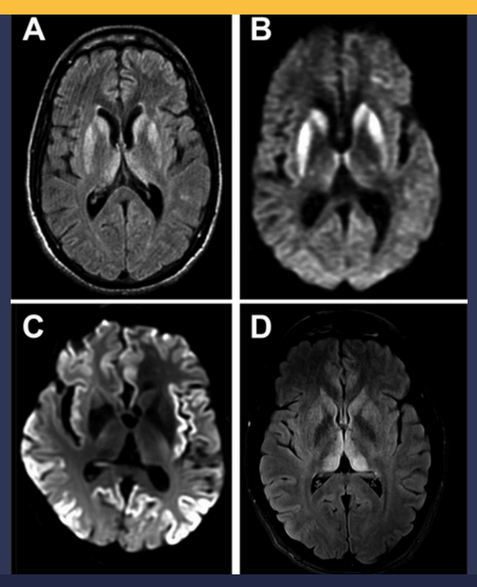
FATAL PROTEIN MISFOLDING: A STORY OF PRIONS AND CREUTZFELDT-JAKOB DISEASE

BY GROUP 40



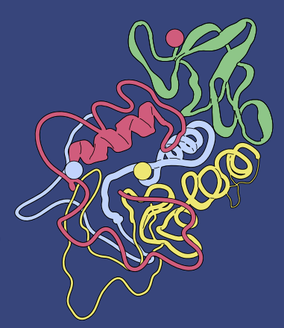
WHAT IS IT?

Creutzfeldt-Jakob Disease (CJD) is a rare, fatal neurodegenerative disorder classified as a transmissible spongiform encephalopathy (TSE)[1]. It is caused by misfolded prion proteins that induce abnormal folding of normal proteins, leading to a "sponge-like" deterioration of brain tissue[1].

ETIOLOGY

TYPES & ENVIRONMENTAL TRIGGERS

Sporadic CJD: Most common form, occurs due to spontaneous protein misfolding without identifiable cause[1]



Variant CJD: Linked to BSE (bovine spongiform encelphalopathy) exposure via consumption of contaminated beef[1]

Iatrogenic CJD: Results from medical transmission, such as contaminated neurosurgical instruments, dura mater grafts, or human-derived growth hormone[2]

Age: Risk increases with age, with most sporadic cases occuring in older adults[3]

GENETIC FACTORS

PRNP Gene: Mutations in the PRNP gene significantly increase susceptibility to the disease & contribute to familial inheritance progression[1]

Host Biology: Individual variation in the structure of prion proteins can affect the likelihood of misfolding and the speed of disease progression[1]

PRION SYSTEM DYSFUNCTION

Chain Reaction: The central mechanim is the conversion of normal prion protein into the abnormal, protease-resistant protein[1]

Aggregation: Misfolded prions act as templates, inducing a chain reaction that forms protien aggregates in neural tissue[1]

Tissue Destruction: Aggregates cause synaptic dysfunction and neuronal death, leading to characteristic “holes” or spongiform vacuolation in the brain[2]

EMERGING HYPOTHESIS

CJD is unique because it lacks nucleic acids, making it an entirely protein-based infectious disease[1]

Research suggests different prion strains influence how the disease is transmitted, the length of the incubation period, and the specific clinical phenotype[1]

PRIONS AND PROTEIN MISFOLDING

Normal Prion Protein (PrP^c)

Alpha-helix structure

CONVERSION

leading to diseased version

Misfolded Prion Protein (PrP^{sc})

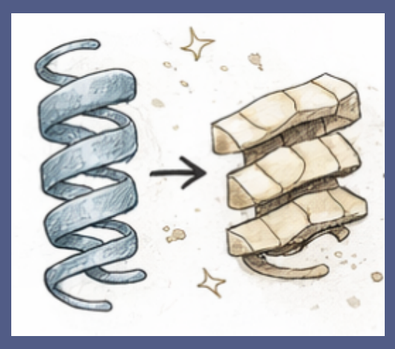
Beta-sheet structure

Normal PrP^c misfolds from an alpha-helical structure into the beta-sheet rich PrP^{sc} form. This abnormal protein is insoluble, protease-resistant, and induces further misfolding, causing prion aggregation, neuronal damage, and spongiform change in the brain.[1]

What differs in different types of CJD is the trigger for the first misfolding event: in sporadic CJD, PrP^c spontaneously converts into PrP^{sc}; in variant CJD, exposure to BSE-associated infectious prions seeds the conversion of normal prion proteins; in familial CJD, a PRNP gene mutation makes the prion protein structurally more likely to misfold; and in iatrogenic CJD, infectious prions are introduced through contaminated medical tissue or instruments. Once misfolding begins, the same self-propagating cycle of prion accumulation leads to neuronal damage, gliosis, and spongiform degeneration.[4]

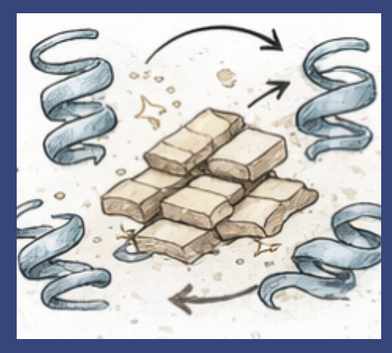
MECHANISMS OF PRION PATHOGENESIS

CONFORMATIONAL CHANGE



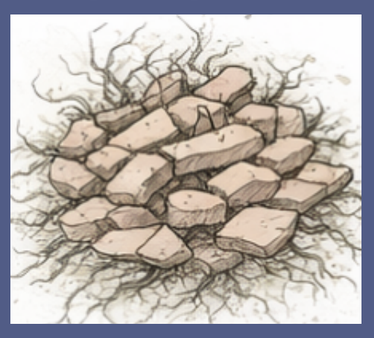
The normal cellular prion protein, PrP^c, which is alpha-helix rich, changes into PrP^{sc}, an abnormal beta-sheet rich form. This new form is insoluble, highly stable, and resistant to protease degradation, so it is not cleared normally and begins to accumulate in brain tissue.[5]

SEEDING



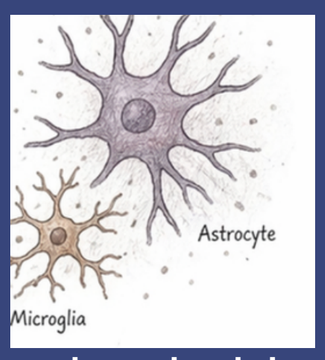
Once PrP^{sc} is present, it acts as a template or seed, binding to normal PrP^c and forcing it to adopt the same abnormal shape. This creates a self-propagating cycle in which each newly misfolded protein can convert more normal proteins.[4]

ACCUMULATION



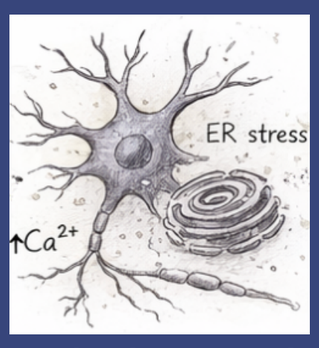
As more PrP converts into PrP^{sc}, the misfolded proteins aggregate into oligomers and larger deposits that spread through the central nervous system. Because these aggregates resist breakdown, they progressively build up and interfere with normal cellular function. [4]

GLIOSIS



In response to ongoing prion injury, astrocytes and microglia become activated. This reactive gliosis is the brain's attempt to respond to damage, but it also adds to neuroinflammation and can worsen surrounding neuronal injury. [6]

NEUROTOXICITY



The buildup of abnormal prion protein causes cellular stress, including endoplasmic reticulum stress, disrupted intracellular trafficking, and calcium imbalance. These changes impair neuronal metabolism and signalling, eventually triggering neuronal apoptosis and degeneration. [6]

SPONGIFORM CHANGE

As neurons are damaged and lost, the brain develops many tiny vacuoles, giving affected tissue a sponge-like appearance on microscopy. This spongiform degeneration is one of the classic pathological features of prion disease. [4]

SIGNS AND SYMPTOMS

Symptoms in CJD patients are usually characterized by quickly worsening neurological abilities. Symptoms may vary based on variant of CJD. [5]

Cognitive and Behavioural changes: [5]
- Memory loss
- Worsening judgement / cognition
- Confusion and delusion
- Personality changes, anxiety
- Insomnia

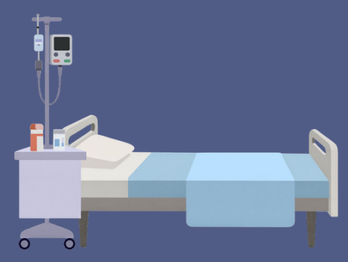
Problems with Vision and Speech: [7]
- Visual hallucinations
- Blurry vision
- Difficulty speaking / slurred speech

Movement and Coordination: [7]
- Jerky movements, tremor
- Muscle twitching / spasms
- Worsening coordination and reflexes
- Problems with walking and balance
- Dizziness

COMPLICATIONS

Complications in later stages of disease will lead to: [5]

- Dementia and mental deterioration
- Loss of independence
- Blindness
- Inability to move or speak
- Coma

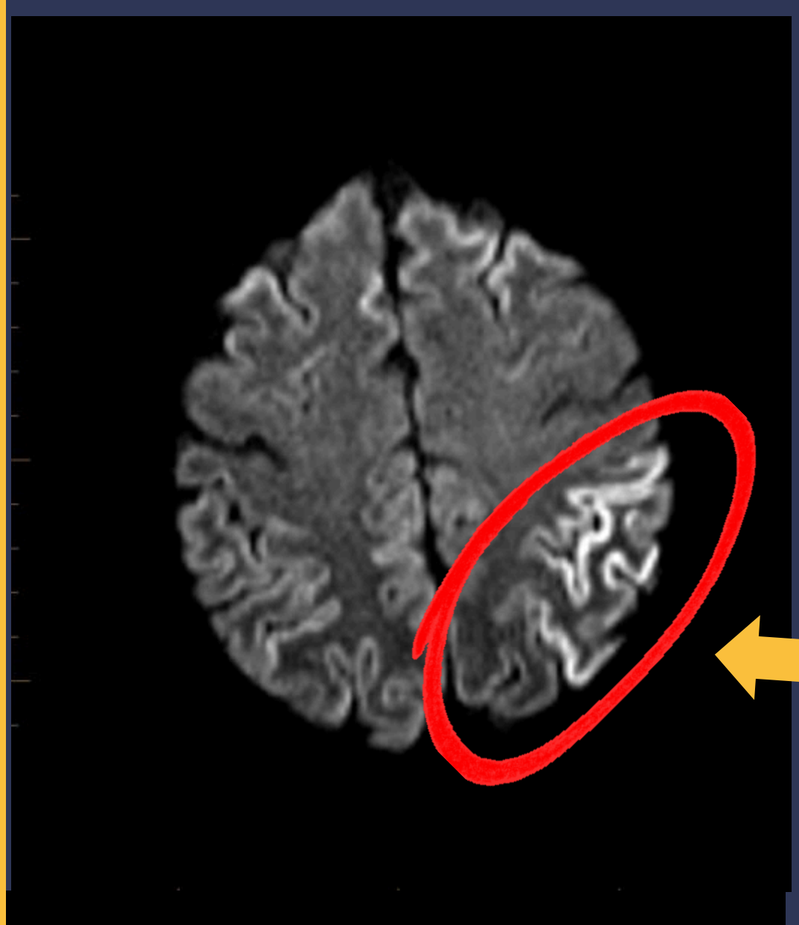


DIAGNOSIS

MRI (MAGNETIG RESONANCE IMAGING)

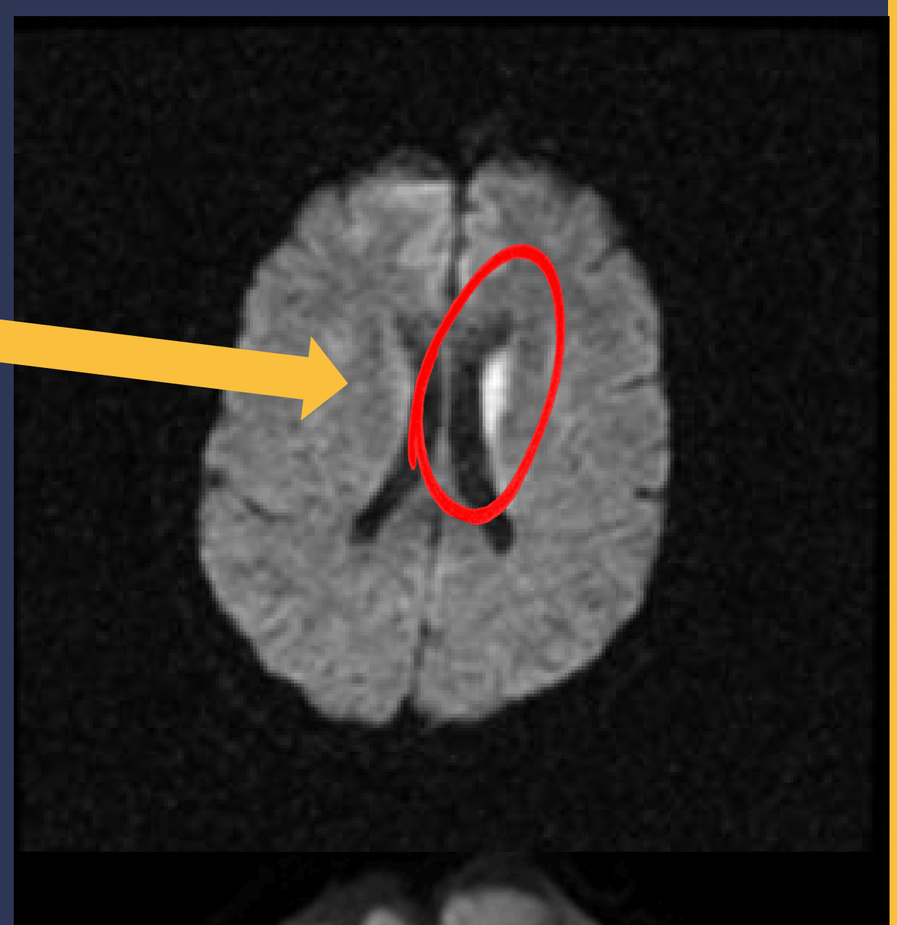
Diffusion-Weighted Imaging (DWI), a special form of MRI that uses a process called diffusion restriction, is often used to diagnose CJD. DWI allows visualization of high signal intensity areas of the brain that are indicative of CJD. [8]

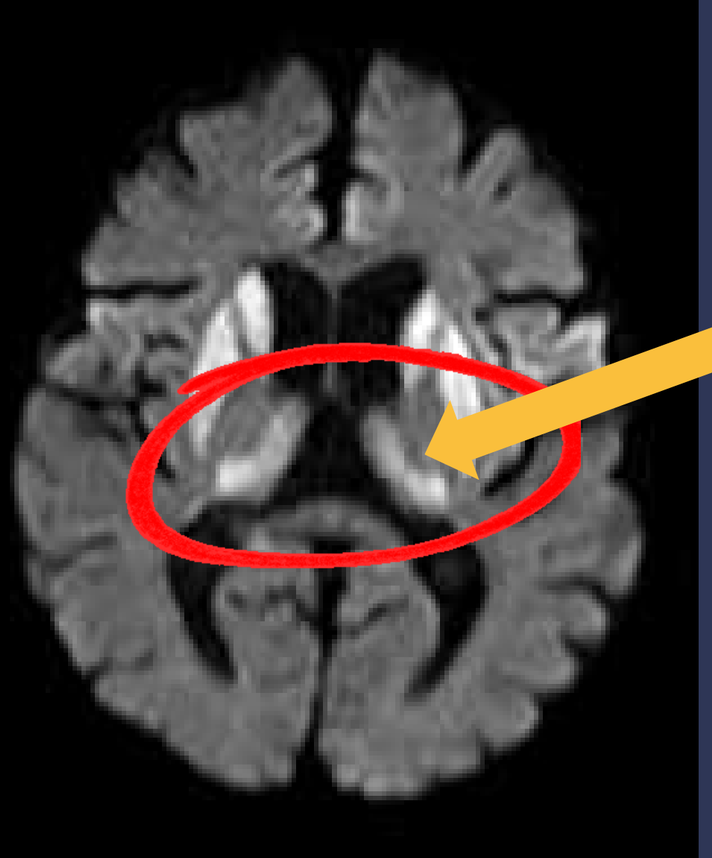
Let's take a look at a few cases... [8]



Prominent diffusion restriction in caudate nucleus

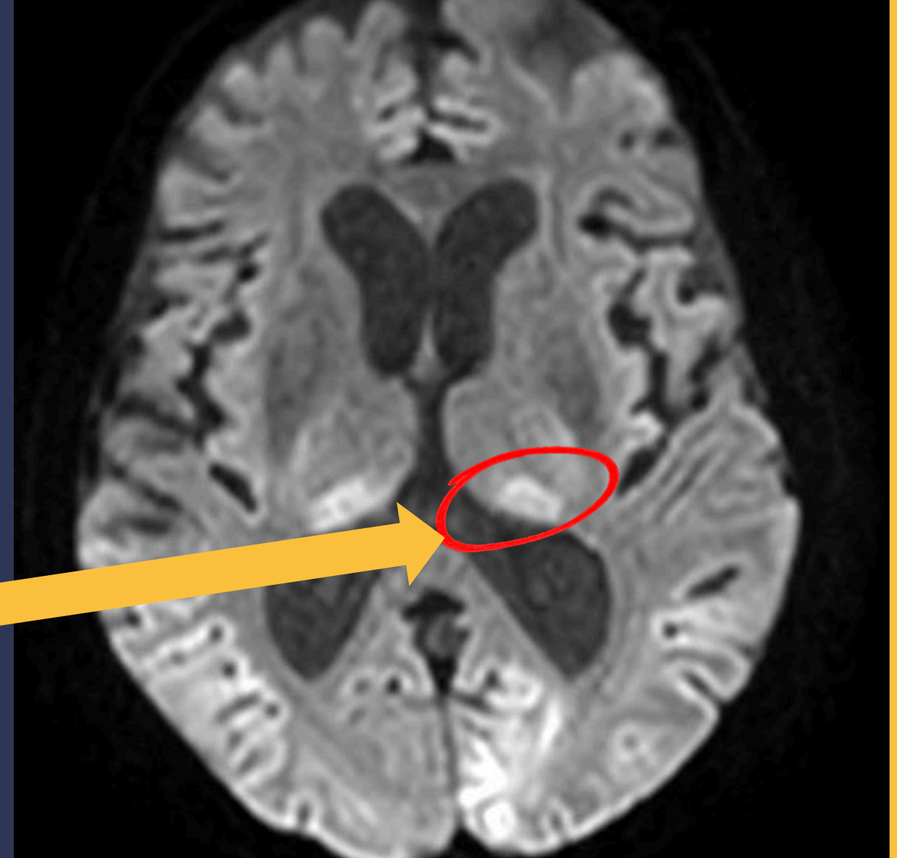
Characteristic cortical ribboning





"Hockey stick" sign (L-shaped diffusion in Thalamus)

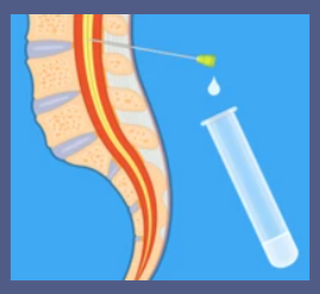
Pulvinar sign (Pulvinar nucleus of the Thalamus)



LUMBAR CISTERN (CSF TEST)

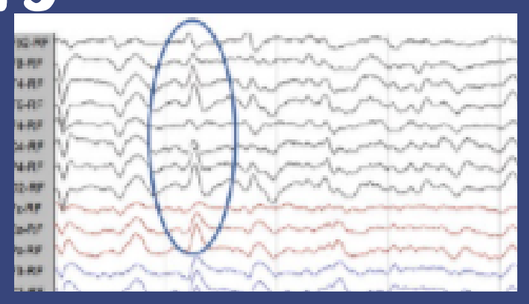
A puncture is made in the lumbar region of the spine to collect a sample of CSF (cerebrospinal fluid). This fluid is tested for 14-3-3 and tau proteins that serve as markers for nervous system degeneration. [7]

Alternatively, a newer test called RT-QuIC can detect specific prion proteins in CSF. [7]



OTHER DIAGNOSTIC TESTS

EEG: An Electroencephalogram measures electrical activity in the brain and can detect characteristic abnormal wave complexes. [9]

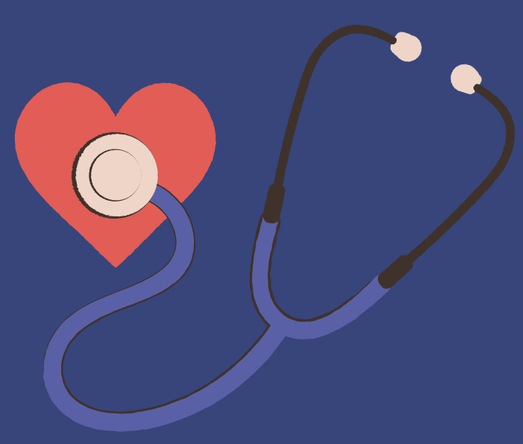


NEUROLOGICAL TEST: Can measure certain neurological processes such as reflexes, muscle twitching, etc, associated with CJD. [8]

BRAIN BIOPSY: A small piece of brain tissue can be sampled by a neurosurgeon and examined by a pathologist for a definitive diagnosis. Undesirable and rarely performed. [8]

PROGNOSIS

- CJD is ultimately fatal[10]
  - 70% of patients die within one year after symptoms show[11]
  - In some cases, death occurs within six months after symptoms begin[10]
  - Genetic CJD can have a survival time of one to ten years after symptoms begin[11]
- Patients with CJD usually die of complications associated with the disease[12]
  - Complications include trouble swallowing, heart issues, lung failure, pneumonia or other infections[12]
- CJD causes about 1-2 deaths per 1 million people per year[13]
  - About 500-600 cases are reported each year in the United States[13]



TREATMENT

- CJD is incurable and there is no effective treatment available[11]
  - Management of CJD focuses on symptom relief and patient comfort
- Symptom management includes:
  - Treating anxiety and depression with sedatives and antidepressants[14]
  - Treating tremors and muscle jerks with clonazepam or sodium valproate[14]
- Supportive care may improve a patient's quality of life while affected by CJD[11]

TRANSMISSION

- CJD is not easily transmitted between individuals. However, transmission can occur through:
  - Infected organ or tissue transplants[4]
  - Certain hormone treatments from affected donors [4]
  - Blood transfusions[4]
- Preventive measures include:
  - Restricting blood donation among first-degree relatives[11]
  - Testing elk or deer meat before consumption[11]
  - Using contraception in families at risk for genetic CJD to prevent transmission to offspring[11]

REFERENCES

1. Bellini P, Ruggiero F, Benedetti A, Cereda CW, Gobbi C, Bianco G, et al. Human Prion Disease: Pathogenesis, Diagnosis and Public Health. Viruses. 2026 Feb 6;18(2):216. Available from: https://www.mdpi.com/1999-4915/18/2/216
2. Collinge J. Variant Creutzfeldt-Jakob disease. The Lancet [Internet]. 1999 Jul 24 [cited 2020 Nov 7];354(9175):317–23. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0140673699051284
3. Salehi P, Clark M, Pinzon J, Patil A. Sporadic Creutzfeldt-Jakob disease. The American Journal of Emergency Medicine. 2022 Feb;52:267.e1–3. Available from: https://pubmed.ncbi.nlm.nih.gov/34334283/
4. 1.NHS Choices. Causes - Creutzfeldt-Jakob disease [Internet]. NHS. 2019. Available from: https://www.nhs.uk/conditions/creutzfeldt-jakob-disease-cjd/causes/
5. Mayo Clinic. Creutzfeldt-Jakob disease [Internet]. Mayo Clinic. 2023. Available from: https://www.mayoclinic.org/diseases-conditions/creutzfeldt-jakob-disease/symptoms-causes/syc-20371226
6. Sitammagari KK, Masood W. Creutzfeldt Jakob Disease [Internet]. Nih.gov. StatPearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507860/
7. National Institute of Neurological Disorders and Stroke. Creutzfeldt-Jakob Disease [Internet]. www.ninds.nih.gov. 2023. Available from: https://www.ninds.nih.gov/health-information/disorders/creutzfeldt-jakob-disease
8. Ho ML. Creutzfeldt-Jakob disease | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia. [cited 2020 Nov 6]. Available from: https://radiopaedia.org/articles/creutzfeldt-jakob-disease
9. Mundlamurri RC, Shah R, Adiga MS, Chatterjee A, Gautham B, Raghavendra K, et al. EEG Observations in Probable Sporadic CJD. Annals of Indian Academy of Neurology [Internet]. 2020 [cited 2021 Apr 6];23(6):760–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7900740/
10. Diagnosis [Internet]. CJD Foundation. Available from: https://cjdfoundation.org/diagnosis/
11. McQuain J, Galicia-Castillo M, Morris D. Palliative Care Issues in Creutzfeldt-Jakob Disease | Palliative Care Network of Wisconsin [Internet]. Palliative Care Network of Wisconsin. 2023. Available from: https://www.mypcnow.org/fast-fact/palliative-care-issues-in-creutzfeldt-jakob-disease/
12. CDC. Classic Creutzfeldt-Jakob Disease [Internet]. Creutzfeldt-Jakob Disease (CJD). 2024. Available from: https://www.cdc.gov/creutzfeldt-jakob/about/index.html
13. NHS. Treatment - Creutzfeldt-Jakob disease [Internet]. NHS. 2019. Available from: https://www.nhs.uk/conditions/creutzfeldt-jakob-disease-cjd/treatment/
14. Cleveland Clinic. Creutzfeldt-Jakob Disease (CJD): Types, Causes, Symptoms & Outlook [Internet]. Cleveland Clinic. 2022. Available from: https://my.clevelandclinic.org/health/diseases/6001-creutzfeldt-jakob-disease