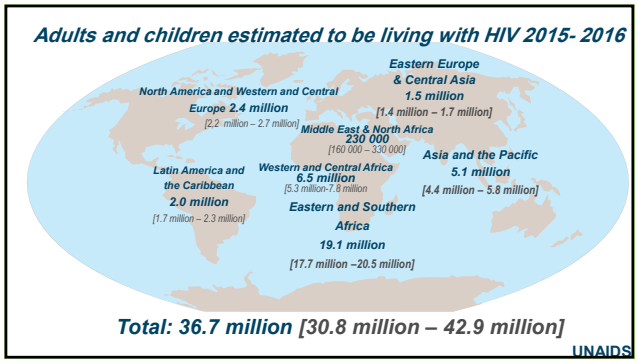
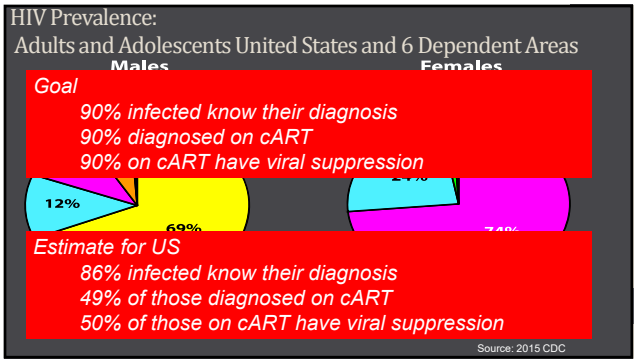
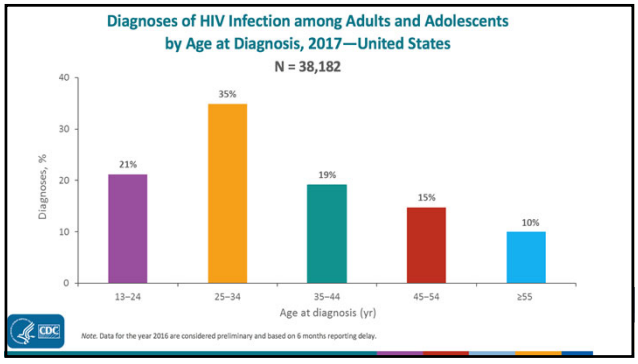
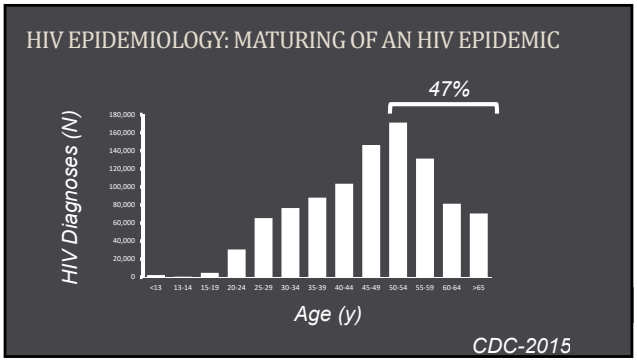
28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD







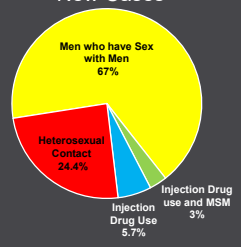


28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

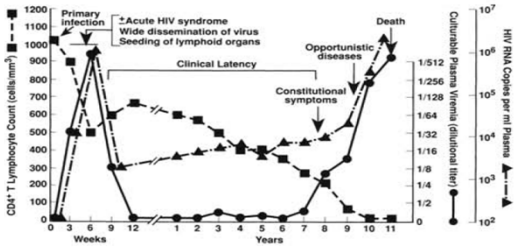
Trends in US HIV Epidemic (CDC)

- Race/ethnicity
  - African Americans exceed white/not hispanic as most common patients with AIDS
- Geography
  - ~12% of cases in locations with population <50,000
  - Outbreaks in rural US
- Gender
  - Females comprise > 25% of all AIDS cases
- Age
  - Nearly 50 of persons living with HIV is ≥ 50 yo
  - MSM most common risk



CDC 2016

HIV INFECTION COURSE

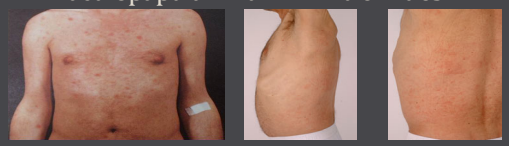


Acute HIV Syndrome

Sign/symptom	Percent Reporting NEJM Review	Kenyan sex workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-2
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	21	nd	nd
Too ill to work	nd	44	58

Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities



Enanthem

Aphthous ulcer

HIV Diagnosis: Question #1

A 23 year old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, adenopathy.

HIV-1/2 ELISA is reactive, viral RNA level 500,000 c/ml.

He is started immediately on antiretrovirals.

His confirmatory assay is negative, and repeat assays sent 3 weeks, 3 months, and one year after starting antiretrovirals are also negative.

ELISA remains reactive. HIV-2 assay is negative.

Viral RNA on therapy is <40 c/ml.

HIV Diagnosis: Question #1 continued

Which of the following is correct:

A. The patient was infected with a strain of HIV-1 that was not detected by the confirmatory assay
B. The patient is HIV-infected but did not develop a positive confirmatory assay because of the early antiretroviral therapy intervention
C. The patient never had HIV infection.
D. The patient had HIV but is now cured of HIV and antiretrovirals can safely be stopped

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Early Antiretroviral Therapy

- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may become unreliable
- HIV-1 DNA PCR has been useful in documenting infection

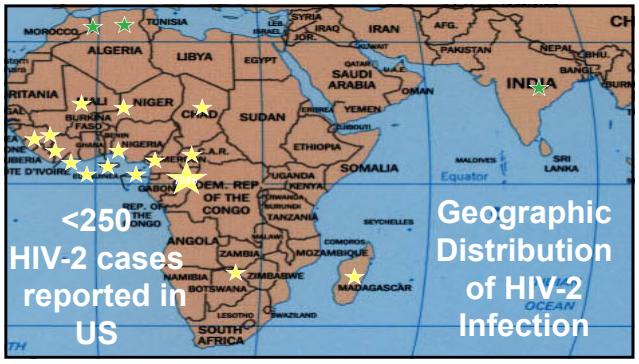
HIV Clinical Presentation: Question #2

A 49 year old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV multispot positive for HIV-2 and negative for HIV-1.

CD4 cell count is 350 cells/µl.

Which of the following is correct?

A. HIV-2 is less pathogenic than HIV-1 so she only needs therapy with one antiretroviral drug
B. She should not be treated with protease inhibitors because HIV-2 is naturally resistant to PIs.
C. She should not be treated with NNRTI therapy because HIV-2 is naturally resistant to NNRTIs.
D. Use of routine HIV-1 viral load assays is useful in patient management



HIV-1 and HIV-2 Contrasting Retroviral Infections

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West Africa +	Worldwide
Local Distribution	Urban=rural	Urban>rural
Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less common (10X)	More common
Therapy	NRTI, PI, INSTI, Corec	NRTI, PI, NNRTI
	NOT NNRTI NOT Fusion	INSTI, Corec, Fusion
Diagnosis		
Screening	HIV1/2 ELISA	HIV1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental Qual. HIV RNA)
Monitoring	HIV-2 RNA Assay	HIV-1 RNA assay

Question #3

A 42 year old man from the Haiti presents with fever, moderate respiratory distress, and nonproductive cough. HIV-1/2 ELISA is reactive and discriminatory test is positive for HIV-1. A PCR test of the induced sputum is positive for *Pneumocystis jiroveci.* On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and th hematology technician remarks that some of the lymphocytes are "flower cells". Which of the following is most correct in explaining the hematology findings:

A. The patient has B cell lymphoma
B. The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia
C. The patient has HTLV-1 infection only the HIV test is a false positive
D. The patient has both HIV infection and HTLV-1 infection

Question #4

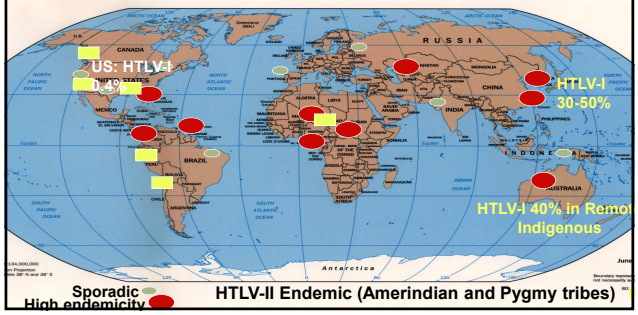
A 25 year old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot. Which of the following statements is true:

A. The risk of HTLV-I transmission can be entirely eliminated by caesarean section.
B. The risk of HTLV-I transmission will be entirely eliminated by not breastfeeding.
C. Breastfeeding will provide sufficient immunity to prevent infection with HTLV-I.
D. The risk of HTLV-I transmission will be significantly decreased but not entirely eliminated by avoiding breastfeeding.
E. There is no risk of HTLV-I disease. In this ethnic group, the HTLV-I test was likely a false positive.

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HTLV DISTRIBUTION



HTLV-I Transmission

- Breastfeeding
  - Prolonged duration: 20-30% seroconvert if breastfed >12 mos
  - High maternal HTLV proviral load in breastmilk: 28.7 infections/1000 person months with 1.5% HTLV+ lymphs
- Sexual
- Transfusion
  - Risk of seroconversion: 40-60%
- Testing Sequential ELISA/Western blot

Question #5

37 year old Jamaican female with diffuse pruritic rash (right), bone pain with lytic bone lesions.

WBC: 50,000, 90% lymphocytes

Which is most likely cause of her presentation?

A. HTLV-I
B. HTLV-II
C. HIV-1
D. HTLV-IV

HTLV-I Acute T cell Leukemia (ATL)

- Long Latency (>30 years)
  - Small pediatric series in SA
- Epidemiology
  - Approximately 1% of HTLV- I infected adults
  - M>F (Japan); M=F (Jamaica)
- Associated syndromes
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - Recurrent Strongyloides
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- Therapy
  - Cytotoxic chemotherapy
  - AZT+Ifn
  - Transplant
  - Mogamulizumab (Poteligeo, anti CCR4 monoclonal) APPROVED in Japan for ATL
  - Lenalidamide

Question #6

38 year old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence. Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex

WBC = 7500 cells/ul

CD4 T cell = 1000 cells/ul

CSF cell count: 10 cells/mm^3 (lymphocytes)

CSF protein: 75 mg/dl

Question #6 Continued

The etiologic agent associated with this illness is also associated with

A. Acute T cell leukemia
B. Multiple sclerosis
C. Variant Creutzfeldt-Jacob
D. Hemorrhagic cystitis

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HTLV-I Tropical Spastic Paraparesis /HTLV-1 Associated Myelopathy

- Epidemiology
  - <1% of HTLV-I develop HAM/TSP
  - The second most common neurologic syndrome in Jamaica after stroke
  - Latency may be short--several years
  - Female predominance

HTLV-I TSP/HAM

- Presentation
  - Spastic paraparesis
    - Lower>upper
    - Proximal>distal
  - Bladder disturbance
  - Hyperreflexia
  - Positive Babinski reflex
- Differential Diagnosis
  - Cord compression
  - B12 deficiency
  - Syphilis
  - HIV-1 myelopathy
  - Multiple sclerosis

Therapy of HTLV-I TSP/HAM

- No randomized trials
- Corticosteroids
  - May slow progression and reduce disability
- Antiretroviral therapy is NOT effective

Question #7

You are asked to see a 62 year old male smoker, former IV drug user for evaluation of recurrent cough and weight loss. Evaluation reveals metastatic non-small cell lung cancer. Serologic testing notes he is HIV negative, HTLV-1 negative, but HTLV-2 positive . The oncology team calls regarding your advice about HTLV-2 and treating the patient with the checkpoint inhibitor durvalumab (blocking PDL-1 interactions with PD-1) in addition to chemotherapy. Which of the following is most correct:

A. **He should not be treated with durvalumab**
B. **He can be treated with durvalumab, but will also require therapy for HTLV-2 infection**
C. **He can be treated with durvalumab, but is at increased risk for other infectious complications, like *Pneumocystis jiroveci* compared with HTLV-2 uninfected individuals.**
D. **He can be treated with durvalumab and does not require additional therapy for HTLV-2 infection**

Summary

HTLV-1 Infection

- **Asymptomatic -95%**
- **Acute T cell Leukemia**
- **HAM/TSP**
- **But also**
  - **Bronchiectasis**
  - **Uveitis**
  - **Rheumatologic syndromes**
  - **Lymphocytic pneumonitis**
  - **Infective Dermatitis (pediatric)**
- **"Flower" cells**
  - **Lymphocytes with HTLV provirus present**
  - **Frequency in HIGHER in ATL and HAM/TSP**
  - **NOT an indication for specific therapy**

Associated Infections

- **Strongyloides hyperinfection**
- **Norwegian Scabies**
- **Pneumocystis**
- **MAC**

HTLV-2 is a distractor

SLOW VIRUSES

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

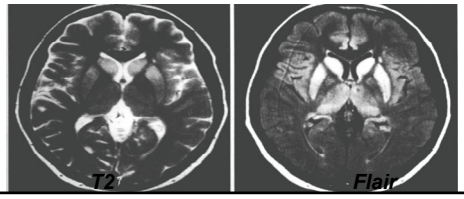
Speaker: Frank Maldarelli, MD

Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
D. A spontaneous event

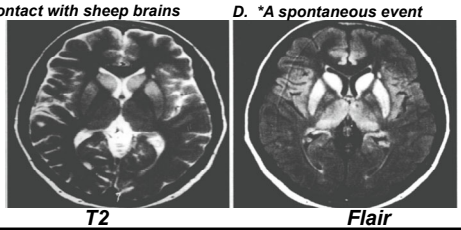


Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
D. *A spontaneous event

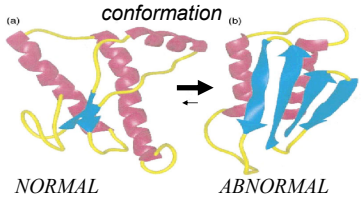


Prion Diseases: Transmissible Spongiform Encephalopathies

- **Spontaneous (N=~6000 worldwide per year)**
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
- **Associated with specific ingestion**
  - Beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "vCJD" (N ~ 220 total cases)
  - Human brains
    - Kuru (N= ~2700 total cases)
- **Associated with a medical procedure (N ~ 450 total cases)**
  - Iatrogenic
  - Denoted "iCJD"
- **Hereditary (N ~600-900 worldwide per year)**
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)

Prion Disease Pathogenesis A. Initiation

The prion protein is a host protein with a normal and abnormal conformation



NORMAL *ABNORMAL*

Transition to abnormal conformation is rare but essentially irreversible

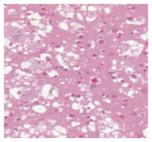
Naturally occurring mutations favor interconversion

Prion Disease Pathogenesis B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation

Direct contact

Prion Protein Mutant conformation



Prion Protein Mutant conformation

Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- Most common human Transmissible Spongiform Encephalopathy (TSE)
  - 95% cases
- Incidence estimated 1 per million
  - US: 0.1/million in <55 yo, 5.3/million >55 yo
  - Mean age of onset is 60 years

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Dementia Comparison

Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2 y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4 y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α- Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate,Pons Thalamus Ovoid Nuc

Prion Disease Question #2

A 68 year old man with dementia progressing over the last 6 months undergoes evaluation. Which of the following CSF results is most consistent with Creutzfeld Jakob Disease: .

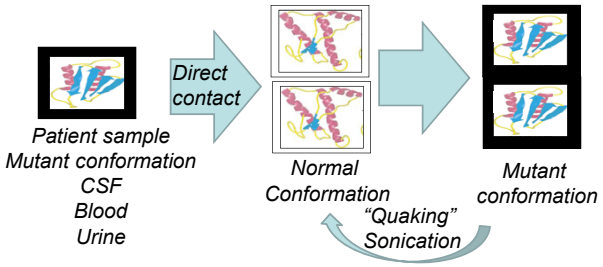
A. 14-3-3 protein: Positive
B. RT-QuIC: Positive
C. T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
D. Abeta42: 1250 (normal >1026 pg/mL

Spontaneous Creutzfeldt-Jacob Disease

Typical Clinical Presentation

- Rapid progression
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for CJD

Abnormal Prion Detection RT-QuIC



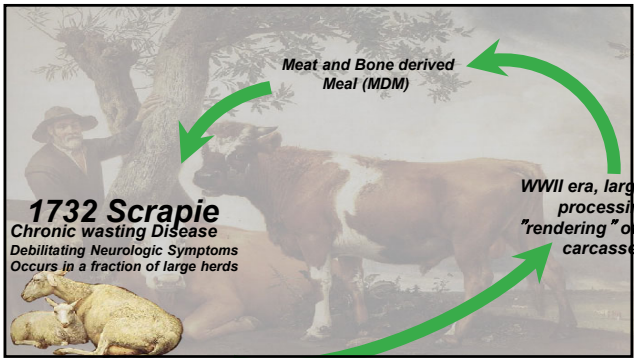
Sensitivity 92% Specificity >99%

Prion Disease Question #2

A 30 year old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1990 – 2010, then moved to Philadelphia.

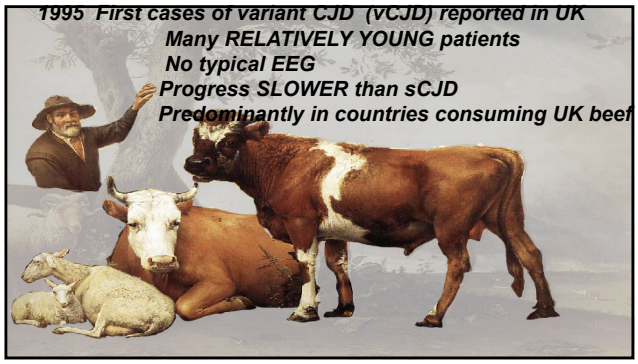
Which of the following diseases is most likely the cause of his symptoms:

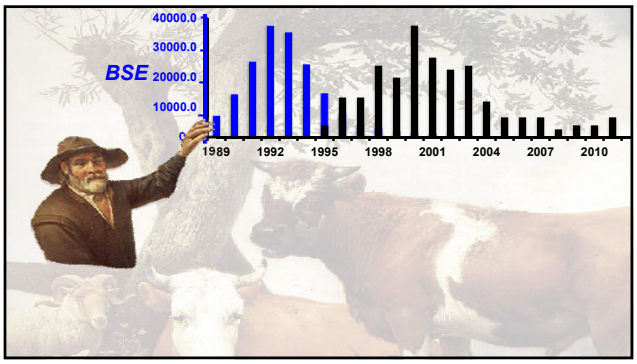
A. Kuru
B. variant Creutzfeldt-Jacob Disease
C. Familial Creutzfeldt-Jacob Disease
D. Rabies



28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD





Question #4 vCJD Geographic Distribution

Residence in which of the following countries after 1980 represents the highest risk for acquiring variant CJD (vCJD):

A. *France*
B. *Borneo*
C. *United States*
D. *Australia*
E. *Argentina*

Numbers of vCJD Cases Worldwide

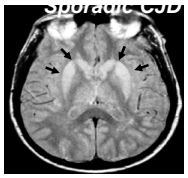
- United Kingdom: 178
- France: 28
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

(Nat'l CJD Res. Surv. Unit, U. Edinburgh, www.cjd.ed.ac.uk 2019)

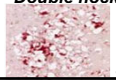
vCJD vs. sCJD

	sCJD	vCJD
Source	Spontaneous event	Ingested beef
Distribution	Worldwide	Linked to Beef originating largely in UK
Median Age (y)	68	28
Progression	SHORTER	LONGER
EEG	Typically abnormal	NOT Typically abnormal
MRI Basal ganglia	"Double Hockey Stick"	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	"Florid Plaques"

sCJD

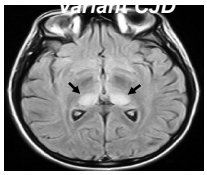


T2 axial proton weighted Putamen and caudate head "Double hockey stick sign"

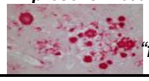


"Abnormal Prion accumulation"

vCJD



T2 axial proton weighted "Pulvinar Sign" present >75% cases



"florid plaques"

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Prion Diseases Question #5

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia.

He underwent a meningioma resection with dura mater graft in Japan 35 years ago.

He is an avid deer hunter and consumes venison.

What is the most likely cause of his dementia:

A. **Iatrogenic CJD from the dura mater graft**
B. **Iatrogenic CJD from eating deer.**
C. **HTLV-I**
D. **Spontaneous CJD**

Iatrogenic CJD ~450 cases

Definite Causes

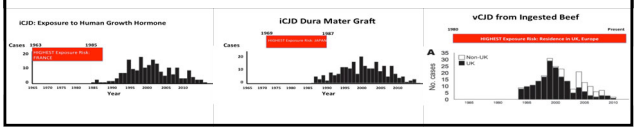
- **Pituitary extracts**
  - **Human Growth Hormone**
  - **Gonadotrophin**
  - **Delay may be >30 y**
  - **(Role in AD as well?)**
- **Dura mater grafts**
  - **Mostly Lyodura brand**
- **Transplants**
  - **Corneal**
  - **Pericardium**
  - **Liver**
- **Instrumentation**
  - **Implantable Neurosurgical-EEG, stereotactic**

No Link

- **Vaccines**
- **Feces**
- **Saliva**
- **Sputum**
- **Bovine insulin**
- **Semen, vaginal secretions**

Transmissible Spongiform Encephalopathy:Time and Place

Mode of transmission	Geographic Region	Risk Window
Beef ingestion	UK, France, Europe	1980-present
Human growth hormone	France	1963-1985
Dura mater graft	Japan	1969-1987



Zoonotic Transmission CJD

Documented Risk

- Ingestion of Beef
  - Geographically limited
  - Emphasis on UK, France

No Documented Risk

- Mink:
  - Transmissible Mink Encephalopathy
- Elk, Mule deer:
  - Chronic Wasting Disease
- Sheep, goats
  - Scrapie
- Cat:
  - Feline Spongiform Encephalopathy

CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferred from blood donation
  - Dura mater graft or human growth hormone
  - Donors with CJD or family history of CJD
  - Residence in Europe after 1980
  - Transfusion in Europe after 1980
  - Bovine insulin after 1980 unless certain that insulin was not from UK

Transmissible Spongiform Encephalopathy

Infection Control Issues

- **Universal precautions**
- **No confirmed occupational transmissions**
  - CJD in health care workers occurs, occupational links have been suggested
- **Incinerate single use instruments**
- **Inactivate other instruments and materials**
  - 1N NaOH
  - autoclave 121° C, 15 psi 30 min
  - Formic acid for tissue sections
  - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
  - REMEMBER: Infectivity is STABLIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
  - **http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf?ua=1**

28 - Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

Transmissible Spongiform Encephalopathy

Therapy

- **None**
  - **uniformly fatal**

Kuru "shivering,trembling"

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
  - Ambulant, leaning (pictured)
  - Sedentary
  - Terminal "laughing death"
  - "Florid plaques" (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991

Resources

- **RT-QuIC: Case Western**
  - https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information
- **Epidemiology**
  - https://www.cdc.gov/prions/cjd/resources.html
- **Patient support**
  - https://cjdfoundation.org/other-resources
- Fmalli@mail.nih.gov