2023 GW Epilepsy Board Review & Best Practices

Management in Special Situations: Neonates, developmental delay, cognitive impairment

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OUTLINE

1. Neonates
2. Developmental Delay/Cognitive Impairment

Neonates

- Hypoxic Ischemic Encephalopathy
- Acute Symptomatic seizures
- Neonatal onset epilepsy

Neonates - HIE

- Hypoxic Ischemic Encephalopathy
  - Commonly will monitor with video eeg while cooling and 6 hours after re-warming goal temperature
  - Treating seizures with phenobarbital (goal level 35-40), fosphenytoin, levetiracetam , topiramate (via NG)
  - Rarely needing to escalate to anesthetic drips like midazolam

Neonates - HIE

- Hypoxic Ischemic Encephalopathy
  - If seizures stop, discontinue AED DOL 7-10 – one at a time
  - Consider repeat EEG in 1 week if discontinuous background, or if discontinuing AED

Neonates – Acute symptomatic

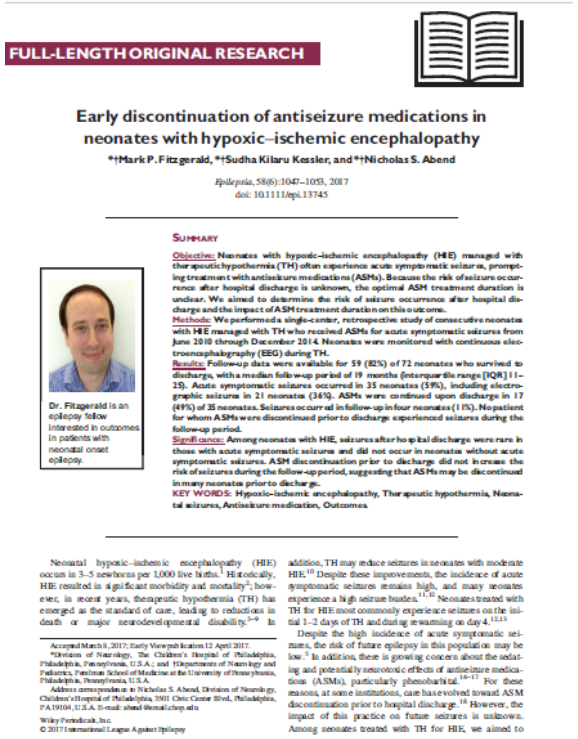
- Excluding HIE, may see stroke, hemorrhage, metabolic derangement (hypoglycemia, -ca, -mg) or infection present as early in life seizure
- Similar AEDs: phenobarbital, fosphenytoin, levetiracetam and topiramate
- Again consider weaning off medications in ~7-10 days after seizures stop

Neolev 2

https://clinicaltrials.gov/ct2/show/NCT01720667

Neonates – Acute symptomatic

- Consider weaning off medications in ~7-10 days after seizures stop
- "Early Discontinuation of antiseizure medications in neonates with hypoxic-ischemic encephalopathy" Abend N. 2017
  - 51% ASM discontinued upon discharge of those with seizures and HIE/cooling
  - 11% neonates had seizures in follow up (19 months)
  - None of those who had discontinue ASM had seizures in follow up



FULL-LENGTH ORIGINAL RESEARCH

Early discontinuation of antiseizure medications in neonates with hypoxic–ischemic encephalopathy

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doi: 10.1111/epi.13745

Dr. Fitzgerald is an epilepsy fellow interested in outcomes in patients with neonatal onset epilepsy.

SUMMARY

Objective: Neonates with hypoxic–ischemic encephalopathy (HIE) managed with therapeutic hypothermia (TH) often experience acute symptomatic seizures, prompting treatment with antiseizure medications (ASMs). Because the risk of seizure occurrence after hospital discharge is unknown, the optimal ASM treatment duration is unclear. We aimed to determine the risk of seizure occurrence after hospital discharge and the impact of ASM treatment duration on this outcome.

Methods: We performed a single-center, retrospective study of consecutive neonates with HIE managed with TH who received ASMs for acute symptomatic seizures from June 2010 through December 2014. Neonates were monitored with continuous electroencephalography (EEG) during TH.

Results: Follow-up data were available for 59 (82%) of 72 neonates who survived to discharge, with a median follow-up period of 19 months (interquartile range [IQR] 11–25). Acute symptomatic seizures occurred in 35 neonates (59%), including electrographic seizures in 21 neonates (36%). ASMs were continued upon discharge in 17 (49%) of 35 neonates. Seizures occurred in follow-up in four neonates (11%). No patient for whom ASMs were discontinued prior to discharge experienced seizures during the follow-up period.

Significance: Among neonates with HIE, seizures after hospital discharge were rare in those with acute symptomatic seizures and did not occur in neonates without acute symptomatic seizures. ASM discontinuation prior to discharge did not increase the risk of seizures during the follow-up period, suggesting that ASMs may be discontinued in many neonates prior to discharge.

KEY WORDS: Hypoxic–ischemic encephalopathy, Therapeutic hypothermia, Neonatal seizures, Antiseizure medication, Outcomes.

Neonatal hypoxic–ischemic encephalopathy (HIE) occurs in 3–5 newborns per 1,000 live births.[1] Historically, HIE resulted in significant morbidity and mortality[2]; however, in recent years, therapeutic hypothermia (TH) has emerged as the standard of care, leading to reductions in death or major neurodevelopmental disability.[3–9] In addition, TH may reduce seizures in neonates with moderate HIE.[10] Despite these improvements, the incidence of acute symptomatic seizures remains high, and many neonates experience a high seizure burden.[11,12] Neonates treated with TH for HIE most commonly experience seizures on the initial 1–2 days of TH and during rewarming on day 4.[12,13]

Despite the high incidence of acute symptomatic seizures, the risk of future epilepsy in this population may be low.[5] In addition, there is growing concern about the sedating and potentially neurotoxic effects of antiseizure medications (ASMs), particularly phenobarbital.[14–17] For these reasons, at some institutions, care has evolved toward ASM discontinuation prior to hospital discharge.[18] However, the impact of this practice on future seizures is unknown. Among neonates treated with TH for HIE, we aimed to

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Neonates – Epilepsy

- Only AEDs not associated with apoptosis in animal models are: topiramate, levetiracetam and lamotrigine
- Commonly used include: phenobarbital, phenytoin, oxcarbazepine, clonazepam
- Continue to work up underlying cause; epilepsy gene panel and metabolic testing, MRI/MRS
- Trials of pyridoxine especially if fails 2nd AED

› Ann N Y Acad Sci. 2003 May;993:103-14; discussion 123-4. doi: 10.1111/j.1749-6632.2003.tb07517.x.

Antiepileptic drugs and apoptosis in the developing brain

Petra Bittigau [1], Marco Sifringer, Chrysanthy Ikonomidou

Affiliations + expand

PMID: 12853301 DOI: 10.1111/j.1749-6632.2003.tb07517.x

Abstract

Epilepsy is the most common neurologic disorder in young humans. Antiepileptic drugs (AEDs), used to treat seizures in children, infants, and pregnant women, cause cognitive impairment, microcephaly, and birth defects by unknown mechanisms. We tested whether common AEDs cause neurodegeneration in the developing rat brain. Rats aged 3-30 days received phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid. Histologic examination of the brains revealed that these drugs cause widespread and dose-dependent apoptotic neurodegeneration in the developing rat brain during the brain growth spurt period. Apoptotic neurodegeneration was triggered at plasma drug levels relevant for seizure control in humans. Antiepileptic drugs lead to reduced expression of neurotrophins and decreased concentrations of the active forms of ERK1/2, RAF, and AKT. beta-Estradiol, which stimulates pathways that are activated by neurotrophins, ameliorated AEDs-induced apoptotic neurodegeneration. Our findings present one

Neonates – Epilepsy

- Be cautious: Valproic Acid – may affect organic acid, fatty acid metabolism along with mitochondrial disorders.
- If under 2 years old consider: genetic epilepsy panel (rule out POLG among other disorders), lactate/pyruvate ratio, ammonia, plasma amino acid, urine organic acids, free and total carnitine, acylcarnitine profile

Valproate-induced hyperammonemic encephalopathy

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PMID: 12602513 DOI: 10.1023/a:1021918104127

Abstract

Valproic acid (VPA) is an effective anticonvulsant useful in many types of epilepsy and, although it is usually well tolerated, it has been associated with many neurological and systemic side effects. Among these, one of the most important is VPA-induced hyperammonemic encephalopathy (VHE): its typical signs are acute onset of impaired consciousness, focal neurologic symptoms, and increased seizure frequency. The pathogenesis of VHE is still unclear, but it has been suggested that hyperammonemia can produce encephalopathy via inhibition of glutamate uptake by astrocytes which may lead to potential neuronal injury and perhaps cerebral edema. Glutamine production is increased, whereas its release is inhibited in astrocytes exposed to ammonia. The elevated glutamine increases intracellular osmolarity, promoting an influx of water with resultant astrocytic swelling. This swelling could compromise astrocyte energy metabolism and result in cerebral edema with increased intracranial pressure. Moreover, VHE seems to be more frequently in patients with carnitine deficiency or with congenital urea cycle enzymatic defects.

Cognitive Impairment/ Developmental Delay

- Autism
- Delays
- Refractory Epilepsy

Cognitive Impairment/ Developmental Delay

- Autism
  - Anywhere from 4-86% of children with autism have EEG abnormalities, but only 12-37% have epilepsy.

medicina

MDPI

Review

Electroencephalographic Abnormalities in Autism Spectrum Disorder: Characteristics and Therapeutic Implications

Francesco Precenzano [1,2,†], Lucia Parisi [2,3,†], Valentina Lanzara [1,2], Luigi Vetri [4,*], Francesca Felicia Operto [5], Grazia Maria Giovanna Pastorino [2,5], Maria Ruberto [6], Giovanni Messina [7], Maria Cristina Risoleo [1,8], Claudia Santoro [1], Ilaria Bitetti [1] and Rosa Marotta [8]

A large body of literature reports the higher prevalence of epilepsy in subjects with ASD compared to the general population. From literature data, the prevalence of epilepsy in patients with ASD widely varies from 2% [3] to 46% [4]. The largest study focusing on the comorbidity between epilepsy and autism included nearly 6000 patients from a pre-existing research database and reported the presence of epilepsy in 12.5% of patients under 17 years old [5], whereas in a previous report on 1000 patients with ASD, about 37% showed epilepsy [6].

The presence of epilepsy also correlates with more severe autism symptoms as reported by Shubrata et al. with deficits in imitation (p = 0.011) and hearing domains (p = 0.018). The same authors also reported that a history of regression and loss of acquired skills seems to be more frequent in epileptic ASD patients (36%) than in patients without epilepsy [7].

Many reports have shown the presence of SEAs in ASD with estimates widely varying from 4% to 86% even in the absence of a clinical history of epileptic seizures [16,22,23,24].

However, SEAs in patients with ASD exceed those of the general population (ranges from 2% to 8.7%), and this seems to be regardless of age or gender in some studies while in others they seem to decrease with puberty [25,26,27,28].

Several studies have reported SEAs in children with ASD without clinical seizures underlying that they are not signs of epilepsy but rather signs of cerebral dysfunction. (Table 1).

Cognitive Impairment/ Developmental Delay

- Autism
  - Abnormal Epileptiform activity may be sign of cerebral dysfunction
  - Majority of SEA (subclinical epileptiform abnormalities) do not develop epilepsy
  - Treatment of SEAs in order to prevent epilepsy is not supported by evidence

medicina

MDPI

Review

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The decision to start a treatment of SEAs in seizure-free patients should be based on two assumptions. First, SEAs directly cause cognitive and behavioral impairment in children with ASD.

Second, treating SEAs could prevent the onset of seizures.

However, what is the predictive value of EEG abnormalities in the development of later epilepsy remains an open question. In a study, Parmeggiani et al. analyzed a large sample of 345 subjects with autism where EEG SEAs without clinical seizures are present in 81 (23.5%) cases. Isolated EEG abnormalities preceded epilepsy onset only in 8 cases (9.3%). EEG abnormalities are mainly present in childhood ($p < 0.05$) (peak from 5 to 10 years) while epilepsy tends to occur significantly ($p < 0.001$) later (peak from 20 to 25 years) [8].

Another study performed by Kanemura and colleagues had similar results. They followed 21 children (between the ages of 3 and 6 years) with ASD over a 6-year period and documented SEAs in 52.4%. Six of these patients (28.6%) developed epilepsy. The presence of frontal epileptiform abnormalities was significantly associated with later development of epilepsy compared to centrotemporal paroxysms ($p < 0.003$) [73].

A similar association has been found in a study that analyzed 16 children with high functioning autism in which only one patient with abnormal frontal fast activity developed seizures later in time [74].

The current clinical experience in autistic patients suggested that a large percentage of these patients could develop seizures in adolescence or adulthood [75]. However, the small number of longitudinal studies does not allow to clearly establish the predictive value of SEAs for subsequent epilepsy. Therefore, pharmacological treatment of SEAs in order to prevent epilepsy is to date not supported by evidence.

Cognitive Impairment/ Developmental Delay

- Many patients with cognitive impairment/developmental delay have epilepsy:
  - mild ~11%
  - severe ~ 23% (up to 43% in one study)
  - institutionalized ~30%

Note: many have non-epileptic behavior - video eeg monitoring helpful, up to 2/3 of institutionalized patients have stereotypical behaviors including head moving, rocking, jerking

Cognitive Impairment/ Developmental Delay

- Higher rates of morbidity and mortality
  - including Vitamin D deficiency with limited mobility, AEDS and higher risk of fractures
- Remember to consider epilepsy surgery and ketogenic diet
- For many goals are minimizing side effects
- Trying to reduce epileptiform discharges – sometimes increased discharges correlates with worse cognitive/developmental function

Board Review questions

Board Review questions

1. A 2 hour old baby with difficulty birth has been evaluated for HIE and is being set up for hypothermia protocol. The baby has a 10 minute seizure of right arm shaking. EEG is not available yet. What is the best course of action?

A. Give phenobarbital 20mg/kg bolus one time
B. Start phenobarbital 5mg/kg/day divided twice a day as a maintenance medication
C. Give levetiracetam 20mg/kg bolus
D. Start levetiracetam 20mg/kg/day divided twice a day as maintenance medication
E. Give pyridoxine 100mg IV bolus

Board Review questions

1. A 2 hour old baby with difficulty birth has been evaluated for HIE and is being set up for hypothermia protocol. The baby has a 10 minute seizure of right arm shaking. EEG is not available yet. What is the best course of action?

Correct answer:
A. Give phenobarbital 20mg/kg bolus one time

Of the choices available, phenobarbital has the best evidence for stopping an acute seizure in neonates. It is likely an acute symptomatic seizure in this baby with HIE and a single dose of medication may be adequate. It has been shown that short courses of medication has overall best effect and low risk of recurrent seizures. Additionally this baby will be monitored clinically and on EEG for any recurrence of seizures.

Board Review questions

2. A 7 day old baby with moderate hypoxic ischemic encephalopathy, is on phenobarbital twice a day for a few seizures that started on day of life 1 and last seizure was on day of life 2, after which seizures stopped. MRI shows no clear abnormalities. Baby is on room air and feeding well. What should you do with the phenobarbital?

A. Stop phenobarbital with no follow up needed
B. Stop phenobarbital and repeat EEG in a week
C. Wean phenobarbital over 2 weeks
D. Continue phenobarbital for 6 months
E. Transition to levetiracetam

Board Review questions

2. A 7 day old baby with moderate hypoxic ischemic encephalopathy, is on phenobarbital for seizures that started on day of life 1, after which seizures stopped. MRI shows no clear abnormalities. Baby is on room air and feeding well. What should you do with the phenobarbital?

B. Stop phenobarbital and repeat EEG in a week

If baby has otherwise good prognostic factors (normal MRI, progressing with clinically exam), it is reasonable to stop the phenobarbital without weaning and then recheck an EEG for any recurrence of epileptiform activity.

Board Review questions

3. A 10 day old baby with normal APGARs and normal Mri continues with brief daily seizures and poor feeding and low tone despite phenobarbital and levetiracetam. What is next best medication to try?

A. Fosphenytoin
B. Valproic Acid
C. Topiramate
D. Pyridoxine
E. Midazolam drip

Board Review questions

- 3. A 10 day old baby with normal APGARs and normal MRI continues with brief daily seizures and poor feeding and low tone despite phenobarbital and levetiracetam. What is next best medication to try?

  Correct answer:
  D. Pyridoxine

  There should be concern for underlying metabolic or genetic disorder in this child with an uneventful birth and MRI and continued seizures. It is appropriate to try a pyridoxine trial after two anti-seizure medications. If it is not helpful, further traditional anti-seizure medications could be tried. A midazolam drip would not be needed for a few brief seizures at this time.

Board Review questions

4. An 8 year old with autism and staring spells has a routine EEG that captured awake and sleep and shows rare bilateral posterior sharp waves and mild slowing. The parent pushed an event button for staring during the EEG which showed awake patterns. What is the best course of action?

1. Start Depakote
2. Get a prolonged 24 hour EEG
3. Start levetiracetam
4. Observation
5. Start methylphenidate

Board Review questions

4. An 8 year old with autism and staring spells has a routine EEG that captured awake and sleep and shows rare bilateral posterior sharp waves and mild slowing. The parent pushed an event button for staring during the EEG which showed awake patterns. What is the best course of action?

Answer: Observation

Anywhere from 4-86% of children with autism have EEG abnormalities, but approximately 15-30% of children have epilepsy. If the event of concern was captured it is reasonable to just observe the patient. It is reasonable to obtain a prolonged eeg, however if it is abnormal with no seizures it may not provide additional information. If events are proven to be seizures Depakote is reasonable due to mood stabilizing effects and treatment of multiple type of seizures including absence seizures. Levetiracetam may be used with caution with seizures but it has a high rate of irritability and worsened mood. Evaluation for ADHD is appropriate, but would not start methylphenidate until then.

Board Review questions

5. A 8 year old with spastic quadriparesis and is nonverbal has 5 minutes of myoclonic seizures upon awakening despite levetiracetam, valproic acid and topiramate. Currently, they no longer have any tonic or generalized tonic clonic seizures. The patient has Embrace watch to monitor nocturnal seizures. The last EEG showed infrequent multifocal epileptiform discharges in awake and sleep.

Parents note giving clonazepam 1mg as a trial did reduce seizures to 1 minute but the patient was drowsy the rest of the day and could not go to school and participate in therapies. What is the next best treatment plan?

1. Start clobazam
2. Start epidiolex
3. Start phenobarbital
4. Increase levetiracetam to three times a day dosing
5. Observation

Board Review questions

5. . A 8 year old with spastic quadriparesis and is nonverbal has 5 minutes of myoclonic seizures upon awakening despite levetiracetam, valproic acid and topiramate. Currently, they no longer have any tonic or generalized tonic clonic seizures. The patient has Embrace watch to monitor nocturnal seizures. The last EEG showed infrequent multifocal epileptiform discharges in awake and sleep.

Parents note giving clonazepam 1mg as a trial did reduce seizures to 1 minute but the patient was drowsy the rest of the day and could not go to school and participate in therapies.

What is the next best treatment plan?

- Correct answer:

5. Observation

This patient has intractable /medically refractory epilepsy. If the seizures are not interfering with daily activities watchful observation may be most appropriate. Their other seizures are well-controlled and family is educated on SUDEP. Additional medicine may not be helpful and may cause more side effects, particularly sedation. Optimizing seizure control while also balancing side effects for quality of life may be a goal for medically refractory epilepsy in those with developmental delay/cognitive impairment. Although not an option, ketogenic diet evaluation and epilepsy surgery evaluation are also appropriate choices.

Board Review questions

6. A 3 month old baby who has thus far been normally developing has their 3rd unprovoked focal seizure. MRI is normal. Genetic epilepsy panel and metabolic testing results are pending. What medication is safest to start at this time?

1. Clobazam
2. Lacosamide
3. Levetiracetam
4. Phenobarbital
5. Valproic acid

Board Review questions

6. A 3 month old baby who has thus far been normally developing has their 3rd unprovoked focal seizure. MRI is normal. Genetic epilepsy panel results are pending. What medication is safest to start at this time?

Correct answer:

2. Levetiracetam

Animal models have show apoptosis with all antiseizure medications except: topiramate, levetiracetam and lamotrigine

References

1. Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci. 2003 May;993:103-14; discussion 123-4. doi: 10.1111/j.1749-6632.2003.tb07517.x. PMID: 12853301.

2. Fitzgerald MP, Kessler SK, Abend NS. Early discontinuation of antiseizure medications in neonates with hypoxic-ischemic-encephalopathy. Epilepsia. 2017 Jun; 58(6): 1047-1053. doi: 10.1111/epi.13745

3. Forsgren L, Edvinsson SO, Blomquist HK, Heijbel J, Sidenvall R. Epilepsy in a population of mentally retarded children and adults. Epilepsy Res. 1990 Aug;6(3):234-48. doi: 10.1016/0920-1211(90)90079-b. PMID: 2148725.

4. Garfinkle J, Shevell MI. Cerebral palsy, developmental delay, and epilepsy after neonatal seizures. Pediatr Neurol. 2011 Feb;44(2):88-96. doi: 10.1016/j.pediatrneurol.2010.09.001.

5. Mariani E, Ferini-Strambi L, Sala M, Erminio C, Smirne S. Epilepsy in institutionalized patients with encephalopathy: clinical aspects and nosological considerations. Am J Ment Retard. 1993;98 Suppl:27-33. PMID: 8352919.

6. McPherson C, O'mara K. Provision of sedation and treatment of seizures during neonatal therapeutic hypothermia. Neonatal Network. 2020 Jul;39(4): 227-235 . DOI: 10.1891/0730-0832.39.4.227

7. Precenzano F, Parisi L, Lanzara V, Vetri L, Operto FF, Pastorino GMG, Ruberto M, Messina G, Risoleo MC, Santoro C, Bitetti I, Marotta R. Electroencephalographic Abnormalities in Autism Spectrum Disorder: Characteristics and Therapeutic Implications. Medicina (Kaunas). 2020 Aug 19;56(9):419. doi: 10.3390/medicina56090419. PMID: 32825169; PMCID: PMC7559692.

8. Price KE, Pearce RE, Garg UC, Heese BA, Smith LD, Sullivan JE, Kennedy MJ, Bale JF Jr, Ward RM, Chang TK, Abbott FS, Leeder JS. Effects of valproic acid on organic acid metabolism in children: a metabolic profiling study. Clin Pharmacol Ther. 2011 Jun;89(6):867-74. doi: 10.1038/clpt.2011.47. Epub 2011 May 4. PMID: 21544075; PMCID: PMC3822904.

9.

References, Cont

8. Shubrata KS, Sinha S, Seshadri SP, Girimaji S, Subbakrishna DK, Srinath S. Childhood autism spectrum disorders with and without epilepsy: clinical implications. J Child Neurol. 2015 Mar;30(4):476-82. doi: 10.1177/0883073814540521. Epub 2014 Jul 17. PMID: 25038126.

9. Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonemic encephalopathy. Metab Brain Dis. 2002 Dec;17(4):367-73. doi: 10.1023/a:1021918104127. PMID: 12602513.

10. Zhou KQ, Davidson JO, et al. Treating seizures after hypoxic-ischemic encephalopathy- current controversies and future directions. International J of Molecular Sciences. 2021, 22, 7121 https://doi.org/10.3390/ijms22137121

THANK YOU