rejection is part of dating for everyone, worse with epilepsy
- Many people don't know much about epilepsy, education can help- educating friends about what seizures look like and how to respond if someone has a seizure

Marriage

- More likely to never be married, particularly if earlier onset epilepsy
- May be a greater problem in less developed countries
- Can worsen QOL for other family members
  - Unpredictable, potential for injury/death, frequent comorbidities, stigma
  - Negative effect on emotional/psychological health
  - Restricted social and leisure activities
  - Employment: missed work
- Need information about community resources, support services, respite care/day services

Women of childbearing age

- Effect of AEDs on oral contraceptives
- Teratogenicity with AEDs- risks, benefits, need to stay on treatment during pregnancy
- Importance of close follow up prior to planning and during pregnancy
- Caring for baby- sitting on floor or bed while holding, not bathing the baby alone, pros and cons of breast feeding

Patient and Family Education: Pediatric Issues

- School
  - Managing seizures at school
  - Common learning problems, IEP
  - Participation in activities
  - Career planning
- Mental health
  - ADHD, ASD
  - Social withdrawal/ making friends
- Dealing with fears
  - Stigma / telling others
  - Future (career, family, independence, driving)
  - Death
- Lifestyle management
  - Healthy habits (stress management, sleep)
  - Puberty, sexuality, drugs and alcohol
- Transition to independence
  - Career/employment
  - Transportation
  - Disease related
    - Which provider to contact
    - Getting to appointments
    - How to fill prescriptions
    - Medication adherence strategies
    - Obtaining and paying for medications

Patient and Family Education: Adult Issues

- Career / vocational
  - Discussions with employers
  - Driving regulations/transportation concerns
- Reproductive health
  - Family planning
  - Effects of seizure medicines on pregnancy and breastfeeding
  - Hormonal changes and seizure frequency
  - Sexual dysfunction
  - Fertility rates
- Social Issues:
  - Seizures in public
  - Drugs and alcohol
  - Impact on relationships
  - Independent living
- Lifestyle:
  - Sleep and fatigue
  - Stress management
- Medication interactions / adherence
- Risk of injury with aging and falls
- Cognitive problems

Patient and Family Education: Caregiver Issues

- First aid for seizures
- Parenting concerns
  - Overprotection, discipline, accessing needed services
- Emotional response
- Typical child cognitive and psychosocial development
- Sources of age-appropriate information for children
- Resources
  - Respite care, support groups, equipment, assistance in navigating health care, school and community services
- Advocacy skills

How and When to Educate

How

- Orally during visit with provider
  - Limited time, lots of information
- Nurses, other allied staff
- Written materials
- Websites
  - www.epilepsyfoundation.org
  - www.epilepsy.com
  - www.ilae-epilepsy.org
  - Dravet.org
- Community resources:
  - Support groups
  - Epilepsy Foundation affiliates
  - Community Agencies
- Word of mouth / friends / acquaintances
- Must be targeted (take into account severity of epilepsy, age, educational background, etc)

When

- At diagnosis
- During the first year
- When there is a change or new concerns develop
  - Change in developmental status
  - Change in seizures
  - Treatment related concerns
  - When treatment fails
  - Health status changes
  - Life stressors
  - Travel
  - Comorbidities
  - Employment/vocational status

Overview

Psychosocial Management

- Psychiatric comorbidities
- Patient and family education
  - Seizure education
  - Drug information, compliance
  - Safety issues
  - Lifestyle – sleep, exercise, drugs and alcohol
  - Prognosis and additional concerns
- School and work situations, Legal protections

Systems Based Practice Issues

- Community Education and Support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

School

- Risk factors for academic underachievement:
  - Poor cognitive functioning
  - Younger age of seizure onset
  - More frequent seizures or more severe seizure conditions
  - Presence of comorbidities (ADHD)
  - Psychosocial adjustment problems
- Many children with epilepsy can have cognitive difficulties
  - Intellectual disability is a risk factor for developing epilepsy
  - Consider effects of seizures, medications, psychosocial factors
- Screen early for cognitive problems and ADHD (particularly inattentive form)
  - Consider neuropsychological testing
    - mild cognitive impairments that can be missed on standardized testing
    - can use to develop IEPs

1973 Rehabilitation Act and amendments

- School districts must provide a free appropriate public education regardless of the nature or severity of the disability
- Nondiscrimination is mandated including nonacademic activities (athletics, transportation, health services, recreational activities, special interest groups/clubs)
- Requires reasonable accommodation while attending school for students with disabilities who do not qualify for an IEP
  - Qualify if have a physical or mental impairment that substantially limits one or more major life activities
- Section 504 educational plan outlines educational services and accommodations necessary to ensure equal access to education:
  - Schedule modification
  - Structured learning environment
  - Modified test instructions and test delivery
  - Assistive technology
  - Medical and transportation services
  - OT/PT/speech and language services

Individuals with Disabilities Education Act (IDEA) 2004

- Mandates free and appropriate public education for all students with disabilities ages 3-21 or high school graduation
  - Children with epilepsy qualify if it adversely affects their educational performance
  - Infants and toddlers who have developmental disabilities or who are at risk of having a disability may be eligible for early intervention services
- School districts must identify, evaluate, reevaluate and provide services to children who need special education and related services
- Education should be provided for students in the least restrictive environment and alongside of students without disabilities whenever possible
- Nondiscrimination in testing and evaluation services
- Individualized education programs (IEPs)

Individualized education program (IEP)

- Written statement
- Annual academic and functional goals
- Plans on how progress will be measured on those goals
- Details special education and other services to be provided
- Information on appropriate accommodations necessary to measure the academic achievement and functional performance of the child on assessments
- By 16 years of age, must include a discussion of post-secondary goals and transition services needed
- Parents allowed to attend and help to formulate the plan

Employment issues

- In general, rate of unemployment/underemployment ~2-5X the general population
  - Seizure-related (type, frequency, age of onset, perceived impact)
  - Stigma (felt and enacted)
  - Comorbid conditions (psychological, cognitive, social)
  - Lack of educational/vocational training
  - Driving restrictions
  - Adverse effects of seizure medications
  - Discrimination
- More likely to be employed in unskilled/manual jobs
- Lower levels of education, income and employment (Kobau 2008)
- No significant difference in rate of accidents in the workplace (3% vs 1% controls)
  - Rate of accidents fell only slightly when removing seizure-related accidents
  - Likely related to medication side effects, neurologic deficits
- In one study – when seizures are well controlled and no other handicaps, no employment problems

Employment Legislation

- 1973 Rehabilitation Act
  - Title V: mandates nondiscrimination on the basis of disability in federal hiring and employment
  - Section 504: prohibits disability-based exclusion of otherwise qualified persons with disabilities from participation in any federal program or activity or from any program or activity that receives federal funding

1990 Americans with Disabilities Act (ADA)

- "Equality of opportunity, full participation, independent living, and economic self-sufficiency" for those with disabilities
- Definition of disability:
  - a) Have or have a record of physical or mental impairment that b) substantially limits c) one or more major life activities
  - Limitations: mitigating factors such as medication must be taken into account when determining if a disability exists
    - If a person is seizure free on medications, they are not protected by the ADA
- Title 1: employment discrimination in hiring, advancement or discharge, compensation, job training, and other terms, conditions and privileges of employment (applies if >15 employees)
- Title 2: public services
- Title 3: public accommodations

ADA: Title 1

- Must be able to perform the essential functions of the job with or without reasonable accommodation
  - Examples of accommodations:
    - If driving is marginal – have another employee drive
    - Allow time off for doctor's visits or to recover from seizures
    - Install a safety device around a piece of machinery
    - Padded floor
    - Work from home
  - Not required if it would cause "undue hardship" (difficulty or expense)
  - Does not apply if individual poses a "direct threat" to safety, defined as "a significant risk of substantial harm which cannot be lessened by reasonable accommodation"
    - Simply having a seizure is not a direct threat unless there is a specific duty that poses a risk
    - People with active seizures should avoid driving, open fire, hot substances, dangerous moving objects, mechanical and electrical hazards, situations with danger of falling
  - Employer is permitted to reassign if reasonable accommodations cannot be made; can be lower grade only if that is the only position available for which the individual is qualified

ADA: Title 1

- Medical inquiries:
  - Do not have to disclose a disability in the interview unless it affects performance of the job's essential functions
  - Employers are prohibited from asking questions about condition or nature or severity until after job offer is extended
    - May then ask questions, request examination if all employees selected for that job classification are required to do so
    - Once on the job, must be related to job performance or safety; or in response to a request for accommodations
- Complaints about employment discrimination can be filed under the US Equal Employment Opportunity Commission (EEOC)

More legal issues

- 2008 ADA Amendments Act
  - 2008 amendments expand the definition of major life activities to include learning, reading, concentrating, thinking
  - Act now covers impairments that are episodic in nature or in remission and that substantially limit a major life activity when not in remission
- Family and Medical Leave Act (FMLA)
  - Requires employers with >=50 employees to provide up to 12 weeks unpaid leave and to retain employee's benefits for care of family members with medical problems
  - This isn't protected under ADA

Systems-based practice issues

- Community education and support
- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Stigma

- "Process in which adverse social judgments are made that are medically unwarranted" (Weiss and Ramakrishna (2001)
- Enacted vs felt stigma (Jacoby 1994)
  - Felt: internal experience of "difference," fear of prejudice experienced by people with epilepsy; present in 1/5 newly diagnosed epilepsy
  - Enacted: external, actions of others toward people with epilepsy
- Poorer QOL with higher stigma even if seizures controlled
  - Degree of stigma greater with ongoing seizures vs seizure free (Jacoby 2002)
- Negative images of people with epilepsy in the media: violent, retarded, antisocial, physically unattractive
- Cultural beliefs: punishment for sins, lack of faith, result of illegal drug use, possessed by spirits

Stigma

- Many possible arenas: family, local community, health and social care systems, educational institutions, legal systems, employment, insurance
- Lower levels of knowledge about epilepsy associated with institutional and interpersonal stigma
  - Identified negative stereotypes, described personal and social avoidance (Austin 2002, Dilorio 2004)
- Strategies to improve attitudes toward epilepsy:
  - Education, advocacy, increased level of contact with people with epilepsy, inducing empathy for a person with epilepsy

Effects of Stigma

- Lack of social support from extended family members
- Feelings of parental guilt
- Social isolation, embarrassment, fear
- Discrimination
- Impaired self-esteem, self-efficacy, sense of mastery, perceived helplessness, increased rates anxiety and depression, increased somatic symptoms, reduced life satisfaction

Community Resources

- Counselling
- Social skills training
- Cognitive rehabilitation
- Support networks
- Peer mentoring
- Vocational rehabilitation
- Independent living programs
- Providers include nurses, social workers, psychologists, psychiatrists, educators, vocational rehabilitation therapists, recreation therapists, resource specialists

Public policy issues

- Health care reform in US
  - Access to care (specialists, medications, surgery)
  - Increasing costs of private insurance
  - Benefits being trimmed to control costs
  - Changes to increase access to insurance for those with chronic health conditions or disabilities
- State-financed health care systems
  - looking for ways to limit expenditures
- Developing countries
  - large needs, inadequate economic resources

Epilepsy and Public Health

- Primary prevention:
  - Infectious diseases (neurocysticercosis, meningoencephalitis)
  - Maternal-infant care (perinatal injuries, infections)
  - Traffic accidents/head trauma (seat belts, helmets)
  - Stroke (risk factor reduction)
- Secondary prevention (pre-symptomatic):
  - Not currently possible
  - Need biomarkers of epileptogenesis and development of early intervention measures
- Tertiary prevention (disease management):
  - Early identification of medically refractory patients
  - Screening/interventions for comorbidities

Efforts to make epilepsy a public health priority

- U.S. Commission for the Control of Epilepsy and Its Consequences (1978)
- Living Well with Epilepsy conferences (1997, 2003)
- Vision 20-20 coalition (2004-)
- US DHHS: Interagency Collaborative to Advance Research in Epilepsy (2011)
- Global Campaign Against Epilepsy: Out of the Shadows (2011)
  - ILAE, International Bureau of Epilepsy, World Health Organization
- Strategy and Plan of Action on Epilepsy (2011)
  - Pan American Health Organization (PAHO)
- Written Declaration on Epilepsy (2011) - EU

Public policy: public health

- IOM report: Epilepsy Across the Spectrum: Promoting Health and Understanding (2012)
  - Epilepsy surveillance efforts (data collection)
  - Enhanced prevention programs and well-designed epidemiologic studies focusing on areas for further preventive efforts
  - Access to patient-centered care for all individuals with epilepsy
  - Up to date high quality clinical care, education and coordination and community resources
  - Well informed health care teams that take into account health literacy, cultural and psychosocial factors
  - Tailored patient and family education to promote patient-centered care, achieve optimal self-management of their epilepsy, and to attain the highest possible physical and emotional well-being
  - An improved public understanding of what epilepsy is – and is not – to promote inclusion and eliminate stigma

Public policy: research

- NIH/NINDS report: Curing Epilepsy Conferences and Epilepsy Research Benchmarks (updated 2010)
  - Understand causes of the epilepsies and epilepsy-related neurologic, psychiatric and somatic conditions
  - Prevent epilepsy and its progression
  - Improve treatment options for controlling seizures and epilepsy-related conditions without side effects
  - Limit or prevent adverse consequences of seizures and their treatment across the lifespan
- NIH FY2011 epilepsy research funding was ~$134 million
  - Meador 2011: epilepsy got less funding than 5 other neurologic diseases when adjusted for prevalence

Systems-based practice issues

- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Clinical Trials of New Therapies

- In vitro, animal model testing for preclinical evidence of efficacy and safety
- Investigational new drug application
- Phase I:
  - Safety, PK, human metabolism using dose escalation in healthy volunteers
  - Find maximum tolerated dose
- Phase II:
  - Initial efficacy and safety testing in population of interest
  - "Proof of principle" – worth investing in?
- Phase III:
  - Larger scale safety and efficacy testing
  - Trials for specific indications
- Phase IV:
  - Postmarketing studies
  - Define optimal use in general clinical practice population, broaden the safety database

Trial Design

- Need for blinding and control groups
  - 0-36.5% patients in placebo arm of blinded studies showed a >=50% seizure reduction over 3 month period
- Active vs placebo comparisons
  - FDA does not accept active control trials as proof of monotherapy efficacy
- Adjunctive vs monotherapy trials
  - Can't ethically treat epilepsy patients with placebo only
  - Drawbacks to adjunctive trials: hard to prove efficacy, increased side effects, PK interactions
- Parallel vs crossover designs
  - Crossover designs require fewer patients but take longer, risk of drop outs, potential unblinding due to awareness of side effects on active treatment
- Consideration of new trial designs
  - Outcomes measures (seizure diaries?)
  - Monotherapy trials
  - Adaptive designs
  - Non-inferiority trials
  - Combination therapy trials
  - Targeted population trials
  - Modeling from prior trials

Clinical trials: methodological issues

- Inconsistent/incorrect phenotyping lead to variability
- Inclusion/exclusion criteria
- Reluctance to enroll patients when other approved medications are available to try
- Retention problem
- Placebo response
- Pediatrics
- Acute vs chronic treatment

Clinical Trials: Patient Issues

- Epilepsy syndrome selection:
  - Usually use complex partial seizures – most common uncontrolled seizure type
- Seizure severity:
  - Is a drug effective in highly refractory epilepsy the best for new onset seizures?
- Women of childbearing age:
  - Previously excluded from studies; now included with strict contraception guidelines
- Children:
  - Age related changes in brain and overall physiology
  - Different epilepsy syndromes
  - Different methods / scales used to monitor behavioral and cognitive side effects

Clinical Trials: other issues

- Drug:
  - Know about drug interactions, tolerability of rapid titration, appropriate dose range (toxicity vs decreased efficacy)
- Analysis of results:
  - Choosing an outcome variable (usually reduction in complex partial seizures)
  - Handling seizure data (vast array of methods, hard to compare)
  - Intent to treat:
    - As treated vs intention to treat vs per protocol
    - Missing data from dropouts:
      - Last observation carried forward – assumes no change from last observation to end point – not valid for many clinical conditions
        - » May overreport efficacy, underreport harms
  - Counting seizure clusters
  - Noncompliance
  - Nonstandard outcome measures (seizure severity, QOL, time on the drug)

Clinical Trials: Safety

- Toxicity is amplified in add-on studies
- May be hard to distinguish dose-related from idiosyncratic side effects
- 3 month trials cannot assess long-term toxicity; likely to miss rare idiosyncratic toxicities (found in open label or postmarketing)
  - Vigabatrin visual field defects
  - Topiramate and glaucoma
  - Hypohidrosis and renal calculi with topiramate and zonisamide
  - Bone marrow suppression and hepatic insufficiency with Felbamate
- Children:
  - Effects on brain growth, neurologic and cognitive development
  - Follow development, head circumference
  - Weight gain, hormones, height

Systems-based practice issues

- Public policy issues
- Working with educational systems
- Employment issues
- Clinical trials of new therapies
- Forensic epilepsy
- Ethics

Forensic Epilepsy

- Arrest for seizure-related behavior
  - Public intoxication, trespassing, breaking and entering, resisting arrest, assault
  - Assault sometimes from reflexive resistance to restraint during a seizure
  - Treating neurologist may be asked if behavior in question was consistent with the individual's seizures – can lead to dropped charges
  - "Automatism" defense in some countries and US states if individual not aware of their actions at the time of the behavior
  - EFA and Police Executive Research Forum: training materials for police officers to reduce # of inappropriate arrests
    - Should consider information from bystanders or observation at the scene that give indication of whether confusion or unusual behavior was seizure related
- Aggressive/psychotic behavior as a side effect of AEDs
- Epilepsy as a defense against charges of serious violent crimes- controversial

Ethics

Issues in epilepsy

- Genetic testing
- Clinical trial participation
  - Disclosure, informed consent
  - Helsinki charter
  - Institutional review boards
- Study design
  - Use of placebos
  - Children
    - Assent
    - Severity of disease vs toxicity
  - Pregnancy
- Epilepsy and driving
- Access to care

Ethical principles

- Autonomy
  - Self-determination
- Confidentiality
- Beneficence
  - Maximizing benefit to health
- Non-maleficence
  - Avoid/prevent/reduce harm
- Justice
  - Equity of access
- Human dignity and human rights
- Respect for national laws and international conventions

Resources

- Epilepsy: A Comprehensive Textbook; Engel and Pedley
- IOM (Institute of Medicine), 2012. Epilepsy across the spectrum: Promoting health and understanding. Washington DC: The National Academies Press.
- www.epilepsyfoundation.org
- www.epilepsy.com

Driving in Epilepsy

Jay Foreman, MD