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Creutzfeldt Jakob Disease-A Review

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ABSTRACT:
CreutzfeldtJakob diseaseis a rare and neurodegenerative disorder. It is also called subacute spongiform encephalopathy or neurocognitive disorder.CreutzfeldtJakob diseaseis caused by abnormal folding of a protein known as a prion. Early symptom includes memory problems, behavioural changes, poor coordination etc. while later symptoms include dementia, involuntary movements, and blindness. Average onset of disease is around 60 years old and more than 70% of cases are resulting in death within year after diagnosis. Induction of disease can vary from regions to sexes. Definite disease diagnosis for Creutzfeldt-Jakob disease since 2018 is positivebrain tissue testing (PBTT).

KEYWORDS: CreutzfeldtJakob Disease, Prion proteins, Dementia, Sub-acute spongiform encephalopathy.

INTRODUCTION:

Creutzfeldt-Jakob disease (CJD) also known as Sub-acute spongiform encephalopathy, Bovine spongiform encephalopathy (BSE), mad cow disease or Neurocognitive disorder. [2] In 1920 CJD was first outlined by Hans Creutzfeldt and later by AlfonsJakob in 1921 and 1923, Clarence J. Gibbs was the one who started the term 'Creutzfeldt-Jacob disease' because it is closer to his initials.CJD is a rare disease and rapidly spreading, Primarily CNS is affected.[3]This worsening brain disorder can cause odd changes in brain tissues and affects memory, thinking, or coordination.[2] Disease occurs as a result of prion proteins, which forms atypical 3D forms and this gradually affects prior proteins present in the brain to fold in the same unique forms. These abnormal prion proteins can destroy brain cells and cause damage in processes like thinking, reasoning, and involuntary muscle movements.[11]

BSE is a fatal condition with symptoms like slurred speech, numbness, hallucinations, insomnia, and double vision and can leads to advanced symptoms like paranoia, and memory loss. [11]Mostly those affected with the disorder die within a year from symptoms in the form of infections. Immobility is the reason which makes people with CJD more exposed to infection. CJD causes specific types of dementia which worsens rapidly. Mostly older adults are affected by the disease.[3]

Major categories of CJD are:
1. Sporadic CJD
2. Hereditary CJD
3. Acquired CJD [11]

The incidence of this rare disease has been seen as 1 case per million per year and fewer than 5000 cases per year in India. CJD can also be caused by family history and in such cases, there are more than 50 mutated prion proteins. Variation of the genetics of the prion proteins at a location can be termed as 'codon 129' this can increase the risk of rapid misfolding. [11]There is no specific single or combination test to identify the particular disease. [4]MRI can detect the slight variation in the brain changes and Lumbar puncture test or spinal fluid can be used to detect the presence of certain proteins. During the last stage of disease IV fluids as well as machine feeding is used. [2,3,4,11]

EPIDEMIOLOGY:

BASED ON REGIONS: The disease is changing in strength every dozen years, till today most cases are found in the United Kingdom (350

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cases between 1999 and 2000) [9]. Other regions include China, Japan, Saudi Arabia. In the case of INDIA, taking the billion population into account there would be at least 500 cases every year.

BASED ON AGE: Most common between 55-75 years of age, average will be the 60s, and the highest mortality rate is 5.9% per million cases between ages 70-76 years. [2]

BASED ON GENDER: The ratio of CJD is 1:1 in case of males and females. In united states between 1979-2006, 52.6% of cases were females. The onset of CJD was earlier in females (before 65 years old) than males (generally after 69 years old). The mortality rate is higher in women between 45-55 and in men between 80-89 years of age.

BASED ON COLOUR: About 94.8% of death cases are reported in whites. Mortality rate is only 40% for blacks against whites. [1,3]

ETIOLOGY: A normal prion protein is a flexible alpha-helical structure that is soluble, has normal cellular function, and is sensitive to proteases. MisfoldedPrP is an abnormally folded form of PrP, which is infectious and causes CJD and other transmissible spongiform encephalopathies like bovine spongiform encephalopathy. This damages brain tissue and causes characteristic symptoms of CJD.[3]Prion proteins convert alpha-helices into indigestible beta-pleated sheets, which induce normal PrP to misfold, resistant to degradation, replicate, and accumulate in the brain. [1]Prions have a long incubation period. They also contain no genetic information in the form of nucleic acids such as DNA and RNA. [6]

Types of Prion proteins: -

1. Sporadic: No known cause, accounting for 85% of cases.
2. Familial: Inherited mutations in the PRNP gene, accounting for 10-15% of cases.
3. Iatrogenic: Transmission through medical procedures, such as contaminated surgical instruments, infected tissue transplants, human growth hormone injections, etc.
4. Variant: Linked to consumption of beef contaminated with bovine spongiform encephalopathy (BSE or mad cow disease) prions.
5. Other rare causes like Gerstmann-Straussler-Schenker disease (GSS), Fatal familial insomnia (FFI), and Kuru (transmitted through cannibalism in Papua New Guinea). [3]

PATHOPHYSIOLOGY: The most of the Creutzfeldt Jakob disease are contemplation to occur infrequently from prion by an unknown route of transmission. The defective protein associated with Creutzfeldt-Jakob disease can be inherited form or iatrogenic form. It includes human growth hormone (HGH), corneal grafting, electrode implants, consumption of infected animals, and cannibalism. The incubation period of the disease is not known, but the disease may develop in many years up to 50 years after the initial response. The CreutzfeldtJakob disease prion promotes refolding of the native proteins into the diseased state. The number of misfolded protein molecules will increase, and the process leads to a large quantity of insoluble protein in the affected cells. Therefore, misfolded proteins disrupt cell function and causes cell death. Once the prion is transmitted, the defective proteins invade the brain and are produced in a self-sustaining feedback loop, causing the spread of the prion. [1] [2]

MUTATIONS: Mutation in the gene responsible for the production of the prion protein can cause misfiling of the alpha-helical regions into beta-pleated sheets. This change in the conformation dysfunction the ability of the protein to undergo dissolution. Individuals may also acquire CJD genetically through the mutation occurring Prion Protein Gene (PNRP). [1][2]CJD is rare. Prion misfolding: A normal prion protein misfolds into an abnormal form of Protein, which is resistant to degradation. Prion replication: The abnormal prion Proteins replicate by converting normal prion Proteins into more abnormal prion proteins. Accumulation and aggregation: Abnormal prions accumulate and aggregate in brain cells, leading to (a)Neurodegeneration: Death of brain cells (neurons) and their connections (synapses).(b) Spongiform change: Formation of characteristic holes (vacuoles) in brain tissue, giving it a "spongy" appearance. (c) Inflammation and immune response: The immune system responds to the abnormal prions, leading to inflammation and further brain damage. (d) Disruption of brain function: CJD affects various brain regions, leading to (1) Cognitive dysfunction: Memory loss, confusion, and personality changes.(2) Motor dysfunction: Coordination, balance, and movement problems.(3) Vision changes: Blindness, double vision, or blurred vision.(4) Rapid progression: CJD progresses rapidly, with most patients dying within 1-2 years after symptom onset[3].

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SYMPTOMS: Symptoms of CJD depend upon its severity. Symptoms of this disease get worse day by day.
Initial stage: Amnesia (memory loss), Blurred vision, Dysarthria (speaking difficulty), Insomnia (difficulty to fall asleep), Personality changes, Headache, Fatigue
Intermediate stage: Dementia, Ataxia (impaired coordination), Muscle tightness, Jerking movement, Dysphagia (difficulty in swallowing), Seizures.
Final stage: Complete loss of cognitive function, Coma, Paralysis, Blindness, loss of urine and stool control, high chance for infections. [2,3,14]

DIAGNOSIS: Creutzfeldt-Jakob disease can be confirmed by brain biopsy or autopsy. The brain biopsy test was carried out under general anesthesia because the patient should be unconscious during the procedure. A specialized instrument is employed to drill a small hole into the skull. A thin biopsy needle was inserted through a hole and the target area was shown by imaging techniques. A biopsy was done by collecting a small piece of brain tissue through a needle. After removing the needle, the hole is closed. [2,12,13]CJD Can also be diagnosed based on personal and medical history, neurological examination, and various diagnostic tests. Abnormalities in brain electrical impulses can be detected by the EEG, and changes can be detected during disease progression. MRI(Magnetic resonance imaging) can detect abnormal brain signals and also identify other neurological disorders. It is most useful in the diagnostic technique RT-QuIC (Cerebrospinal fluid real-time quaking-induced conversion) can detect prion protein, and if the test is positive, it indicates that the patient may have a CJD. A spinal tap or lumbar puncture, detect definite proteins that indicate CJD. Levels of prion proteins that indicate CJD can be detected through CT scans.CSF increased levels of the 14-3-3 protein in CSF may be seen in patients with CJD although it's not a screening test it can help diagnose CJD if it's suspected. In addition, there are blood tests, genetic tests (PRNP gene mutations), and neuropsychological tests that also can be used for the diagnosis of CJD. Western blotting (confirming protease-resistant PrP), immunocytology, or the presence of scrapie-associated fibrils are all neuropathological techniques that can be used to diagnose various forms of CJD. [2,3,12,13,14]

TREATMENT: Currently, no treatment has been found for these diseases. Medicines are given according to the symptoms of these diseases. For the CJD may cause epilepsy can be treated with anti-epileptic drugs such as valproic acid, clonazepam, and anti-depressant drugs can also be given as a treatment option, when patients are showing any type of psychiatric illness. Opioid analgesics should be used as pain relievers. This disease can't be completely cured. [10,11]

PREVENTION: Since there is no cure for CJD Prevention of spreading is essential. The sterilization method is useful to prevent bacterial and viral spreading and also has a complete effect against the prion disease which causes CJD. [1] Only use a synthetic human growth hormone instead of using growth hormone obtained from the pituitary gland of cadavers. Destroy the surgical instruments that are contaminated by CJD patients. People who have CJD should not transfer the cornea and other body fluids or body parts. [2]The person has to wear a mask and gloves while handling the condemning fluids, tissues, and organs from the infected persons. Follow strict guidelines.[3] Avoid eating contaminated meat: Some cases of variant CJD have been linked to consuming beef contaminated with bovine spongiform encephalopathy (BSE or mad cow disease). Follow proper protocols for disinfection, cleaning, and waste disposal. Be aware of CJD symptoms, such as memory loss, personality changes, and coordination problems, and seek medical attention if they arise. Inform public health authorities if anyone suspects a case of CJD. Encourage and participate in research to better understand and prevent CJD.[4]

COMPLICATIONS: Complications include both mental and physical difficulties:
Difficulty in identifying friends and family, Inability to do daily activities, Loss of bowel and bladder control, Blindness and double vision, Difficulty with eye movements, Frequent and recurring seizures, Pneumonia, Choreoathetosis, Cerebellar ataxia, Myoclonus, Dysphagia. [1,3]

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