Prion-related encephalopathies are uncommon causes of severe, a progressive cognitive impairment that are fatal. Sporadic and familial cases have been described, but familial cases seem to be extremely rare. Sporadic cases are usually more severe compared to familial prion-related encephalopathies. Patients develop symptoms after a long period of incubation. The symptoms are mainly of global cognitive impairment, cerebellar signs, and neurodegeneration on MRI. There is no current treatment for prion-related encephalopathies.

Definition of Prion-Related Encephalopathy

Prion diseases include a large group of related neurodegenerative diseases that can affect both humans and animals. In humans, the most common forms of prion diseases include, but are not limited to, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease and, in animals, the bovine spongiform encephalopathy commonly known as Mad
Cow disease.

Prion diseases are characterized by **prolonged incubation periods** and are a **very fast progressive disease** once symptoms start.

**Epidemiology of Prion-Related Encephalopathy**

In man, the most common forms of prion-related encephalopathies include Creutzfeldt-Jakob Disease, Kuru (exclusive to Papua New Guinea), and Gerstmann-Straussler syndrome, with Creutzfeldt-Jakob Disease being the commonest. In animals, Bovine spongiform encephalopathy is the most prevailing form of encephalopathies. Other less common forms include Scrapie of sheep and goats and Transmissible mink encephalopathy.

The estimated incidence of CJD is at **1 case per million** in the United States. **Familial cases** of prion-related encephalopathies are much rarer compared to **sporadic cases** but have been described, especially with Gerstmann-Straussler-Scheinker disease. Familial cases are thought to be related to **mutations in the PRNP gene**.

![Image: “Tonsil biopsy in variant CJD. Prion protein immunostaining.” by Sbrandner – Own work. License: GFDL](image)

**Mortality**

Although prion-related encephalopathy is a rare condition in the general population, it is a devastating and incurable condition with a very high mortality rate. In one study, 153/159 patients diagnosed with CJD have died. The condition is more common among **Libyan-born Israelis** and in certain populations coming from **Slovakia**. The incidence in these specific populations is at least 60 times higher compared to the general population.

Prion-related encephalopathies are **very progressive** and ultimately **cause death**. The mean survival for patients with CJD is **8 months**. Familial cases are usually milder, but ultimately, by 60 months, all patients are dead. These conditions are more common among people in their sixties but have been diagnosed in young adults as well.
### Risk Factors

Sporadic cases are usually more severe compared to familial prion-related encephalopathies.

- For familial prion-related encephalopathies, the major risk factor is a family history of prion disease.
- Eating meat infected by “Mad Cow disease” in sporadic cases.
- Infection from receiving contaminated corneas or from contaminated medical equipment.

### Pathophysiology of Prion-Related Encephalopathy

All prion diseases affect the gray matter of the central nervous system. The hallmark pathologic features of prion encephalopathies are neuronal cell loss, gliosis, and spongiform changes. The amyloid deposition has also been reported in prion-related encephalopathies. These amyloid depositions are different from the typical beta-amyloid deposits in Alzheimer disease.

Prions are thought to be protein-only particles, but some hypothesize and might actually be nucleic acid-only particles; however, the most accepted theory is that they are protein-only particles. Prions invade the body through the skin or orally, and they then get entry to the central nervous system.

Once prions enter the body, they are thought to first reside and replicate in the peripheral lymphoid tissue such as the spleen. After a long period of incubation, the particles eventually invade the central nervous system.

Once inside the central nervous system, prions tend to be location-specific and start replicating within the central nervous system. Once symptoms start happening, neurodegeneration becomes pronounced and very rapid. Patients usually die within months from symptoms onset.

### Clinical Presentation of Prion-Related Encephalopathy

Common symptoms in prion-related encephalopathy include the following:

- Dementia
- Difficulty in mobility
- Hallucinations
- Tiredness
- Speech defect

Patients with CJD develop progressive dementia, myoclonic jerks, in addition to extrapyramidal signs. Cerebellar ataxia is also commonly associated with CJD. Electroencephalogram changes of CJD include slow-wave changes that are of very high amplitude. Sometimes, this picture is also complicated by low-voltage sharp waves.

**Family history** of CJD is evident in about 10% of the cases. Patients diagnosed with sporadic CJD are usually severely impaired cognitively within a few months of diagnosis and die within 8 months of diagnosis. Cerebellar dysfunction is reported in about 40%
The diagnosis of CJD can be classified as definite when neuropathology can be identified from **brain biopsy** and **protease-resistant PrP western blot** is positive. Patients with **progressive dementia, typical electroencephalogram picture** and two of the following: **myoclonus, visual impairment, cerebellar ataxia, extrapyramidal signs or mutism** have probable CJD.

Possible CJD is characterized by progressive dementia, atypical EEG findings, in addition to two of the previously mentioned signs for probable CJD. The duration of the symptoms should be less than 2 years because CJD patients **rarely survive for more than 2 years**. Physical examination reveals **global cognitive decline, ataxia, and cortical blindness**.

**Diagnostic Workup of Prion-Related Encephalopathy**

**Liver function tests, ammonia levels, and electrolytes** should be checked to exclude systemic and metabolic causes of cognitive impairment. Patients with a previous history of the malignant disease might have a **paraneoplastic syndrome**.

**Imaging studies** are important in the evaluation of these patients. **Magnetic resonance imaging** (MRI) shows **hyperintensities in the cortical ribbon, in the basal ganglia, and in the thalamus**. **Diffuse-weighted imaging** is very specific and sensitive for the diagnosis of CJD.

**Positron emission tomography** (PET) is useful in the evaluation of some patients. Areas of **focal glucose hypometabolism** have been found to coincide with the focal neuropathologic lesions at the time of autopsy.

**Electroencephalogram** is also useful in the diagnostic workup of patients with prion-related encephalopathies. Patients can have **slowed on the EEG**.

A **lumbar puncture** when performed can reveal **elevated protein in the cerebrospinal fluid** in some cases of CJD. The decision to perform a biopsy should be cautiously made because the majority of these diseases are not treatable anyway.
Treatment of Prion-Related Encephalopathies

The current treatment options for prion-related encephalopathies are highly dependent on symptomatic relief rather than curative treatment. The most important first step is to stop any drugs known to affect memory or to cause confusion.

Congo-red, anthracyclines, and amphotericin B are being experimentally studied as preventive treatments against prion-propagation. These drugs might delay the incubation period; hence, delaying the onset of the symptoms.

Unfortunately, the results are not always straightforward. Amphotericin B, for example, was found to be ineffective in one patient without any possible scientific explanation.

Acridine and phenothiazine have also shown efficacy against PrP. These drugs are already available as treatment options for malaria, psychiatric disorders, and epilepsy; therefore, the notion to use them for prions diseases is very easily acceptable by physicians because of our current understanding of their toxicity profile.

Recently, the idea of vaccination against prion-diseases was suggested. A-beta1-42 vaccination has been used in Alzheimer’s disease in a recent phase II clinical trial. Unfortunately, the results of these clinical trials are not very encouraging. Patients developed acute encephalitis as a complication to the vaccine; therefore, we currently have a gap between transitional research from animals to humans when it comes to immunological approaches for vaccination against these conditions.

References


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