CREUTZFELDT–JAKOB DISEASE: AN OVERVIEW

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Summary

Creutzfeldt–Jakob disease or CJD is characterized by rapidly progressive dementia. It also tends to cause more rapid deterioration of a person's abilities than Alzheimer's disease or most other types of dementia. The disease is caused by prions which are defective proteins in the brain tissue.Initially, patients experience problem with muscular coordination; personality changes, including impaired memory, judgment, and thinking; and impaired vision. As the illness progresses, the patient's mental impairment becomes severe. They often develop involuntary muscle jerks called myoclonus, and they may go blind. They eventually lose the ability to move and speak and enter a coma. Pneumonia and other infections often occur in these patients and can lead to death. Some symptoms of CJD can be similar to symptoms of other progressive neurological disorders, such as Alzheimer's or Huntington's disease. However, CJD causes unique changes in brain tissue which can be seen at autopsy. There is typical spongiform appearance of brain tissue. Electroencephalography, CSF studies and MRI scan confirms the diagnosis. Many drugs including antibiotics are found to be useless for treatment except quinacrine which has shown some promising results.

Keywords: CJD, Dementia, Prions, Quinacrine

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Introduction

Creutzfeldt–Jakob disease or CJD (sometimes incorrectly referred to as mad cow disease) is a degenerative neurological disorder (brain disease) that is incurable and invariably fatal. It is the most common among the types of transmissible spongiform encephalopathy found in humans. [1]

History

The disease was first described by German neurologist Hans Gerhard Creutzfeldt in 1920 and shortly afterwards by Alfons Maria Jakob, giving it the name Creutzfeldt–Jakob. Some of the clinical findings described in their first papers do not match current criteria for Creutzfeldt–Jakob disease, and it is considered highly likely that at least two of the patients in initial studies were suffering from a different ailment. [2]

Incidence and Prevalence

Although CJD is the most common human prion disease, it is still rare, occurring in about one out of every one million people every year. It usually affects people aged 45–75, most commonly appearing in people between the ages of 60–65. The exception to this is the more recently-recognised 'variant' CJD, which occurs in younger people.[3] CDC monitors the occurrence of CJD in the United States through periodic reviews of national mortality data. According to the CDC:

- CJD occurs worldwide at a rate of about 1 case per million population per year.
- On the basis of mortality surveillance from 1979 to 1994, the annual incidence of CJD remained stable at approximately 1 case per million persons in the United States.
- In the United States, CJD deaths among persons younger than 30 years of age are extremely rare (fewer than five deaths per billion per year
- The disease is found most frequently in patients 55–65 years of age, but cases can occur in people older than 90 years and younger than 55 years of age.
- In more than 85% of cases, the duration of CJD is less than 1 year (median: four months) after onset of symptoms.[4]

Pathophysiology

Transmissible spongiform encephalopathy diseases are caused by prions. The diseases are thus sometimes called prion diseases. Other prion diseases include Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI) and kuru in humans, as well as bovine spongiform encephalopathy (BSE, commonly known as mad cow disease) in cattle, chronic wasting disease (CWD) in elk and deer, and scrapie in sheep. The prion that is believed to cause Creutzfeldt–Jakob exhibits at least two stable conformations. One, the native state, is water-soluble and present in healthy cells. As of 2007, its biological function is presumably in transmembrane transport or signaling.

People can also acquire CJD genetically through a mutation of the gene that codes for the prion protein (PRNP). This only occurs in 5–10% of all CJD cases. The CJD prion is dangerous because it promotes refolding of native proteins into the diseased state. The number of misfolded protein molecules will increase exponentially, and the process leads to a large quantity of insoluble prions in affected cells. This change in conformation disables the ability of the protein to undergo digestion. Once the prion is transmitted, the defective proteins invade the brain and are produced in a self-sustaining feedback loop, causing exponential spread of the prion, leading to death within a few months, although a few patients have lived as long as two years. [5]

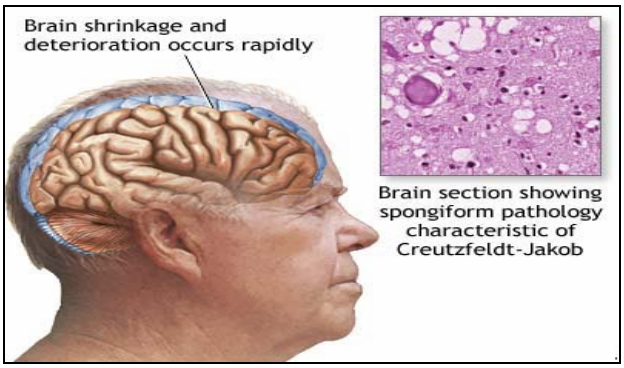

Figure 1: Pathophysiology of Creutzfeldt–Jakob disease

CLINICAL AND PATHOLOGIC CHARACTERISTICS [6, 7]

Characteristic	Classic CJD
Median age at death	68 years
Median duration of illness	4–5 months
Clinical signs and symptoms	Dementia; early neurologic signs
Periodic sharp waves on electroencephalogram	Often present
Signal hyperintensity in the caudate nucleus and putamen on diffusion-weighted and FLAIR MRI	Often present
"Pulvinar sign" on MRI	Not reported
Immunohistochemical analysis of brain tissue	Variable accumulation.
Presence of agent in lymphoid tissue	Not readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistant prion protein	Not reported
Presence of amyloid plaques in brain tissue	May be present

Table 1: Clinical And Pathologic Characteristics

Genomic Structure

The misfolding and aggregation of the prion protein (PrP) is the primary cause of a group of infectious neurodegenerative diseases including Creutzfeldt-Jacob disease in humans and Bovine Spongiform Encephalopathy in cows. A single disease can exhibit different infectious strains distinguishable by incubation time and morphology or distribution of the aggregates. Infected brain tissue from one species can be used to infect other species, but with different efficiencies, suggesting a spectrum of species compatibility.[8] If PrP is, as widely believed, the sole component of infection, then the species and strain differences must be accounted for by the structure of the aggregates, likely influenced by each species' PrP sequence. We selected representative converted structures from each of the four sequences and, with the guidance of experimental data, constructed models of the infectious aggregates. Human and bovine aggregates were similar, with monomers docking in $P3_1$ symmetry to form a left-handed spiral. In contrast, hamster aggregates formed a $P3_1$ right-handed spiral. We detail the differences in the converted monomers that give rise to this difference and show that our results compare favorably with experimental data.[9]

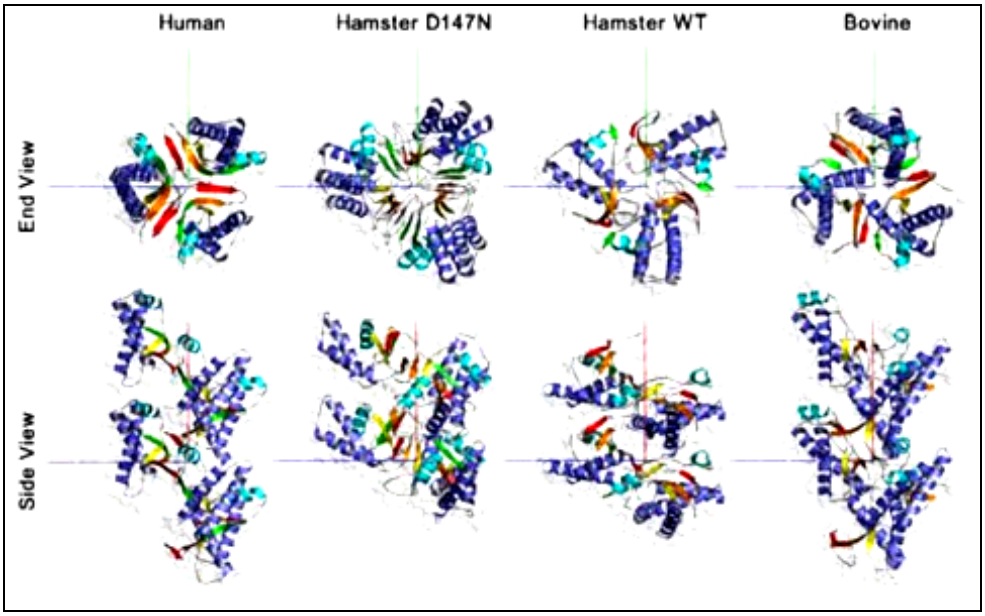

Figure 2: Genomic Structure

Symptoms

The first symptom of CJD is rapidly progressive dementia, leading to memory loss, personality changes and hallucinations. This is accompanied by physical problems such as speech impairment, jerky movements (myoclonus), balance and coordination dysfunction (ataxia), changes in gait, rigid posture, and seizures. The duration of the disease varies greatly, but sporadic (non-inherited) CJD can be fatal within months or even weeks (Johnson, 1998). In some people, the symptoms can continue for years.

In most patients, these symptoms are followed by involuntary movements and the appearance of an atypical diagnostic electroencephalogram tracing.[10]The symptoms of CJD are caused by the progressive death of the brain's nerve cells, which is associated with the build-up of abnormal prion proteins. When brain tissue from a CJD patient is examined under a microscope, many tiny holes can be seen where whole areas of nerve cells have died. The word "spongiform" in "transmissible spongiform encephalopathies" refers to the "spongy" appearance of the brain tissue.[11]

Diagnosis

The diagnosis of CJD is suspected when there are typical clinical symptoms and signs such as rapidly progressing dementia with myoclonus.[12] Further investigation can then be performed to support the diagnosis including

- Electroencephalography often has characteristic triphasic spikes
- Cerebrospinal fluid analysis for 14-3-3 protein
- MRI of the brain often shows high signal intensity in the caudate nucleus and putamen bilaterally on T2-weighted images. [13]

Diffusion Weighted Imaging (DWI) images are the most sensitive. In about 24% of cases DWI shows only cortical hyperintensity; in 68%, cortical and subcortical abnormalities; and in 5%, only subcortical anomalies. The involvement of the thalamus can be found in sCJD, is even stronger and constant in vCJD.[14] Clinical testing for CJD has always been an issue. Diagnosis has mostly been based on clinical and physical examination of symptoms. In recent years, studies have shown that the tumour marker Neuron-specific enolase (NSE) is often elevated in CJD cases[15].In one third of patients with sporadic CJD, deposits of "prion protein (scrapie)," PrP^{Sc}, can be found in the skeletal muscle and/or the spleen. Diagnosis of vCJD can be supported by biopsy of the tonsils, which harbour significant amounts of PrPSc; however, biopsy of brain tissue is the definitive diagnostic test.[16]

Transmission

The defective protein can be transmitted by human growth hormone (hGH) products, Immunoglobulins (IVIG), corneal grafts, dural grafts or electrode implants (acquired or iatrogenic form: iCJD); it can be inherited (hereditary or familial form: fCJD); or it may appear for the first time in the patient (sporadic form: sCJD). In the hereditary form, a mutation occurs in the gene for PrP, PRNP. Ten to fifteen percent of CJD cases are inherited. (CDC)The disease has also been shown to result from usage of HGH drawn from the pituitary glands of cadavers who died from Creutzfeldt–Jakob It is thought that humans can contract the disease by consuming material from animals infected with the bovine form of the disease.[17] When BSE material infects humans the resulting disease is known as (new) variant CJD Disease (nvCJD). While the men of the tribe ate the body of the deceased and were not affected, the women and children ate the brain and contracted the disease from infected brain tissue.Prions, the infectious agent of CJD, may not be inactivated by means of routine surgical instrument sterilization procedures. The World Health Organization and the US Centers for Disease Control and Prevention recommend

that heat and chemical decontamination be used in combination to process instruments that come in contact with high-infectivity tissues. No cases of iatrogenic transmission of CJD have been reported subsequent to the adoption of current sterilization procedures, or since 1976. Copper–hydrogen peroxide has been suggested as an alternative to the current recommendation of sodium hydroxide or sodium hypochlorite. Thermal depolymerization also destroys prions in infected organic and inorganic matter, since the process dissolves protein at the molecular level.[18]

Blood Donor Restrictions

In 2004 a new report published in the *Lancet* medical journal showed that CJD can be transmitted by blood transfusions.[19] The finding alarmed healthcare officials because a large epidemic of the disease might arise in the near future. There is no test to determine if a blood donor is infected during in the latent phase of CJD. In reaction to this report, the British government banned anyone who had received a blood transfusion since January 1980 from donating blood.[20]

Sperm donor restrictions

In the U.S., the FDA has banned import of any donor sperm, motivated by a risk of Creutzfeldt–Jakob disease, inhibiting the once popular[21] import of, for example, Scandinavian sperm. The risk, however, is not known, since artificial insemination has not been studied as a route of transmission.[22] It is also not known whether prions cross the blood–testis barrier.[23]

PRECAUTIONS TO AVOID SPREAD OF THE DISEASE

To reduce the already very low risk of CJD transmission from one person to another, people should never donate blood, tissues, or organs if they have suspected or confirmed CJD, or if they are at increased risk because of a family history of the disease, a dura mater graft, or other factor. [24]

Normal sterilization procedures such as cooking, washing, and boiling do not destroy prions. Caregivers, health care workers, and undertakers should take the following precautions when they are working with a person with CJD:

- Wash hands and exposed skin before eating, drinking, or smoking.
- Cover cuts and abrasions with waterproof dressings.
- Wear surgical gloves when handling a patient's tissues and fluids or dressing the patient's wounds.
- Avoid cutting or sticking themselves with instruments contaminated by the patient's blood or other tissues.
- Use face protection if there is a risk of splashing contaminated material such as blood or cerebrospinal fluid.

- Soak instruments that have come in contact with the patient in undiluted chlorine bleach for an hour or more, then use an autoclave (pressure cooker) to sterilize them in distilled water for at least one hour at 132 - 134 degrees Centigrade. [25]

TREATMENT

As of 2010 no generally accepted treatment for CJD exists; the disease is invariably fatal and research continues. An experimental treatment was given to a Northern Irish teenager, Jonathan Simms, beginning in January 2003.[26] The medication, called pentosan polysulphate (PPS) and used to treat interstitial cystitis, is infused into the patient's lateral ventricle within the brain. PPS does not seem to stop the disease from progressing, and both brain function and tissue continue to be lost. However, the treatment is alleged to slow the progression of the otherwise untreatable disease, and may have contributed to the longer than expected survival of the seven patients who were studied. The CJD Therapy Advisory Group to the UK Health Departments advises that data are not sufficient to support claims that pentosan polysulphate is an effective treatment and suggests that further research in animal models is appropriate. A 2007 review of the treatment of 26 patients with PPS finds no proof of efficacy because of the lack of accepted objective criteria.[27] Scientists have investigated using RNA interference to slow the progression of scrapie in mice. The RNA blocks production of the protein that the CJD process transforms into prions. This research is unlikely to lead to a human therapy for many years.[28] Both amphotericin B and doxorubicin have been investigated as potentially effective against CJD, but as yet there is no strong evidence that either drug is effective. Further study has been taken with other medical drugs, but none are effective. Pilot studies on quinacrine showed that quinacrine permanently cleared abnormal prion proteins from cell cultures, but results have not yet been published on the clinical study.[29]

RESEARCH TAKING PLACE

Many researchers are studying CJD. They are examining whether the transmissible agent is, in fact, a prion or a product of the infection, and are trying to discover factors that influence prion infectivity and how the disorder damages the brain.[30] Using rodent models of the disease and brain tissue from autopsies, they are also trying to identify factors that influence susceptibility to the disease and that govern when in life the disease appears.[31] They hope to use this knowledge to develop improved tests for CJD and to learn what changes ultimately kill the neurons so that effective treatments can be developed.[32]

Conclusion

Creutzfeldt–Jakob disease characterised by extreme dementia, is almost incurable and invariably fatal. Defective protein can be transmitted by human growth hormone products, Immunoglobulins, corneal grafts, dural grafts or electrode implants.It can be inherited or it may appear for the first time in the patient.Blood and sperm donations also attract the similar risk. Normal sterilization procedures such as cooking, washing, and boiling do not destroy prions. Quinacrine although has shown some primary promising results, there is no complete cure for this disease and even not a single vaccine is

prepared. Only alternative remains is to avoid the transmission by careful handling of the suspected and infected objects.

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