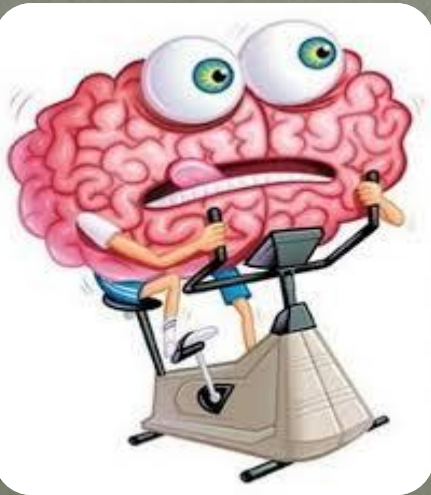


# The Brain Eater

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# What is Creutzfeldt-Jakob disease?

- Creutzfeldt-Jakob disease is a degenerative brain disorder that leads to dementia and, ultimately, death.
- Symptoms of Creutzfeldt-Jakob disease (CJD) sometimes resemble those of other dementia-like brain disorders.
- Creutzfeldt-Jakob is rapidly progressive.



# CJD vs. Control



# History of CJD

- Hans .G Creutzfeldt first described the disorder in 1920.
- In 1921 Alfons M. Jakob described 4 cases with 2 resembling what today is referred to as CJD.



- In 1974, a case iatrogenic CJD was reported via corneal transplantation.



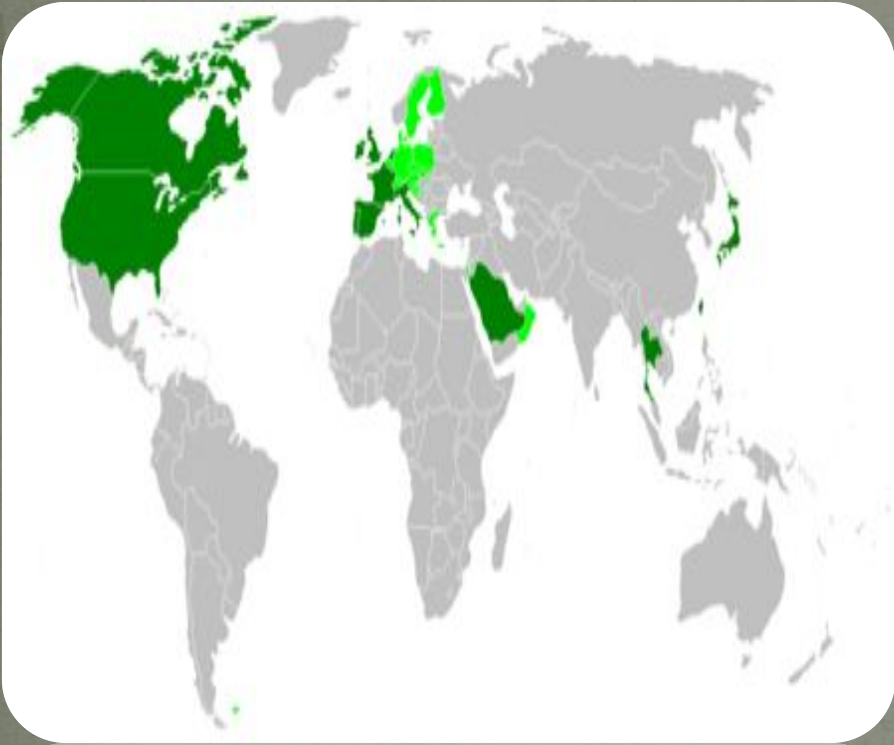
# History of CJD

- In 1985 there were reported cases of spread through contaminated human derived growth hormone.



Foundation, Inc.  
Creutzfeldt-Jakob Disease

# Epidemiology



- Annual incidence rate of Creutzfeldt-Jakob disease (CJD) is approximately equal to one per million
- May be underestimated.
- More common in individuals above 60 years.
- vCJD is more prevalent in younger individuals.
- Average life span after onset of symptoms is 4 months.



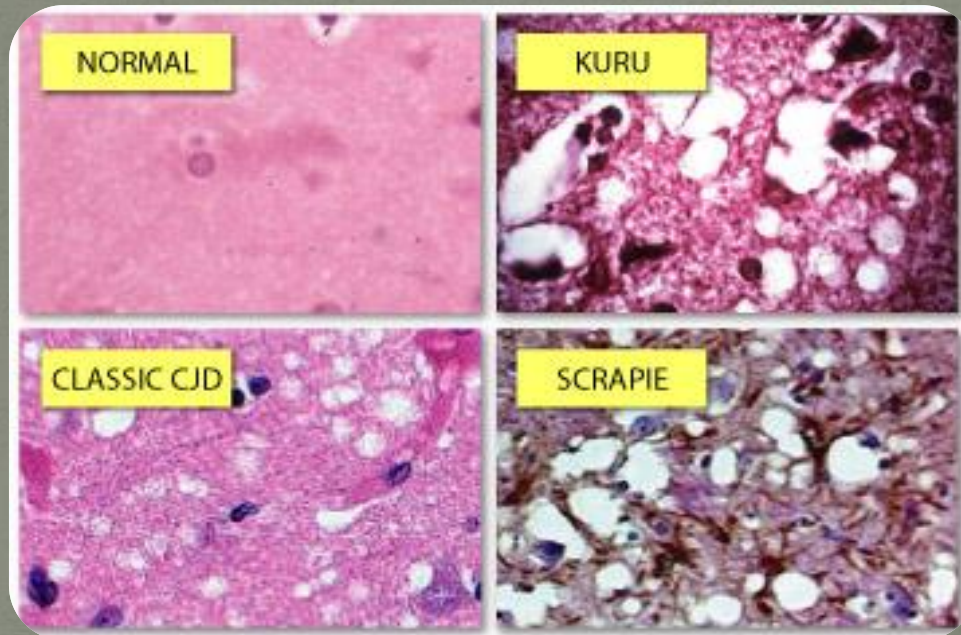
# Classification

## Forms of CJD

Form	Cause	Distinguishing Features
Sporadic/ Classical	Unknown	Affects mainly over 50s. S/S: Ataxia, dementia, spongiform changes, rarely plaques. Short course.
Familial/ Infectious	Inherited mutation in the PrP gene	Younger age of onset than sCJD, symptoms similar to sCJD, longer course.
Iatrogenic	Contamination during brain surgery, corneal transplant, dura mater grafts	Age dependant on the exposure source. Clinical and pathological symptoms indistinguishable from sCJD.
Variant	Exposure to BSE	Younger age of onset, longer duration of symptoms. Psychiatric signs present. Distinctive daisy plaques seen.

# Etiology

- CJD belongs to a broad group of human and animal diseases known as transmissible spongiform encephalopathies (TSEs).





# Etiology

- The causative agent of this disease is an abnormal protein known as a prion.
  - Prions were first discovered in the 1960's by radiation biologist Tikvah Alper and the mathematician John Stanley Griffith.
  - Prions are proteins with an abnormal fold known as an amyloid fold.
  - They have very stable structures in the form of beta pleated sheets.
  - Prions do not multiply in the host organism that they infect.

# Prion theory

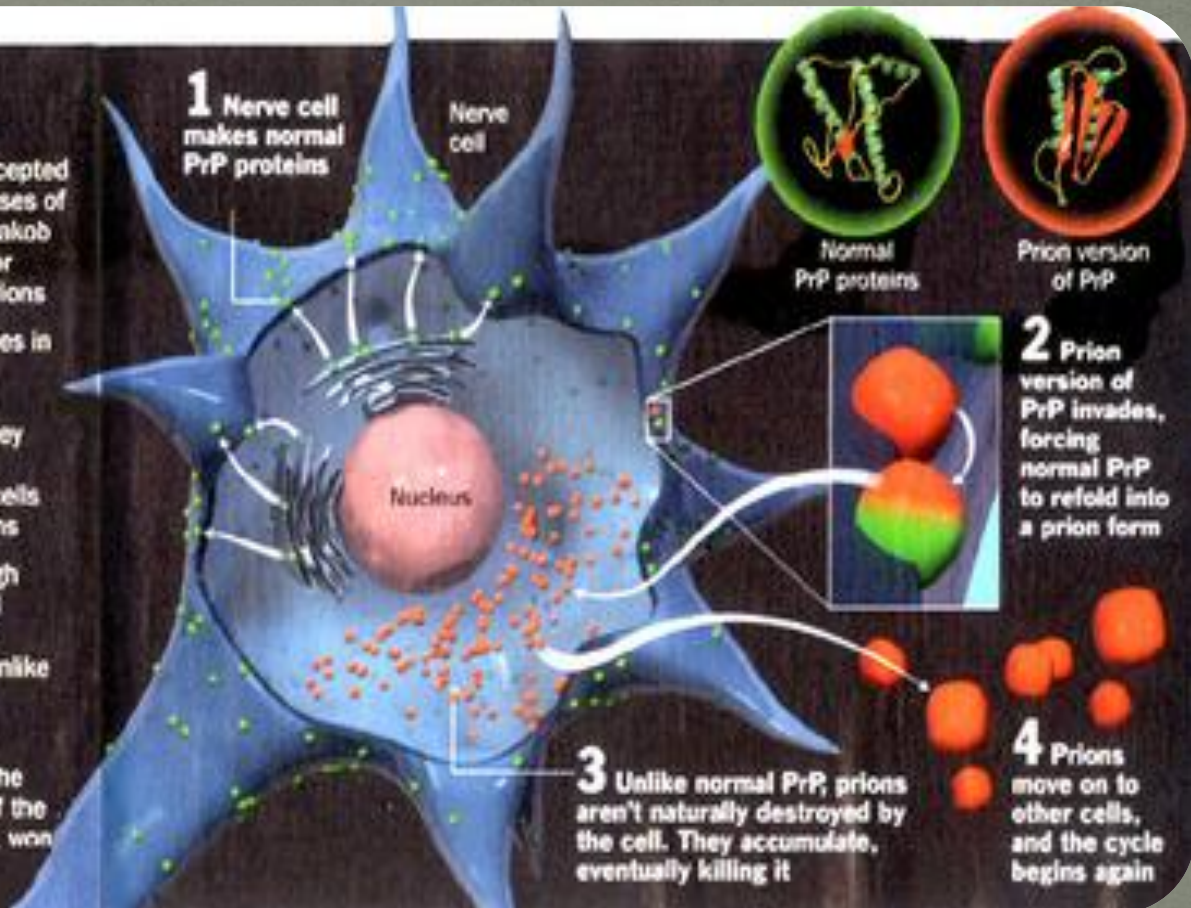
## THE PRION THEORY

It is widely (though not universally) accepted that mad cow and other wasting diseases of the brain—scrapie, kuru, Creutzfeldt-Jakob disease—are caused not by bacteria or viruses but by rogue proteins called prions.

Mad-cow disease starts when molecules in a nervous-system protein called PrP become abnormally folded. When an abnormal PrP touches normal PrPs, they refold to match the abnormal ones, forming new prions. Eventually, brain cells become clogged with abnormal proteins.

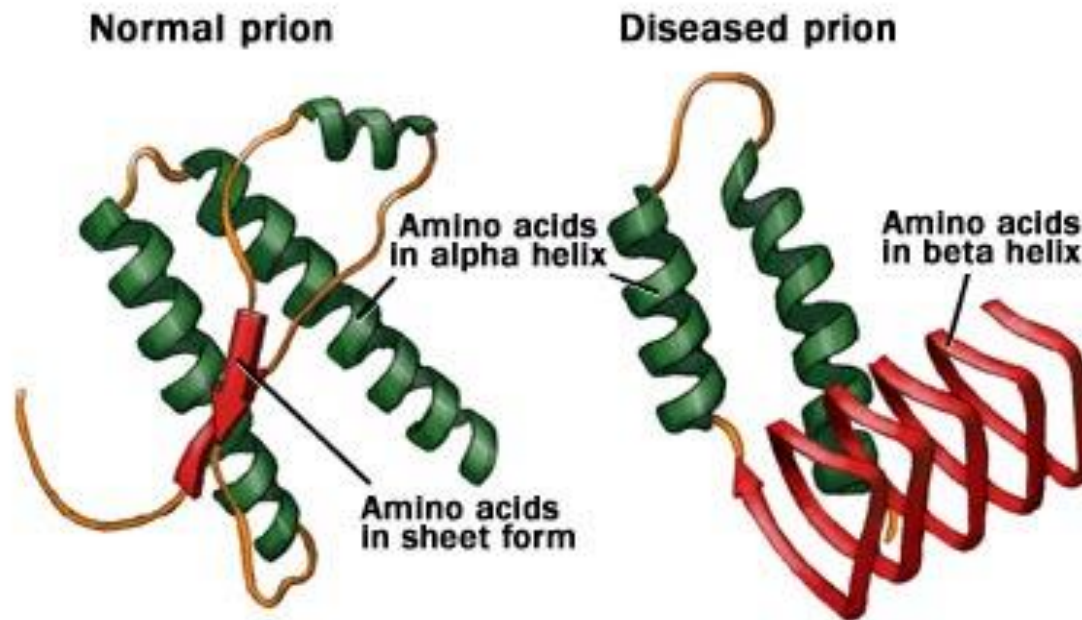
Prions can arise spontaneously, through mutation, but they can also be passed along when an animal or human eats infected nervous-system tissue. And unlike viruses or bacteria, prions can't be destroyed by cooking.

For championing this theory, often in the face of ridicule, Dr. Stanley Prusiner of the University of California, San Francisco, won the 1997 Nobel Prize.





# Prion



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# Transmission

- Sporadic CJD- very rare and occurs due to mutation of an individual's own normal proteins
- Variant CJD- acquired from using contaminated human growth hormone or consuming contaminated meat (bovine or human).
- Familial CJD- inheritance of a mutated gene for PrP.
- Iatrogenic- through contaminated surgical sources.



# Pathogenesis

- A distinctive protein isoform of prion protein, PrP<sup>Sc</sup> is present in CJD CNS tissue.
- The normal variant of this protein is PrP<sup>C</sup>.
- PrP<sup>Sc</sup> deposits in the CNS of CJD patients causing dysfunction, and in the presence of PrP<sup>Sc</sup>, PrP<sup>C</sup> is converted to PrP<sup>Sc</sup>.
- In the case of familial CJD, a mutated form of the prion protein gene appears to lead to prion protein deposition.

# Pathogenesis

- This was tested in several experiments, the presence of a mutated prion protein gene as a transgene in mice was found to induce a spongiform neuropathology.
- This suggests that the mutant PrP<sup>Sc</sup> is sufficient to produce disease.
- The pathogenesis of sporadic Creutzfeldt-Jakob disease remains unclear.
- It has been hypothesized that a spontaneous somatic change in conformation of prion protein in the CNS initiates the disease.



# Pathogenesis

- A number of reports have been published that demonstrate the presence of prion-like elements in yeast.
- Experiments show that these elements lead to aggregation and amyloid formation of a protein.
- These studies suggest that prions as a cause of abnormal phenotypes may be more widespread than realized.

# Pathogenesis

- Recently, misfolded proteins have been hypothesized to underlie a number of neurodegenerative diseases.
- These diseases may not be transmissible in the same way as the sub acute spongiform encephalopathies such as CJD are.
- However, they are assumed to affect the CNS in a prion like mechanism.
- In addition, the pathogenic proteins are also misfolded.

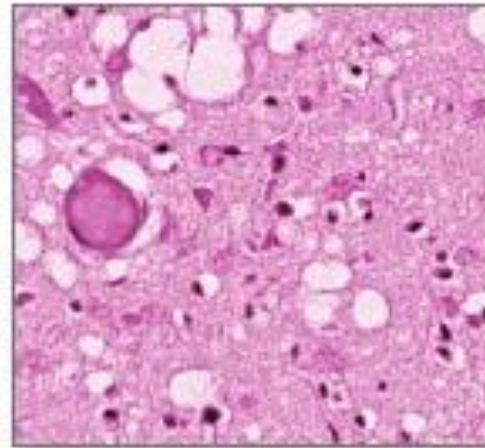


# Pathology

- The pathologic condition is essentially degenerative with grossly evident cerebral atrophy.
- Microscopic findings are similar to those of other prion diseases with neuronal loss, astrogliosis, and the development of cytoplasmic vacuoles in neurons and astrocytes.
- Amyloid plaques that contain the abnormal PrP are found in the areas of infected tissue in most cases.
- There is no inflammation.
- The cortex and basal ganglia are most affected, but all parts of the neuraxis may be involved.
- Early lesions are more severe in the gray matter

# Spongiform pathology

Brain shrinkage and deterioration occurs rapidly



Brain section showing spongiform pathology characteristic of Creutzfeldt-Jakob

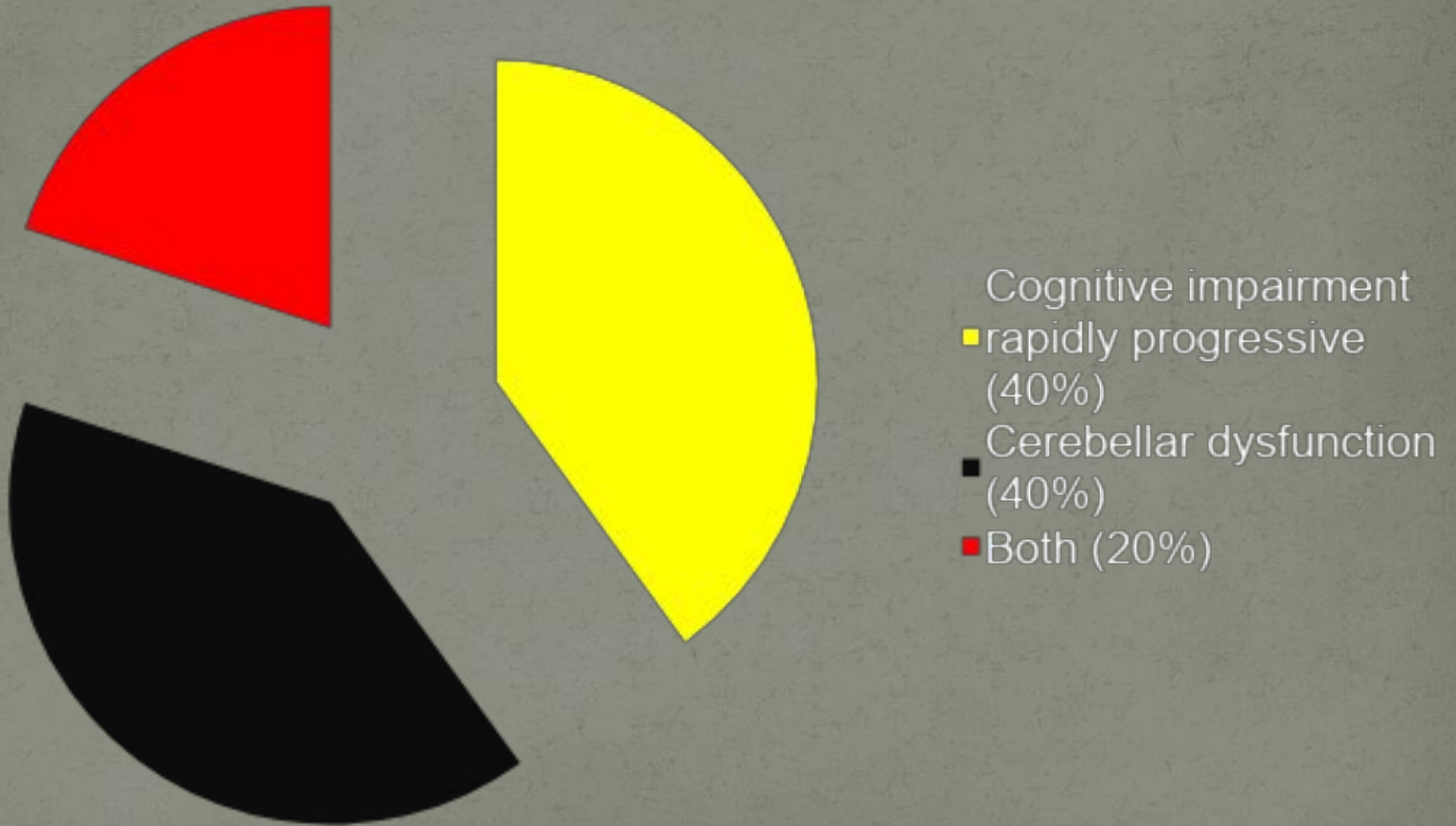


# Clinical Manifestations

## Creutzfeldt-Jakob Disease Symptoms



# Clinical Manifestations





# Clinical Manifestations

- The clinical features include a gradual onset of dementia in middle or late life.
- Vague, prodromal symptoms of anxiety, fatigue, dizziness, headache, impaired judgment, and unusual behavior may occur.
- Once memory loss starts, it progresses rapidly, and other characteristic signs appear, sometimes abruptly.

# Clinical Manifestations

- The most frequently seen signs, aside from dementia, are pyramidal tract disease
  - weakness
  - stiffness of the limbs
  - accompanying reflex changes
- Extrapyramidal signs
  - Tremor
  - rigidity,
  - Dysarthria
  - slowness of movement
  - myoclonus (often stimulus sensitive).



# Clinical manifestations

- In advanced stages of the disease, patients have difficulties with movement, swallowing and talking.
- In the final stage, patients lose all mental and physical function and may lapse into a coma.
- Many patients die from an infection such as pneumonia.
- The average duration of disease from the onset of symptoms to death is four to six months.
- Ninety percent of patients die within a year.

# Diagnostic Criteria CDC

- Sporadic

1. Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant rP; and /or presence of scrapie-associated fibrils



# Diagnostic Criteria CDC

2. Rapidly progressive dementia and at least two out of the following four clinical features:

- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

AND a positive result on at least one of the following laboratory tests:

- a typical EEG (periodic sharp wave complexes) during an illness of any duration; and/or
- a positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years
- Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR).

# Diagnostic Criteria CDC

- Iatrogenic

1. Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone
2. Sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

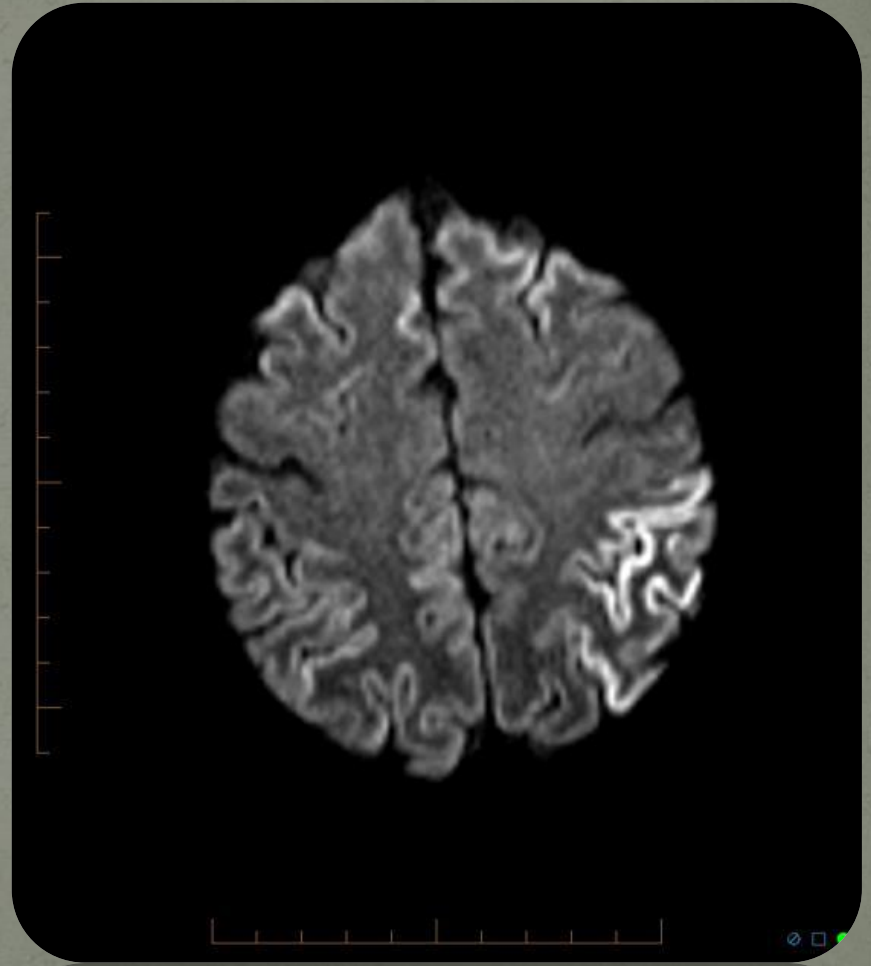
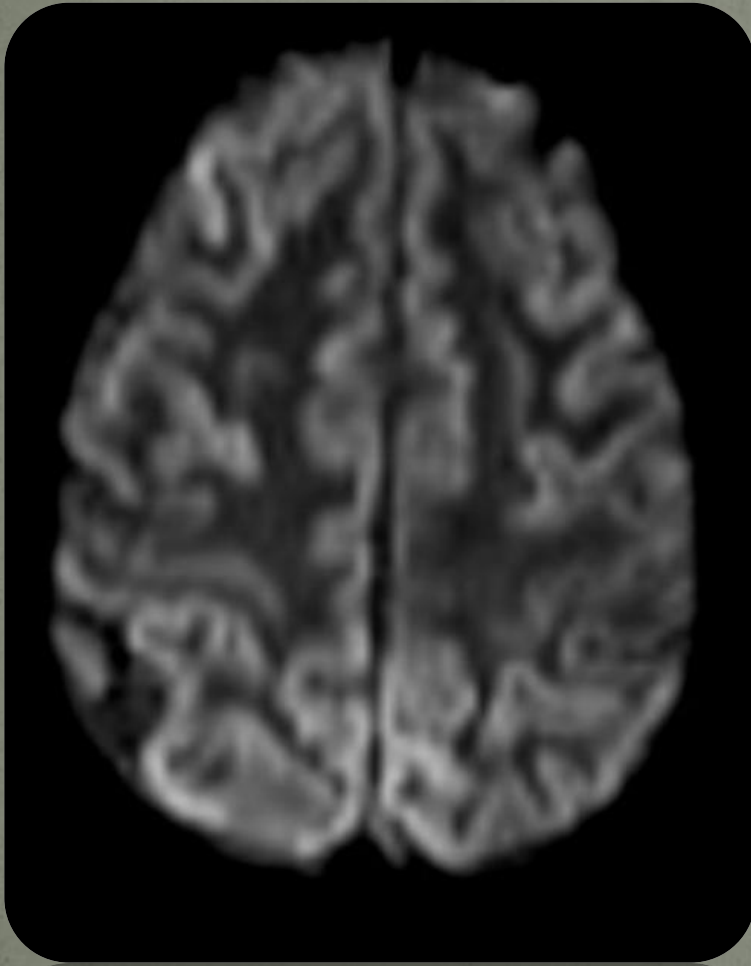


# Diagnostic Criteria CDC

- Familial

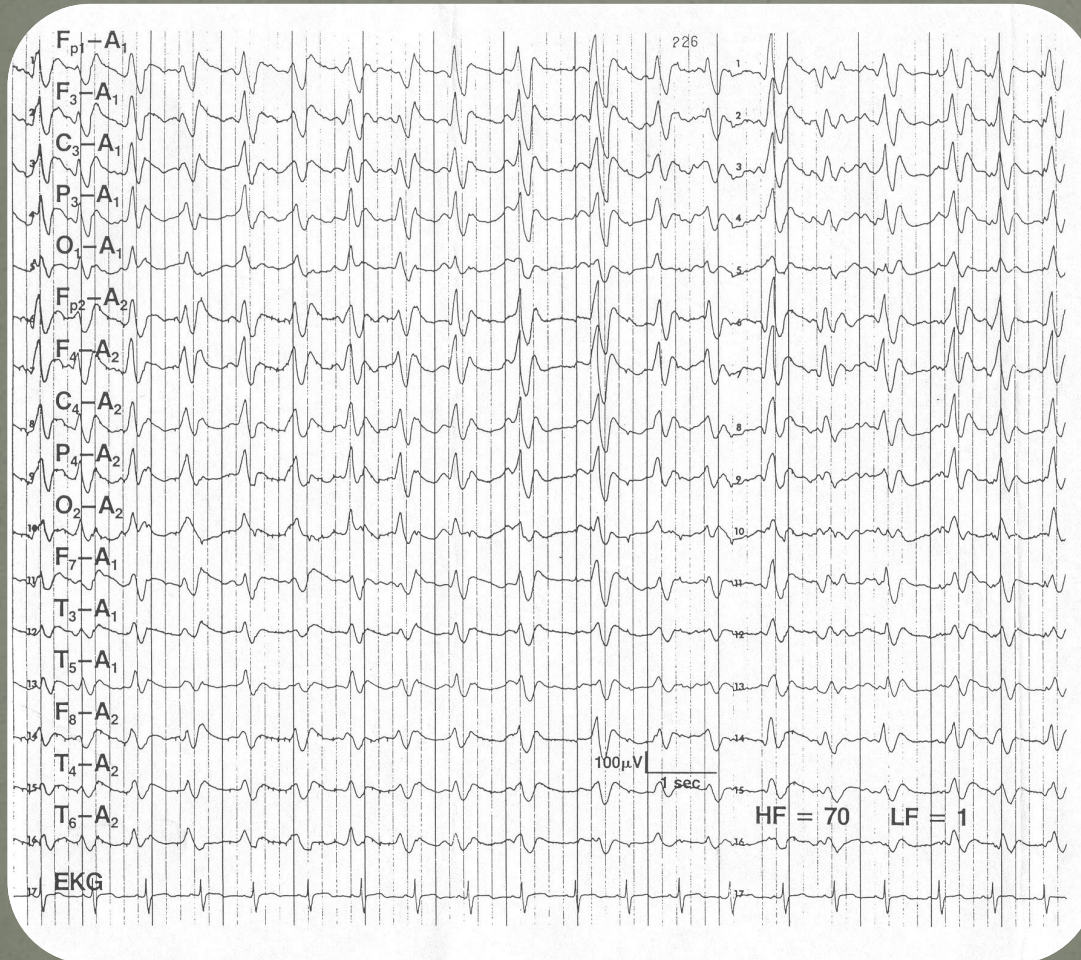
1. Definite or probable CJD plus definite or probable CJD in a first degree relative
2. Neuropsychiatric disorder plus disease-specific PrP gene mutation.

# MRI (Sporadic)





# EEG



- continuous periodic stereotypic 200- to 400-millisecond sharp waves occurring at intervals of 0.5-1.0 seconds.

# Control

## MANAGEMENT OF CASES

- No specific available treatment
- Patients should be excluded from blood, organ or other body tissue donations.
- Identify source of infection

## MANAGEMENT OF CONTACTS

- Patients with potential exposure to CJD should be informed of their risk



# Treatment Options

## Symptomatic

- Antidepressants
  - Clonazepam
- Tremors
  - Sodium Valproate
- Pain
  - Opium based analgesics

# Treatment on trial

- Pentosan polysulphate
  - Infused into the individual's lateral ventricle
  - PPS appears to slow down CJD's progression



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