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Creutzfeldt-Jakob disease as an Example of Prion Disease: IV. Understanding Creutzfeldt-Jakob disease

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Abstract

Creutzfeldt-Jakob disease is a rare, incurable, and always fatal neurodegenerative disease. It is a type of transmissible spongiform encephalopathy caused by prions. It belongs to a group of human and animal diseases known as prion disorders. A brief epidemiological review revealed that the intensity of CJD surveillance increases the number of reported cases, often in countries where CJD epidemics have occurred in the past and where surveillance resources are greatest. Such an increase in surveillance and reporting is most likely in response to bovine spongiform encephalopathy and variant CJD, clinician awareness, more accurate diagnostic methods, and possibly confusion with other neurological conditions such as stroke, acute nephropathy, general dementia, and hyperthyroidism. While there is no cure for CJD, symptoms can be managed with a few available drugs, as will be discussed. There is no known way to prevent the disease although a person having a family history of neurological disease may benefit from genetics counseling. The prognosis is rather bleak as life expectancy is greatly reduced for people with CJD with an average of less than 6 months.

Abbreviations

AD: Alzheimer's disease; ADD: Autosomal dominant disorder; ALP; Alien limb phenomenon; BSE: Bovine spongiform encephalopathy; CDC&P: (US) Center for Disease Control & Prevention; CJD: Creutzfeldt-Jakob disease; CNS: Central nervous system; CSF: Cerebrospinal fluid; CWD: Chronic wasting disease; DWI: Diffusion-weighted inversion; EEG: Electroencephalography; FFI: Fatal familial insomnia; FLAIR: Fluid-attenuated inversion recovery; GSSS: Gerstmann-Straussler-Scheinker syndrome; HGH: Human growth hormone; iCJD: iatrophic CJD; MCD: Mad cow disease; MRI: Magnetic resonance

imaging; NSE: Neuron-specific enolase; PPS: Pentosan polysulfate; PSWC: Periodic shape wave pattern; RT-QICA: Real-time quaking-induced conversion assay; sCJD: sporadic CJD; TSE: transmissible spongiform encephalopathy; UCSF: University of California, San Francisco; vCJD: variant CJD; VPSPr: Variable protease-sensitive prionopathy; WHO: World Health Organization.

Keywords

Creutzfeldt-Jakob disease; chronic wasting disease; fatal familial insomnia; prion diseases; prion-mimic diseases; real-time quaking-induced conversion assay; transmissible spongiform encephalopathy.

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Creutzfeldt-Jakob disease (CJD) is a rare, incurable, and always fatal neurodegenerative disease. It is a type of transmissible spongiform encephalopathy (TSE) caused by prions (Figure 1). It belongs to a group of human and animal diseases known as prion disorders. It received public attention in the 1990s when some people in the United Kingdom became sick with a form of the disease called variant CJD (vCJD) after eating meat from diseased cattle. However, most CJD cases have not been linked to such a cause. The name "Creutzfeldt–Jakob disease" was introduced by Walter Spielmeyer in 1922, after the German neurologists Hans Gerhard Creutzfeldt and Alfons Maria Jakob.

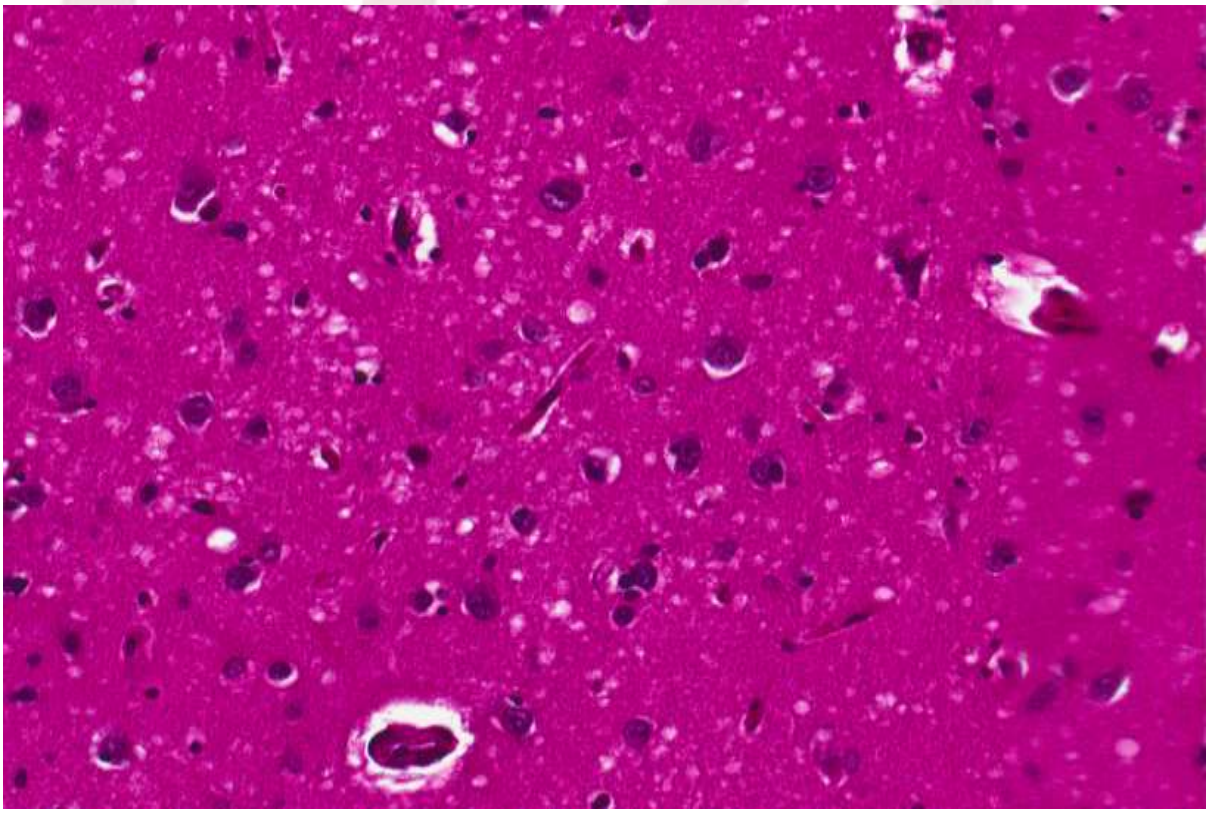


Figure 1: Brain spongiform change in CJD

After a brief review of the epidemiology of the disease, the classification of CJD, its signs and symptoms, risk factors, and etiology will all be presented. The most widely used biomarker tests will be analyzed for a meaningful differential diagnosis. All types of CJD are transmissible irrespective of how they occur in the person. While there is no cure for CJD, symptoms can be managed with a few available drugs, as will be discussed. There is no known way to prevent sCJD. A person having a family history of neurological disease may benefit from genetics counseling. The prognosis is rather bleak as life expectancy is greatly reduced for people with CJD with an average of less than 6 months.

Brief Epidemiology

The (U.S.) Center for Disease Control & Prevention (CDC) monitors the occurrence of CJD in the United States through periodic reviews of national mortality data. According to that institution:

• CJD occurs worldwide at roughly 1–1.5 cases per million people per year. Recent surveillance reports indicate a slight increase in recorded incidence in many countries over time. For example, a study made in 2020 noted that sporadic CJD incidence in the U.K. rose from 1990 to 2018. Several other countries also reported increases in CJD cases in the 2000s.
• Based on mortality surveillance from 1979 to 1994, the annual incidence of CJD remained stable at approximately 1 case per million people in the United States.
• The disease is found most frequently in people 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 one year (median: four months) after the onset of symptoms.

Further:

• The risk of developing CJD increases with age.
• CJD incidence was 3.5 cases per million among those over 50 years of age between 1979 and 2017.
• Approximately 85% of CJD cases are sporadic and 10–15% of CJD cases are due to inherited mutations of the prion protein gene.
• CJD deaths and age-adjusted death rate in the United States indicate an increasing trend in the number of deaths between 1979 and 2017.

Although not fully understood, additional information suggests that CJD rates in nonwhite groups are lower than in whites. While the mean onset is approximately 67 years of age, cases of sporadic CJD (sCJD) have been reported in people as young as 17 years and over 80 years of age. Mental capabilities rapidly deteriorate and the average amount of time from onset of symptoms to death is 7 to 9 months.

In addition, according to a 2020 systematic review on the international epidemiology of CJD:

• Surveillance studies from 2005 and later show the estimated global incidence is 1–2 cases per million population per year.
• sCJD incidence increased from the years 1990–2018 in the U.K.
• Probable or definite sCJD deaths also increased from the years 1996–2018 in twelve additional countries.
• CJD incidence is greatest in those over the age of 55 years old, with an average age of 67 years old.

The intensity of CJD surveillance increases the number of reported cases, often in countries where CJD epidemics have occurred in the past and where surveillance resources are greatest. An increase in surveillance and reporting of CJD is most likely in response to bovine spongiform encephalopathy (BSE) and variant CJD (vCJD). Possible factors contributing to an increase of CJD incidence are an aging population, population increase, clinician awareness, and more accurate diagnostic methods. Since CJD symptoms are like other neurological conditions, it is

also possible that CJD may be mistaken for stroke, acute nephropathy, general dementia, and hyperthyroidism.

Classification

There are four types of CJD, including:

Sporadic CJD

Sporadic CJD (sCJD) is caused by the spontaneous misfolding of prion protein in an individual. This accounts for 85% of cases of CJD. sCJD can be further sub-classified by molecular profile into subtypes (MM1, MV2, etc.), which correlate with certain clinical-pathologic features.

• MM1 / MV1 Subtype:

• Clinical features: Accounts for approximately 75% of sCJD cases. Characterized by rapidly progressive dementia, myoclonus, and typical EEG findings.

• Neuropathology: Synaptic-type PrPSc deposition predominantly in the cerebral cortex. Spongiform changes are widespread, with significant neuronal loss and gliosis.

• MM2 Subtype:

• MM2C (Cortical): Presents with a more prolonged disease course and prominent cortical involvement. Neuropathology reveals PrPSc deposits in the cortex with less spongiform change compared to MM1.

• MM2T (Thalamic): Rare; characterized by predominant thalamic involvement, leading to sleep disturbances and autonomic dysfunction. Neuropathology shows significant PrPSc deposition and neuronal loss in the thalamus.

• VV1 Subtype:

• Clinical features: Rare; presents at a younger age with a slower disease progression.

• Neuropathology: Predominant cortical involvement with synaptic-type PrPSc deposition.

• VV2 Subtype:

• Clinical features: Second most common subtype. Patients often present with ataxia and other cerebellar signs.

• Neuropathology: Significant PrPSc deposition in the cerebellum and basal ganglia, with prominent spongiform changes and neuronal loss.

While transmissible through tissue transplants, sCJD may not be transmitted through blood transfusion.

Familial CJD

Familial or genetic CJD (f/gCJD) is caused by an inherited mutation in the prion-protein gene. This accounts for the majority of the other 15% of cases of CJD.

Iatrogenic or acquired CJD

Iatrogenic or acquired CJD (i/aCJD) is caused by contamination with tissue from an infected person, usually as the result of a medical procedure. Medical procedures that are associated with the spread of this form of CJD include blood transfusion from the infected person, use of human-derived pituitary growth hormones, gonadotropin hormone therapy, and corneal and meningeal transplants.

Variant CJD

Variant CJD (vCJD) is a type of acquired CJD potentially acquired from bovine spongiform encephalopathy (BSE) or caused by consuming food contaminated with prions (Table 1).

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	oDementia o Early neurologic signs	o Prominent psychiatric/ behavioral symptoms o Painful dysesthesia o Delayed neurologic signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
Signal hyperintensity in the caudate nucleus and putamen on diffusion-weighted and FLAIR MRI	Often present	Often absent
Pulvinar sign-bilateral high signal intensities on axial FLAIR MRI. Also, posterior thalamic involvement on sagittal T2 sequences	Not reported	Present in > 75% of cases
Immunohistochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistant prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistant prion protein	Not reported	Marked accumulation of protease-resistant prion protein
Presence of amyloid plaques in brain tissue	May be present	May be present

Table 1: Clinical and pathologic characteristics of classic and variant CJD

In addition, Table 2 provides a comparison between three of the CJD types:

Feature	Sporadic CJD	Variant CJD	Familial CJD
Cause	Unknown (spontaneous)	Ingestion of BSE-infected meat	PRNP gene mutation
Onset age	60-70 years	Usually < 30 years	40-60 years
Duration	~ 4-6 months (very rapid)	12-14 months	~ 1-2 years
Initial symptoms	o Cognitive decline o Ataxia	Psychiatric: o Depression o Anxiety	Variable (like sCJD or insomnia
MRI findings	o Basal ganglia o Cortical ribboning	Pulvinar sign (posterior thalamus)	Like sCJD or normal early on
EEG	PSWCs common	Often normal	May be like sCJD
CSF 14-3-3/Tau	Frequently elevated	Often negative	May be variable
RT/QuIC	Usually, positive	Often negative or weakly positive	Variable
Genetic test (PRNP)	Normal	Normal	Positive mutation (e.g., 200K)
Neuropathology (if known)	Spongiform encephalopathy	o Florid plaques o Prion protein	Spongiform changes; sometimes plaques

Table 2: Comparison: Sporadic vs. Variant vs. Familial CJD

Recall that infectious prions are misfolded proteins that occur in the neurons of the central nervous system (CNS) and can cause normally folded proteins to also become misfolded. The CJD prion is dangerous because it promotes refolding of the cellular prion protein into the diseased state. The number of misfolded protein molecules will increase exponentially, and the process leads to a large quantity of insoluble proteins in affected cells. This mass of misfolded proteins disrupts neuronal cell function and causes cell death. Mutations in the gene for the prion protein can cause a misfolding of the dominantly alpha helical regions into beta pleated sheets. 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 induce other prion protein molecules to misfold in a self-sustaining feedback loop. These neurodegenerative diseases are commonly called prion diseases (see Fymat, 2025).

Other forms of transmissible spongiform encephalopathy (TSE) that are found in humans are Gerstmann-Straussler-Scheinker syndrome (GSSS), fatal familial insomnia (FFI), and kuru, as well as the variably protease-sensitive prionopathy. Susceptibility and disease phenotype are influenced by a common polymorphism at codon 129 of the PRNP gene (methionine/valine). Notably, individuals homozygous at codon 129 are over-represented in sporadic CJD cases and tend to have shorter incubation periods.

The duration of the disease varies greatly, but sporadic (non-inherited) CJD can be fatal within months or even weeks. Most affected people die six months after initial symptoms appear, often of pneumonia due to impaired coughing reflexes. About 15% of people with CJD survive for two or more years.

CJD has serious effects on the brain and body, progressing usually quickly. Over time, people with CJD withdraw from friends and family. They also lose the ability to care for themselves. Many slip into a coma and subsequent death.

Current research suggests that small, oligomeric aggregates of the prion protein PrP^Sc (rather than large fibrils) are the most neurotoxic species, interacting with cell surfaces to disrupt neuronal function. The binding of prion oligomers to normal prion proteins on neurons may trigger toxic signals similar to how oligomeric β-amyloid causes synaptic damage in Alzheimer's disease (AD). Different conformations of PrP^Sc (often termed prion "strains") are thought to cause the distinct subtypes of prion disease, explaining variations in clinical features and progression. They are thought to affect signaling processes, damaging neurons and resulting in degeneration that causes the spongiform appearance in the affected brain.

Signs and symptoms

The first symptom of CJD is usually rapidly progressive dementia leading to memory loss, personality changes, hallucinations, behavioral changes, poor coordination, visual disturbances, and auditory impairments. Other early symptoms include:

- Personality changes.
- Impaired thinking.
- Blurry vision or blindness.
- Insomnia.
- Problems with coordination.
- Trouble speaking.
- Trouble swallowing.
- Sudden, jerky movements.

Myoclonus (jerky movements) typically occurs in 90% of cases but may be absent at initial onset. Other frequently occurring features include anxiety, depression, paranoia, obsessive-compulsive symptoms, and psychosis.

This is accompanied by physical problems such as speech impairment, balance and coordination

dysfunction (ataxia), changes in gait, and rigid posture. In most people with CJD, these symptoms are accompanied by involuntary movements. Rarely, unusual symptoms like the alien limb phenomenon (ALP) have been observed. Although like those of Alzheimer's disease (AD), the above symptoms usually get worse much faster and lead to death.

Later symptoms include dementia, involuntary movements, blindness, deafness, weakness, and coma. Symptoms get worse quickly, usually within several weeks to a few months. About 70% of sufferers die within a year of diagnosis.

The symptoms of CJD are caused by the progressive death of the brain's nerve cells, which are associated with the build-up of abnormal prion proteins forming in the brain. When brain tissue from a person with CJD is examined under a microscope, many tiny holes can be seen where the nerve cells have died. Parts of the brain may resemble a sponge where the prions were infecting the areas of the brain.

In people with vCJD, changes in mental abilities may be more apparent in the beginning of the disease. In many cases, dementia develops later in the illness. Symptoms of dementia include the loss of the ability to think, reason, and remember.

Death usually occurs within a year. People with CJD usually die of medical issues associated with the disease. In addition to the above listed symptoms, conditions might include falls, heart issues, lung failure, pneumonia or other infections.

Another rare form of prion disease is called variable protease-sensitive prionopathy (VPSPr), which can mimic other forms of dementia. It causes changes in mental abilities and problems with speech and thinking. The course of the disease is longer than other prion diseases — about 24 months.

Risk factors

Most cases of CJD occur for unknown reasons so risk factors cannot be identified. However, a few factors seem to be associated with different kinds of CJD.

• **Age:** sCJD tends to develop later in life, usually around age 60; onset of fCJD occurs slightly earlier; and vCJD has affected people at a much younger age, usually in their late 20s.
• **Genetics:** People with fCJD have genetic changes that cause the disease. To develop this form of the disease, a child must have one copy of the gene that causes CJD. The gene can be passed down from either parent. If one has the gene, the chance of passing it on to one's children is 50% (see Figure 3).
• **Exposure to contaminated tissue:** People who have received infected human growth hormone (HGH) may be at risk of iCJD. Receiving a transplant of tissue that covers the brain (the dura mater) from someone with CJD also can put a person at risk of iCJD.

Nowadays, the risk of getting vCJD from eating contaminated beef is very low. In countries that have implemented effective public health measures, the risk is virtually nonexistent. Chronic wasting disease (CWD) is a prion disease that affects deer, elk, reindeer and moose. It has been found in some areas of North America. To date, no documented cases of CWD have caused disease in humans.

Etiology

CJD and related conditions appear to be caused by changes to a type of protein called a prion. Prions are proteins that occur naturally in the brains of animals and people. Normally, the proteins are harmless but, when misshapen, they can cause devastating illnesses such as disease in cattle and CJD in humans. These proteins are typically produced in the body. But when they encounter infectious prions, they fold and assume

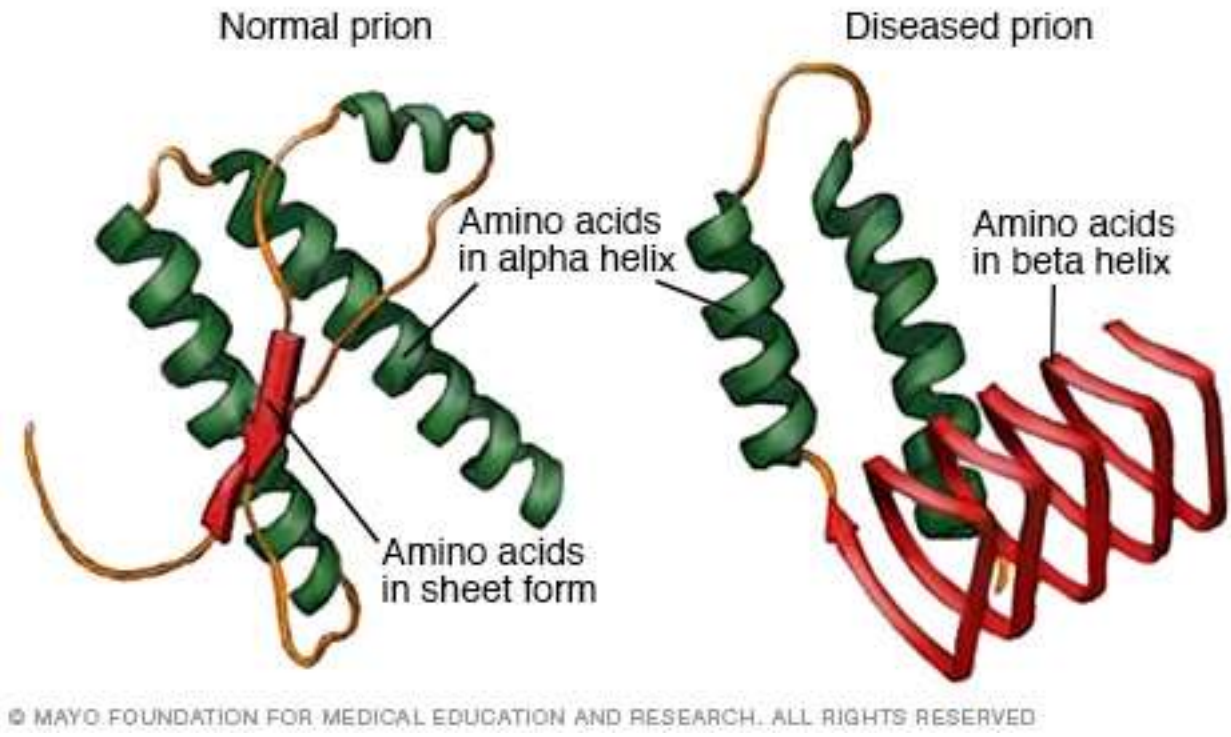
another atypical shape. They can spread and affect processes in the body (Figure 2).

How CJD develops

The risk of getting CJD is low. The disease cannot be spread through coughing or sneezing. It also cannot be spread by touching or sexual contact. It can develop in only three ways:

• **Sporadically:** Most people with CJD develop the disease for no apparent reason. This type, called spontaneous or sporadic CJD (sCJD), accounts for most cases.

• **By inheritance:** Fewer than 15% of people with CJD have a family history. They may test positive for genetic changes associated with the disease. This type is referred to as familial CJD (fCJD). Changes in a gene called PRNP that makes the prion protein cause the genetic forms of the disease. Rare genetic forms also include Gerstmann-Straussler-Scheinker (GSS) syndrome, causing problems with movement and cognition. It often affects people in their 40s. Another rare genetic form includes fatal familial insomnia (FFI), which causes an inability to sleep and changes in memory and thinking.



Reference: Mayo Foundation for Medical Education & Research

Figure 2: Shapes of normal and diseased prions

• **By contamination:** This type is referred to as iatrogenic or acquired CJD (i/aCJD. A small number of people have developed i/vCJD from eating contaminated cattle infected with mad cow disease (MCD) also known as bovine spongiform encephalopathy (BSE). Others have developed the disease because of medical procedures. These procedures included injections of pituitary human growth hormone (HGH) from an infected source. They also include cornea and skin transplants from people who had CJD. Medical centers have changed their procedures to eliminate these risks. Also, a few people have developed CJD after brain surgery with contaminated instruments. This happened because standard cleaning methods do not destroy the prions that cause the disease. Today, instruments that may have been contaminated with CJD are destroyed (see the Sidebar).

Autosomal dominant inheritance pattern

In an autosomal dominant disorder (ADD), the changed gene, also called a mutation, is a dominant gene. It is located on one of the non-sex chromosomes, called autosomes. Individuals need only one changed gene to be affected by this type of disorder. A person with an ADD – the father in the case of Figure 3 — has a 50% chance of having an affected child with one changed gene. The person has a 50% chance of having an unaffected child.

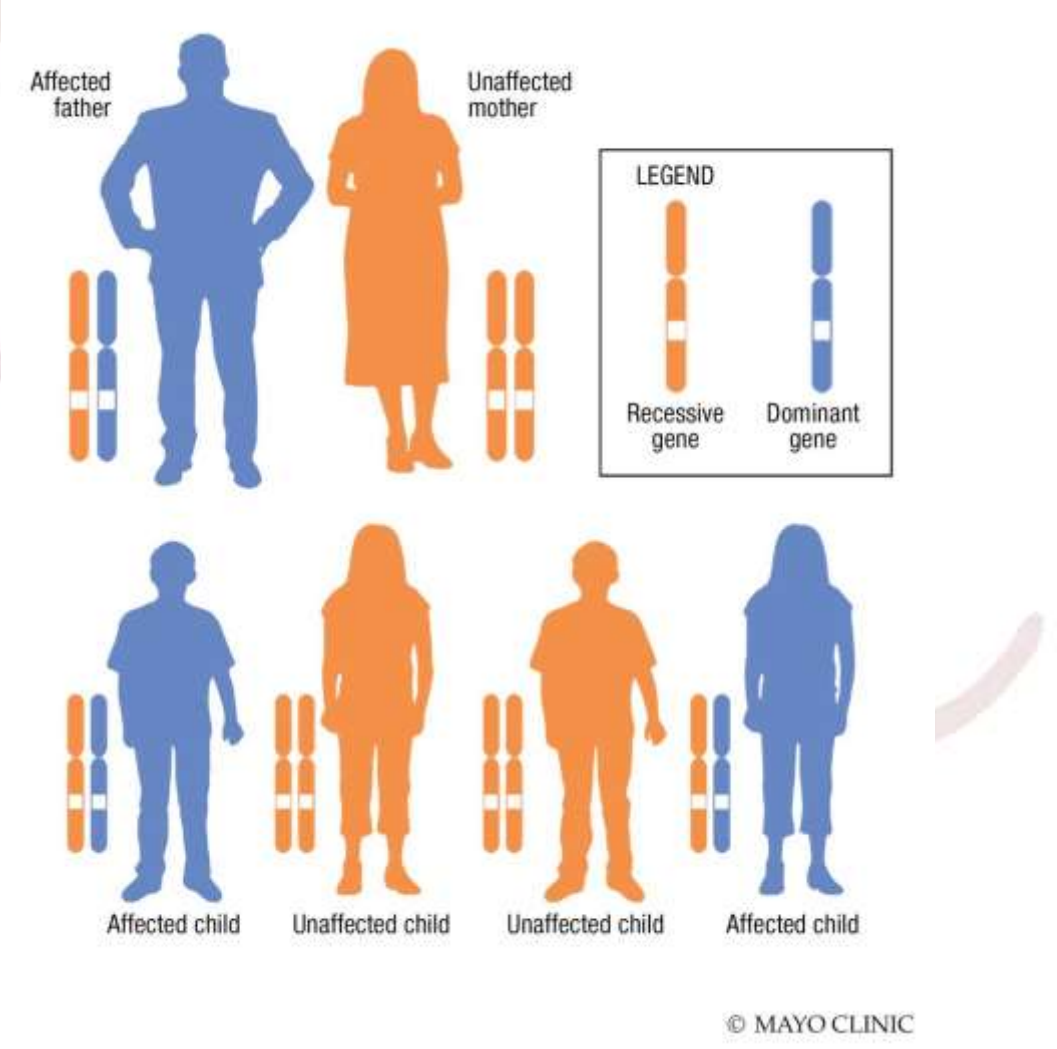


Figure 3: Autosomal dominant inheritance pattern

Testing

Testing for CJD has historically been problematic due to the nonspecific nature of early symptoms and the difficulty in safely obtaining brain tissue for confirmation. Table 3 describes the most widely used biomarkers in CSF tests:

Test	Description	Diagnostic value
Real-time quaking-induced conversion RT-QuIC	Detects misfolded prion proteins	o Most specific and sensitive (>90%) o Now considered the **gold standard *antemortem* test**, especially when combined with suggestive MRI
14-3-3 protein	Marker of neuronal damage	o Sensitive but not specific o Elevated in other encephalopathies, too
Total tau protein	Elevated in neurodegeneration	Often >1,000 pg/mL in CJD
Neurofilament light chain (NfL)	Emerging biomarker of neuronal damage	Non-specific but high in CJD

Further testing can support the diagnosis and may include the following seven approaches in addition to clinical evaluation:

Table 3: Most widely used biomarkers in CSF tests

Clinical evaluation

Key symptoms are rapidly progressive dementia, myoclonus (sudden muscle jerks), visual disturbances or cerebellar signs (e.g., ataxia), pyramidal/extrapyramidal signs (e.g., rigidity), and akinetic mutism (late-stage).

Disease progression is typically rapid with death occurring within 6–12 months in sporadic CJD (sCJD).

Cerebrospinal fluid analysis

Cerebrospinal fluid (CSF) analysis for elevated levels of 14-3-3 protein and tau protein could be supportive in the diagnosis of sCJD – the two proteins being released into the CSF by damaged nerve cells. Increased levels of tau or 14-3-3 proteins are seen in 90% of prion diseases. They may also be elevated in the CSF after ischemic strokes, inflammatory brain diseases, or seizures.

The markers have a specificity of 95% in clinical symptoms suggestive of CJD, but specificity is 70% in other less characteristic cases. They are also less specific in early CJD, genetic CJD, or the bovine variant. However, a positive result should not be regarded as sufficient for the diagnosis.

The real-time quaking-induced conversion (RT-QuIC) assay, which amplifies misfolded PrPSc, now plays a central role in CJD diagnosis. Second-generation RT-QuIC on CSF has sensitivity in the 90–97% range and ~100% specificity in sporadic CJD, which is far superior to earlier CSF tests. A positive RT-QuIC (on CSF or other tissues) is now included as a criterion for probable CJD in many national surveillance centers.

Studies have shown that RT-QuIC can also be done on olfactory mucosa swabs obtained via nasal brushing and on skin biopsies with high diagnostic accuracy (reported sensitivities ~90–100%).

Electroencephalography

Electroencephalography (EEG) may have a

characteristic generalized periodic shape wave pattern (PSWC) in ~ 60-80% of sCJD cases, particularly in the later stages. EEG is not very specific but is useful in the right context (typically in later stages).

Genetic testing

Genetic testing (PRNP gene) is used to diagnose familial CJD, especially if: there is a family history, early onset (<55 years), atypical presentation, or common mutation (E200K, but others include D178N, V210I, etc.).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) with diffusion weighted inversion (MRI-DWI) and fluid-attenuated inversion recovery (FLAIR) scans shows a high signal intensity in certain parts of the cortex (a cortical ribboning appearance), the basal ganglia, and the thalami.

The most common presenting patterns are simultaneous involvement of the cortex and striatum (60% of cases), cortical involvement without the striatum (30%), thalamus (21%), cerebellum (8%), and striatum without cortical involvement (7%).

In populations with rapidly progressive dementia (early in the disease process), MRI has a sensitivity of 91% and specificity of 97% for diagnosing CJD. The MRI changes characteristic of CJD may also be seen in the immediate aftermath (hours after the event) of autoimmune encephalitis or focal seizures.

Tumor marker neuron-specific enolase

In recent years, studies have shown that tumor marker neuron-specific enolase (NSE) is often elevated in CJD cases. However, its diagnostic utility is seen primarily when combined with a test for the 14-3-3 protein.

As of 2010, screening tests to identify infected asymptomatic individuals, such as blood donors, are not yet available, though methods have been proposed and evaluated.

Olfactory mucosa RT-QuIC

Olfactory mucosa RT-QuIC (nasal brushing) is a minimally invasive method to detect prion proteins. It is comparable to CSF RT-QuIC in some studies. Although not yet widespread, it is under clinical evaluation.

Brain biopsy or autopsy

Brain biopsy or autopsy is the only way to definitively confirm CJD. Biopsy is rarely done unless to rule out treatable causes. The risk of contamination (due to prion transmissibility) makes it a last resort.

Table 4 summarizes the various modality employed, their usefulness, and their sensitivity/specificity:

Modality	Usefulness	Sensitivity/specificity
RT-QuIC (CSF)	Gold standard prion detection	~90–95% / ~98%
EEG	Periodic sharp waves	~65% / ~80%
CSF 14-3-3, Tau	Supportive only	Variable
Genetic Testing	Required for inherited CJD	N/A (based on mutation)
MRI (DWI/FLAIR)	Visual signature of CJD	~85% / ~90%
Brain Biopsy	Definitive, rarely done	100% if positive

Table 4: CJD testing modalities, usefulness, and sensitivity/specificity

Further on brain imaging

Imaging of the brain may be performed during medical evaluation, both to rule out other causes and to obtain supportive evidence for diagnosis. Imaging findings are variable in their appearance, sensitivity, and specificity. While imaging plays a lesser role in the diagnosis of CJD, characteristic findings on brain MRI in some cases may precede the onset of clinical manifestations. Most useful sequences are DWI and FLAIR.

Typical findings include hyperintensity in basal ganglia (caudate, putamen), cortical ribboning (especially in parietal/occipital lobes), and symmetry is common but not always present. MRI has a sensitivity of ~85% and specificity of ~90% for CJD.

Brain MRI

Brain MRI is the most useful imaging modality for changes related to CJD. Of the MRI sequences, DWI sequences are most sensitive. Characteristic findings are as follows:

• **Focal or diffuse diffusion-restriction involving the cerebral cortex or basal ganglia:** The most characteristic and striking cortical abnormality has been called "cortical ribboning" or "cortical ribbon sign" due to hyperintensities resembling ribbons appearing in the cortex on MRI. The involvement of the thalamus that can be found in sCJD is even stronger and constant in vCJD (Figure 4).

• Varying degree of symmetric T2 hyperintense signal changes in the basal ganglia (i.e., caudate and putamen), and to a lesser extent globus pallidus and occipital cortex.

Brain FDG PET-CT

Brain FDG PET-CT tends to be markedly abnormal and is increasingly used in the investigation of dementias. Patients with CJD will normally have hypometabolism on FDG PET.

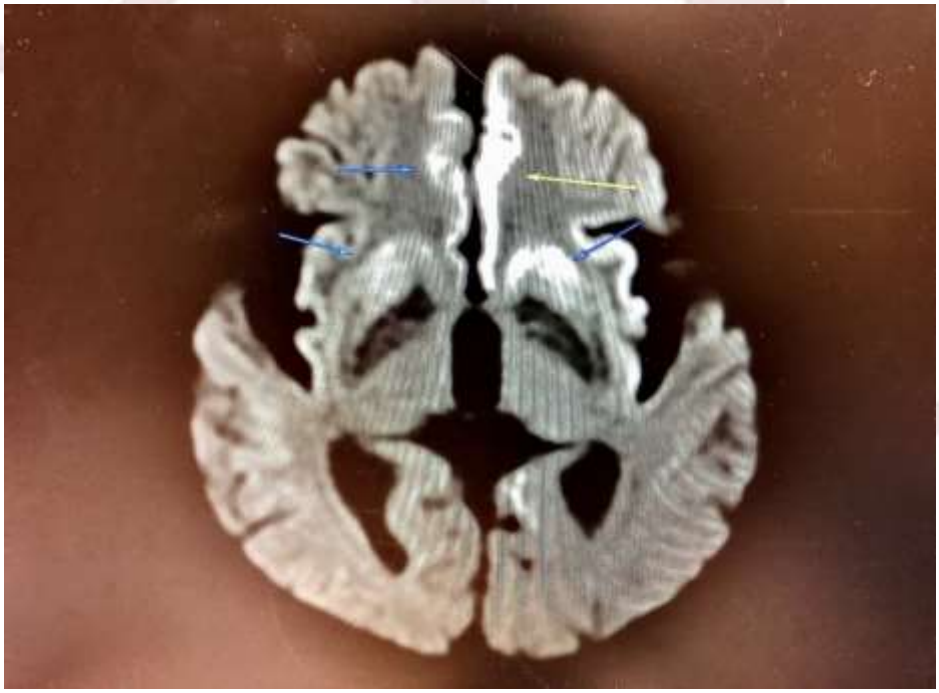


Figure 4: Brain MRI image showing the obvious precipitation of prion protein

Histopathology

Testing of tissue remains the most definitive way of confirming the diagnosis of CJD, although even biopsy is not always conclusive.

In one-third of people with sporadic CJD, deposits of "prion protein (scrapie)", PrPSc, can be found in the skeletal muscle or the spleen. Diagnosis of vCJD can be supported by biopsy of the tonsils, which harbor significant amounts of PrPSc; however, biopsy of brain tissue is the definitive diagnostic test for all other forms of prion disease. Due to its invasiveness, biopsy will not be done if clinical suspicion is sufficiently high or low. A negative biopsy does not rule out CJD, since it may predominate in a specific part of the brain.

The classic histologic appearance is spongiform change in the gray matter; the presence of many round vacuoles from one to 50 micrometers in the neuropil, in all six cortical layers in the cerebral cortex or with diffuse involvement of the cerebellar molecular layer. These vacuoles appear glassy or eosinophilic and may coalesce. Neuronal loss and gliosis are also seen. Plaques of amyloid-like material can be seen in the neocortex in some cases of CJD (Figure 4).

However, extra-neuronal vacuolization can also be seen in other disease states. Diffuse cortical vacuolization occurs in Alzheimer's disease, and superficial cortical vacuolization occurs in ischemia and frontotemporal dementia. These vacuoles appear clear and punched out. Larger vacuoles encircling neurons, vessels, and glia are a possible processing artifact.

Differential diagnosis

The diagnosis may initially be suspected in a person with rapidly progressing dementia, particularly when it is also found with characteristic medical signs and symptoms such as involuntary muscle jerking, difficulty with coordination/balance and walking, and visual disturbances.

Diagnosis involves ruling out other potential causes. An electroencephalogram, spinal tap, or magnetic resonance imaging scan may support the diagnosis. Another diagnostic technique is the real-time quaking-induced conversion assay (QICA) which can detect the disease in early stages.

Because of the progressive neurologic decline, the range of neurologic signs, and the heterogeneous presentation of genetic prion disease, the differential diagnosis is broad and needs to include other hereditary neurodegenerative disorders as well as a variety of acquired disorders. Because potential treatment options depend on identification of the underlying cause, autoimmune and paraneoplastic disorders need to be considered (see Tables 3 and 4).

According to the World Health Organization (WHO) and the (U.S.) Centers for Disease Control & Prevention (CDC&P)/ University of California at San Francisco (UCSF), the diagnosis of probable sporadic CJD requires:

• Rapidly progressive dementia.
• At least two of the following: myoclonus, visual/cerebellar symptoms, pyramidal/ extrapyramidal signs, akinetic mutism
• Plus, one of the following:

O Positive RT-QuIC.
O MRI findings suggestive of CJD.
O EEG with PSWC.
O Elevated 14-3-3 (supportive).

Transmission

The defective protein can be transmitted by

contaminated harvested human brain products, corneal grafts, dural grafts, or electrode implants and pituitary HGH, which has been replaced by recombinant HGH that poses no such risk.

It can be familial (fCJD) or it may appear without clear risk factors (sCJD). In the familial form, a mutation has occurred in the gene for PrP, PRNP, in that family. All types of CJD are transmissible irrespective of how they occur in the person.

It is thought that humans can contract the variant form of the disease by eating food from animals infected with BSE, the bovine form of TSE, also known as mad cow disease (MCD). However, it can also cause sCJD in some cases.

Cannibalism has also been implicated as a transmission mechanism for abnormal prions, causing the disease known as kuru, once found primarily among women and children of the Fore people of Papua, New Guinea, who previously engaged in funerary cannibalism. While the men of the tribe ate the muscle tissue of the deceased, women and children consumed other parts, such as the brain, and were more likely than men to contract kuru from infected tissue.

As indicated in the Sidebar, prions may not be inactivated by means of routine surgical instrument sterilization procedures. The WHO and the CDC&P recommend that instrumentation used in such cases be immediately destroyed after use. Short of destruction, it is recommended that heat and chemical decontamination be used in combination to process instruments that come in contact with high-infectivity tissues. Thermal depolymerization also destroys prions in infected organic and inorganic matter, since the process chemically attacks protein at the molecular level, although more effective and practical methods involve destruction by combinations of detergents and enzymes like biological washing powders.

Symptoms management

There is no specific treatment for CJD. Opioids may be used to help with pain, while Clonazepam or *Sodium valporate* may help with involuntary movements. Some of the symptoms like twitching can be managed, but otherwise treatment is palliative care.

Treatment of manifestations

Supportive care by a multidisciplinary team of specialists including neurologists, psychiatrists, physical therapists, occupational therapists, speech and language therapists, and social workers is recommended.

Because of very rapid disease progression, close periodic monitoring by the multidisciplinary team is needed, typically every 14 days to evaluate the needs for symptomatic treatment. Available treatments are summarized in Table 5:

Drug	Claimed benefit(s)	Notes
Pentosane polysulfate (PPS)	o Slows disease progression o Contributes to longer than expected survival	o Data not sufficient to justify the claims o No proof of efficacy o Lack of significant benefits perhaps due to late administration of the drug
RNA interference	o Blocks production of the prion protein	
Amphotericin B	o Slows the disease	o No evidence of drug efficacity
Doxorubicin	o Slows the disease	o No evidence of drug efficacity

Sodium valproate and Clonazepam	o To relieve symptoms o Against myoclonic jerks	
Benzodiazepine	o To relieve symptoms	
Quinacrine		o No measurable effect on the clinical course
Astemizole	o Has anti-prion activity o May lead to a treatment for CJD	
Monoclonal antibody PRN100	o Accessed the brain to help clear PrP^C o Encouraging results for a larger study o Demonstrated application of immunotherapy against prion diseases.	o No survival longer than anticipated
Sedatives and anti-depressants	o For psychiatric symptoms like anxiety and depression	
Opiates	o Can help pain	
Epileptic drugs	o Against uncommon seizures	

Table 5: Available treatments for CJD

- **Pentosan polysulfate:** Pentosan polysulfate (PPS) may slow the progression of the disease and may have contributed to the longer than expected survival of the seven people studied. The CJD Therapy Advisory Group (CTAG) of the U.K. Health Department advises that data are not sufficient to support claims that PPS is an effective treatment and suggests that further research in animal models is appropriate. A 2007 review of the treatment of 26 people with PPS found no proof of efficacy because of the lack of accepted objective criteria, but it was unclear to the authors whether that was caused by PPS itself. In 2012 it was claimed that the lack of significant benefits has likely been caused because of the drug being administered very late in the disease in many patients.
- **RNA interference:** Use of RNA interference to slow the progression of scrapie has been studied in mice. The RNA blocks production of the protein that the CJD process transforms into prions.
- **Amphotericin B:** Amphotericin B has been investigated as treatment for CJD, but as yet there is no strong evidence that this drug is effective in stopping the disease.
- **Doxorubicin:** Doxorubicin has also been investigated for treating CJD, but there is no evidence for its efficacity.
- **Sodium valproate:** This anticonvulsant may be administered to relieve symptoms.
- **Benzodiazepine:** This anxiolytic agent may also be administered to relieve symptoms.
- **Quinacrine:** Quinacrine, a medicine originally created for malaria, has been evaluated as a treatment for CJD. Its efficacy was assessed in a rigorous clinical trial in the U.K., and the results were published in Lancet Neurology. The study concluded that Quinacrine had no measurable effect on the clinical course of CJD.
- **Astemizole:** Astemizole, a medication approved for human use, has been found to have anti-prion activity and may lead to a treatment for CJD.
- **Monoclonal antibody PRN100:** A monoclonal antibody (code name PRN100) targeting the prion protein (PrP) was given to

six people with CJD in an early-stage clinical trial conducted from 2018 to 2022. The treatment appeared to be well-tolerated and was able to access the brain, where it might have helped to clear PrPC. While the treated patients still showed progressive neurological decline, and while none of them survived longer than expected from the normal course of the disease, the scientists at University College, who conducted the study see these early-stage results as encouraging and suggest conducting a larger study, ideally at the earliest possible intervention.

- **Sedatives and antidepressants:** Psychiatric symptoms like anxiety and depression can be treated with sedatives and antidepressants.
- **Anti-epileptic drugs:** Seizures are very uncommon but can nevertheless be treated with anti-epileptic drugs.

Prevention

There is no known way to prevent sCJD. A person having a family history of neurological disease may benefit from genetics counseling. A counselor can help sort through the risks.

Preventing variant CJD

The risk of getting vCJD in the U.S. remains very low where only four cases have been reported. According to the U.S. Centers for Disease Control & Prevention (CDC&P), strong evidence suggests that these cases were acquired in other countries outside of the U.S.

In the United Kingdom (U.K.), where the majority of vCJD cases have occurred, fewer than 200 cases have been reported. CJD incidence peaked in the U.K. between 1999 and 2000 and has been declining ever since. A very small number of other vCJD cases have also been reported in other countries worldwide.

To date, there is no evidence that people can develop CJD from consuming the meat of animals infected with chronic wasting disease (CWD). However, the CDC&P recommends that hunters strongly consider taking precautions; it recommends having deer and elk tested before eating the meat in areas where CWD is known to be present. Hunters also should avoid shooting or handling meat from deer or elk that appear sick or are found dead.

Regulating potential sources of vCJD

Most countries have taken steps to prevent meat infected with BSE from entering the food supply. Steps include:

• Tight restrictions on importing cattle from countries where BSE is common.
• Restrictions on animal feed.
• Strict procedures for dealing with sick animals.
• Surveillance and testing methods for tracking cattle health.
• Restrictions on which parts of cattle can be processed for food.

Preventing CJD related to medical procedures

Hospitals and other medical institutions follow clear policies to prevent CJD related to medical procedures. These measures have included:

• Using only human-made HGH. This is used instead of taking the hormone from human pituitary glands.
• Destroying surgical instruments that may have been exposed to CJD. This includes instruments used in procedures that involve the brain or nervous tissue of someone with known or suspected CJD.
• Single-use kits for spinal taps (also known as lumbar punctures).

To help ensure the safety of the blood supply, people with a risk of exposure to CJD or vCJD are not eligible

to donate blood in the U.S. This includes people who:

• Have a blood relative who has been diagnosed with fCJD. Blood relatives include parents, aunts, uncles, grandparents, and cousins.
• Have received a dura mater brain graft. (Dura mater is the tissue that covers the brain.)
• Have received HGH from cadavers.

The U.K. and certain other countries also have specific restrictions regarding blood donations from people with a risk of exposure to CJD or vCJD.

Prognosis

Life expectancy is greatly reduced for people with CJD and the average is less than 6 months. As of 1981, no one was known to have lived longer than 2.5 years after the onset of CJD symptoms. One of the world's longest survivors of vCJD was Jonathan Simms, a Northern Irish man who lived for 10 years after his diagnosis and received experimental treatment with Pentosan polysulphate (he died in 2011).

Conclusions and take-aways

- Creutzfeldt-Jakob disease (CJD) is a rare brain disorder that leads to dementia. In many cases, dementia develops later in the illness. Symptoms of dementia include the loss of the ability to think, reason and remember.

- CJD belongs to a group of human and animal diseases known as prion disorders.

- The epidemiology of the disease was reviewed. It must be noted that the intensity of CJD surveillance increases the number of reported cases, often in countries where CJD epidemics have occurred in the past and where surveillance resources are greatest.

- All types of CJD are serious but are very rare. The disease most often affects older adults. Variant CJD affects people at a younger age than CJD; it appears to last 12 to 14 months.

- Symptoms get worse quickly, usually within several weeks to a few months. Early symptoms include: Personality changes; memory loss; impaired thinking; blurry vision or blindness; insomnia; problems with coordination; trouble speaking; trouble swallowing; and sudden, jerky movements. Other conditions might include falls, heart issues, lung failure, pneumonia or other infections.

- Another rare form of prion disease is called variably protease-sensitive prionopathy, which can mimic other forms of dementia. It causes changes in mental abilities and problems with speech and thinking.

- CJD and related conditions appear to be caused by changes to a type of protein called a prion - proteins are typically produced in the body. But when they encounter infectious prions, they fold and become another atypical shape. They can spread and affect processes in the body.

- The risk of getting CJD is low. The disease cannot be spread through coughing or sneezing, touching or sexual contact. It can develop in only three ways: Sporadically, by inheritance, or by contamination. Rare genetic forms also include Gerstmann-Straussler-Scheinker, and fatal familial insomnia. A small number of people have developed variant CJD from eating contaminated beef from cattle infected with mad cow disease also known as

bovine spongiform encephalopathy.

- Testing for CJD has historically been problematic, due to the nonspecific nature of early symptoms and the difficulty in safely obtaining brain tissue for confirmation.

- The diagnosis may initially be suspected in a person with rapidly progressing dementia, particularly when it is also found with the characteristic medical signs and symptoms. Further testing can support the diagnosis and may include: Electroencephalography, cerebrospinal fluid analysis, and magnetic resonance imaging with diffusion weighted inversion, fluid-attenuated inversion recovery, and tumor marker neuron-specific enolase.

- Imaging of the brain may be performed during medical evaluation, both to rule out other causes and to obtain supportive evidence for diagnosis. Brain MRI is the most useful imaging modality for changes related to CJD. Brain FDG PET-CT tends to be markedly abnormal and is increasingly used in the investigation of dementias. Patients with CJD will normally have hypometabolism on FDG PET.

- Histopathology remains the most definitive way of confirming the diagnosis of CJD, although even biopsy is not always conclusive.

- Because of the progressive neurologic decline, the range of neurologic signs, and the heterogeneous presentation of genetic prion disease, the differential diagnosis is broad and needs to include other hereditary neurodegenerative disorders as well as a variety of acquired disorders.

- Types of CJD include: Sporadic CJD which is caused by the spontaneous misfolding of prion-protein in an individual and accounts for 85% of cases of CJD; familial CJD which is caused by an inherited mutation in the prion-protein gene and accounts for the majority of the other 15% of cases of CJD; iatrogenic or acquired CJD which is caused by contamination with tissue from an infected person, usually as the result of a medical procedure; and variant CJD which is a type of acquired CJD potentially acquired from bovine spongiform encephalopathy or caused by consuming food contaminated with prions.

- No treatment of the underlying cause of genetic prion disease is available. Supportive care by a multidisciplinary team of specialists including neurologists, psychiatrists, physical therapists, occupational therapists, speech and language therapists, and social workers is recommended.

- Because of very rapid disease progression, close periodic monitoring by the multidisciplinary team is needed.

- Available treatments have been summarized and tabulated.

- There is no known way to prevent the sporadic form of CJD. A person having a family history of neurological disease may benefit from genetics counseling. To prevent variant CJD, the (U.S.) Center for Disease Control & Prevention recommends regulating potential sources of the disease, including in medical procedures.

The Sidebar will summarize the sterilization methods recommended by the WHO.

Sidebar – WHO-recommended sterilization methods

Infectious particles possessing nucleic acid are dependent upon it to direct their continued replication. Prions, however, are infectious by their effect on normal versions of the protein. Sterilizing prions, therefore, requires the denaturation of the protein to a state in which the molecule is no longer able to induce the abnormal folding of normal proteins.

In general, prions are quite resistant to proteases, heat, ionizing radiation, and formaldehyde treatments although their infectivity can be reduced by such treatments. Effective prion decontamination relies upon protein hydrolysis or reduction or destruction of protein tertiary structure. Examples include sodium hypochlorite, sodium hydroxide, and strongly acidic detergents such as LpH.

The World Health Organization (WHO) recommends any of the following three procedures for the sterilization of all heat-resistant surgical instruments to ensure that they are not contaminated with prions:

1. Immerse in 1N sodium hydroxide and place in a gravity-displacement autoclave at 121 °C for 30 minutes; clean; rinse in water; and then perform routine sterilization processes.

2. Immerse in 1N sodium hypochlorite (20,000 parts per million available chlorine) for 1 hour; transfer instruments to water; heat in a gravity-displacement autoclave at 121 °C for 1 hour; clean; and then perform routine sterilization processes.

3. Immerse in 1N sodium hydroxide or sodium hypochlorite (20,000 parts per million available chlorine) for 1 hour; remove and rinse in water, then transfer to an open pan and heat in a gravity-displacement (121 °C) or in a porous-load (134 °C) autoclave for 1 hour; clean; and then perform routine sterilization processes. [134 °C (273 °F) for 18 minutes in a pressurized steam autoclave has been found to be somewhat effective in deactivating the agent of disease.]

Ozone sterilization has been studied as a potential method for prion denaturation and deactivation. Other approaches being developed include: thiourea-urea treatment; guanidinium chloride treatment; and special heat-resistant subtilisin combined with heat and detergent. A number of decontamination reagents have been commercially manufactured with significant differences in efficacy among methods. A method sufficient for sterilizing prions on one material may fail on another.

Renaturation of a completely denatured prion to infectious status has not yet been achieved; however, partially denatured prions can be renatured to an infective status under certain artificial conditions.

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