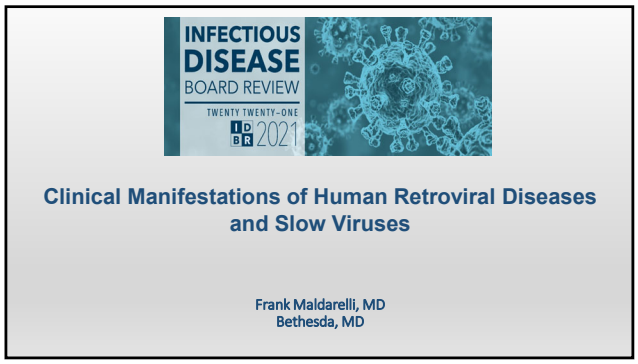
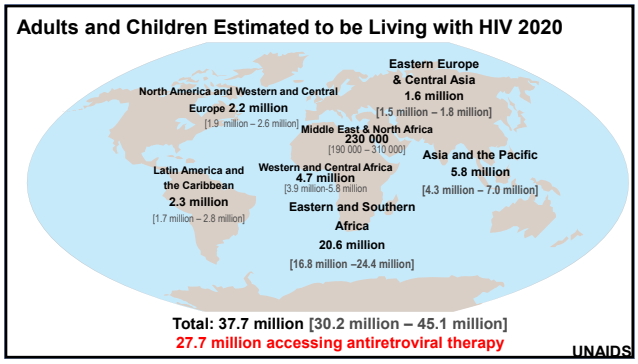
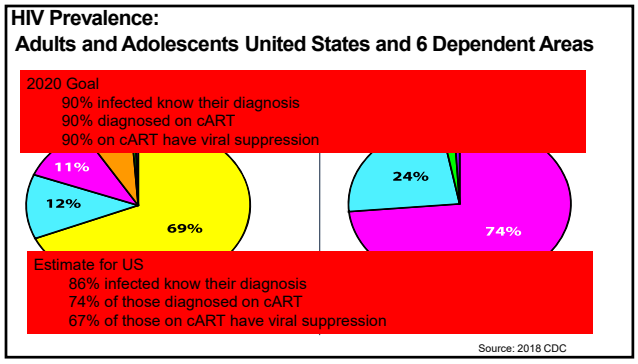
# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

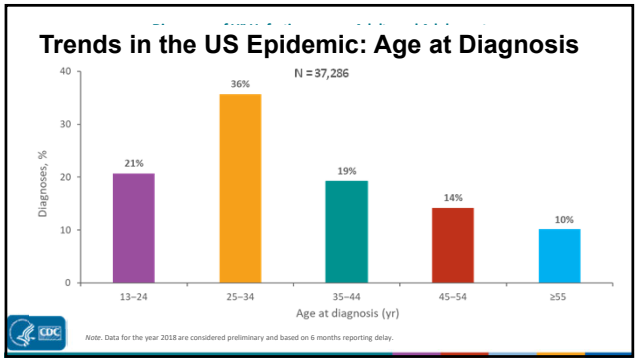
*Speaker: Frank Maldarelli, MD*

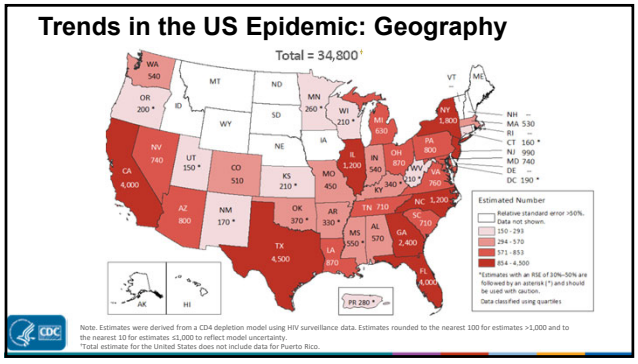






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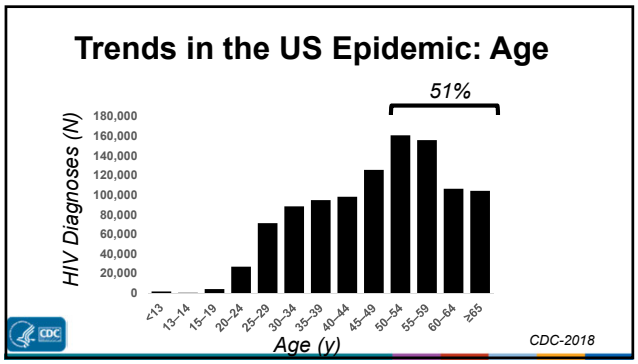
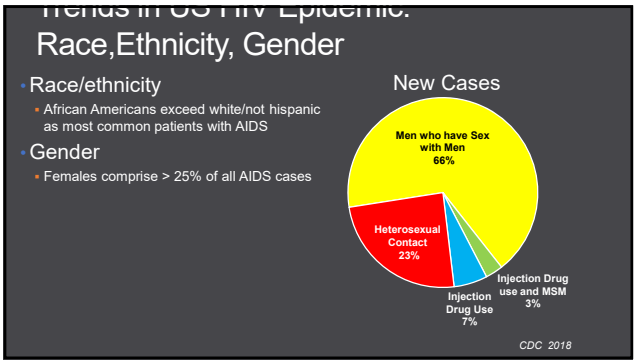
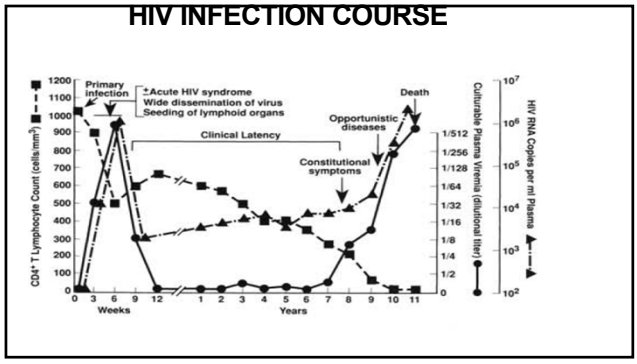


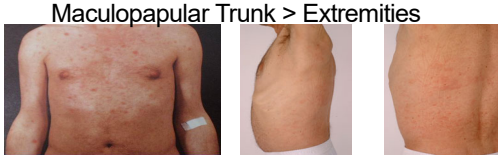



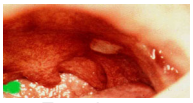

## Acute HIV Syndrome

| 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 | 12-27 |
| 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 | 2 | nd | nd |
| Too ill to work | nd | 44 | 58 |

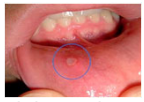
## Primary HIV-1 Infection Syndrome

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 supplemental 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.**

# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## HIV Diagnosis: Question #1 continued

**Which of the following is correct explanation for the absence of positive results with the supplementary HIV test:**

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 results with the supplementary 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**

## Early Antiretroviral Therapy

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

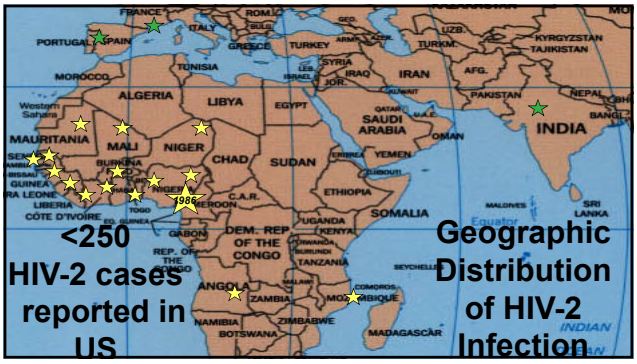
## HIV Clinical Presentation: Question #2

A 49 year old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius 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

| Characteristic | HIV-2 | HIV-1 |
|---|---|---|
| **Epidemiology** | | |
| Geography | West /Central 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 **NOT** NNRTI **NOT** Fusion | NRTI, PI, NNRTI 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 the 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 HIV and 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

# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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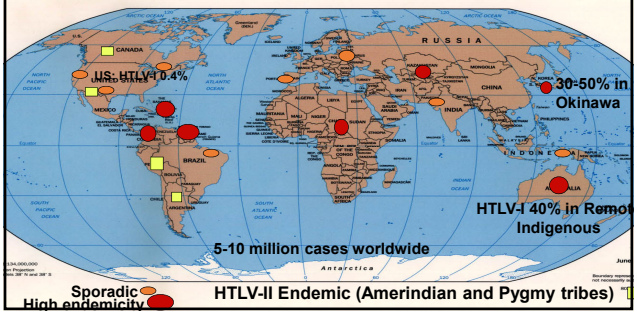
## Question #4

**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.

## HTLV DISTRIBUTION

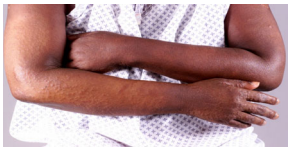



## HTLV-I Transmission

- 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 South America
- 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

# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

*Speaker: Frank Maldarelli, MD*

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

## 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

- Corticosteroids
  - May slow progression and reduce disability
- Mogamulizumab
- 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**

## Pearls

### 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**

**Thanks to Tamara Nawar, Ying Taur, Anna Kaltsas (SKMC, NYC)**

# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

*Speaker: Frank Maldarelli, MD*

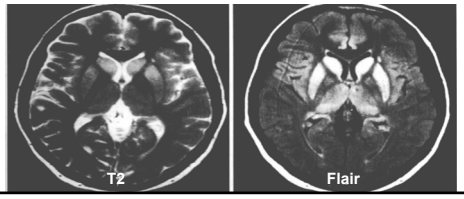
## SLOW VIRUSES

## 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**

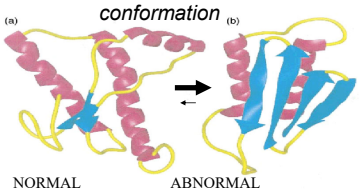



## Prion Diseases: Transmissible Spongiform Encephalopathies

- **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*




Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

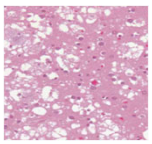
## *Prion Disease Pathogenesis*
## *B. Propagation*

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

# 43 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## Dementia Comparison

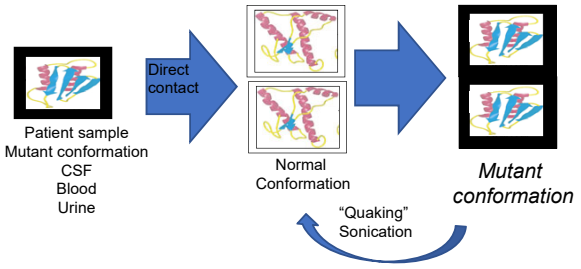
| Type | Protein | Clinical | Course | Path | MRI |
|---|---|---|---|---|---|
| sCJD | Prion | Myoclonus | <2 y | Spongif. Degen. | Caudate Striatum Thalamus |
| Alzheimer | Apo E4, Tau | Memory Language | >4 y | Neurofib. tangles | Hippocampus White matter |
| Lewy Body | α- Synuclein | Parkinsonian 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)

## *Abnormal Prion Detection RT-QuIC*




Sensitivity 92% Specificity >99%

## *Spontaneous Creutzfeldt-Jacob Disease*

### Typical Clinical Presentation

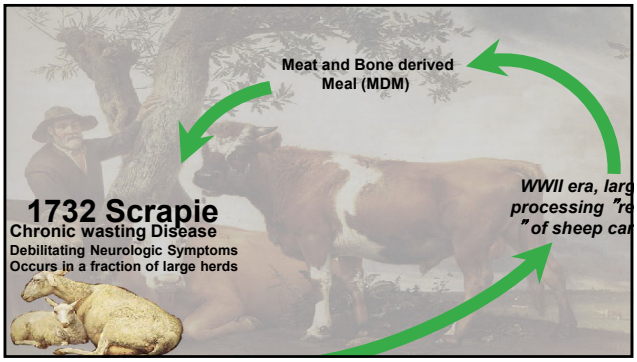
- Rapid progression
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for CJD

## 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



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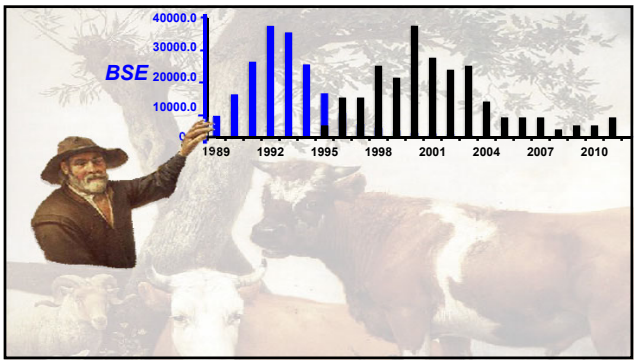



## Question #4 vCJD Geographic Distribution

**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*

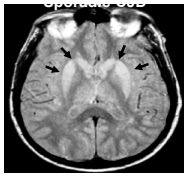
- United Kingdom: 178
- France: 28
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

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

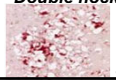
## vCJD vs. sCJD

| | 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" |

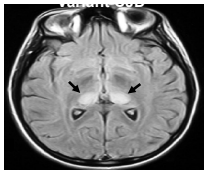
***sCJD*** ***vCJD***



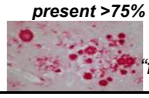
***T2 axial proton weighted Putamen and caudate head "Double hockey stick sign"***



*"Abnormal Prion accumulation"*



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



*"florid plaques"*

# 43 – 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

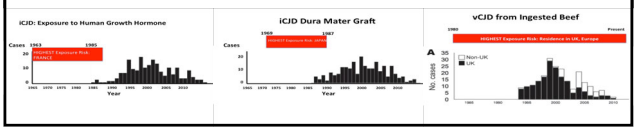
- **Pituitary extracts**
  - **Human Growth Hormone**
  - **Gonadotrophin**
  - **Delay may be >30 y**
  - **(Role in AD as well?)**
- **Dura mater grafts**
  - **Mostly Lyodura brand**
- **Transplants**
  - **Corneal**
  - **Pericardium**
  - **Liver**
- **Instrumentation**
  - **Implantable Neurosurgical-EEG,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

# 43 – 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

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