Prion Diseases

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Abstract

Prion diseases are a group of diseases caused by abnormally conformed infectious proteins, called prions. They can be sporadic (Jakob-Creutzfeldt disease [JCD]), genetic (genetic JCD, Gerstmann-Sträussler-Scheinker, and familial fatal insomnia), or acquired (kuru, variant JCD, and iatrogenic JCD). The clinical features associated with each form of prion disease, the neuroimaging findings, cerebrospinal fluid markers, and neuropathological findings are reviewed. Sporadic JCD is the most common form of human prion disease, and will be discussed in detail. Genetic prion diseases are caused by mutations in the prion-related protein gene (*PRNP*), and they are classified based on the mutation, clinical phenotype, and neuropathological features. Acquired prion diseases fortunately are becoming rarer, as awareness of transmission risk has led to implementation of measures to prevent such occurrences, but continued surveillance is necessary to prevent future cases. Treatment and management issues are also discussed.

Keywords
- prion diseases
- Creutzfeldt-Jakob disease
- Gerstmann-Sträussler-Scheinker disease
- familial fatal insomnia
- rapidly progressive dementia

Prion diseases (PrDs) are a group of neurodegenerative disorders caused by infectious proteins called prions. PrDs occur in many species (such as scrapie in sheep and goats, and bovine spongiform encephalopathy in cattle),[1] but this review will focus on the human forms, most of which are identified by the eponym, Jakob-Creutzfeldt disease (JCD). In this review, the term Jakob-Creutzfeldt is used instead of Creutzfeldt-Jakob, as Creutzfeldt's case did not have what is now considered prion disease, whereas at least two of Jakob's cases did have prion disease.[2]

Human PrDs are classified into three groups: sporadic (85–90%), genetic (10–15%), and acquired (1–3%).[3,4] The sporadic form is called sporadic JCD (sJCD). The genetic forms are subdivided into genetic JCD (gJCD), Gerstmann-Sträussler-Scheinker disease (GSS), and familial fatal insomnia (FFI). The acquired forms include Kuru, iatrogenic JCD (iJCD), and variant JCD (vJCD) disease.

The incidence of sJCD is $\sim$ 1 to 1.5 per million per year.[4,5] The peak age of onset of sJCD occurs around a unimodal relatively narrow peak of $\sim$ 68 years,[6] with an age of onset range of 12 to 98 years (unpublished personal communication).[7,8] Jakob-Creutzfeldt disease is rare in individuals younger than 30 years, and most of those cases are either acquired or genetic.[5,9] There is no gender predilection in sJCD, although there might be a female preponderance, possibly due to survival bias.[5] In the United States, an incidence 2.5 times higher in Caucasians compared to African Americans was found,[5] but other interethnic comparison data are still lacking.

Pathophysiology

PrDs are caused by the propagation of abnormally conformed infectious proteins, prions (also named PrP^{Sc}, in which the superscript Sc comes from scrapie). The normal cellular prion-related protein (PrP^{C}, in which the superscript C stands for the normal cellular form) is a membrane-bound protein that is predominantly expressed in nervous tissue. Although its physiologic function is not entirely known, it probably plays a role in neuronal development and function.[10] Prion infectivity occurs through a mechanism in which the pathogenic PrP^{Sc} act as a template to convert PrP^{C} into PrP^{Sc}.[1,11] So when PrP^{Sc}, which has mostly β-pleated sheet structure, comes in contact with PrP^{C}, which has mostly α-helical

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structure, PrP^C is misfolded into pathogenic PrP^{Sc}. This new PrP^{Sc} then becomes a template for conversion of existing PrP^C, initiating an exponential, cascade reaction, that leads to neuronal injury and death.[1]

PrDs are unique, as they can occur as sporadic, genetic, and infectious diseases.[1] Though the initial pathogenic step is not clear, sporadic PrD is thought to occur by spontaneous folding of PrP^C into PrP^{Sc} (or maybe through a somatic mutation in the PRNP gene).[1,12] In genetic PrDs, it is believed that mutations in the PRNP gene make PrP^C more susceptible to changing conformation into PrP^{Sc}.[13] In the orally acquired forms of PrD (such as kuru and most cases of vJCD), a currently accepted mechanism of neuroinvasion starts with the uptake of prions through the intestinal epithelium. Prions then accumulate in lymphoid tissue before being transported via sympathetic and parasympathetic nerves to the central nervous system.[14]

In sJCD, PrP^{Sc} may be subclassified based on the fragments properties resulting from digestion by proteinase K into type 1 and type 2,[15] which has implications on clinical and pathological features.

The normal cellular prion-related protein is encoded by the prion-related protein gene (*PRNP*). Mutations in *PRNP* cause genetic PrD[16]; there are currently more than 30 known mutations in that gene.[17] The majority of mutations are missense mutations, with some stop codons, insertions (octapeptide repeat insertions [OPRI]), or deletions. Common mutations worldwide are E200K (the most common), D178N, P102L, and V210I.[18,19] The pattern of inheritance is autosomal dominant, and penetrance is high, though age-dependent. Among E200K mutation carriers of Libyan Jewish heritage, for example, while penetrance was calculated to be around 1% at age 40, it was close to 100% after the ninth decade of life; and so it is not uncommon to find older asymptomatic mutation carriers.[19,20] Penetrance in E200K carriers of Slovakian heritage appears to be somewhat lower than in those from other backgrounds.[21]

It is also known that *PRNP* polymorphisms influence an individual's susceptibility to develop disease. The most acknowledged polymorphism is located in codon 129, which can have either valine (V) or methionine (M) as alleles (the three possible combinations are MM, MV, and VV). There is a clear overrepresentation of homozygotes (MM or VV) among PrD patients. Whereas in a normal Caucasian population, 50% are heterozygous (MV), 40% are MM, and $<10\%$ VV.[22] In every form of PrD, more than 65% of the patients are either MM or VV.[4]

Sporadic Jakob-Creutzfeldt Disease

The clinical presentation of sJCD is highly variable. In most cases, onset is subacute, although in rare cases onset may be acute or stroke-like.[23] In $\sim$ 40% of patients, the initial symptom is cognitive (most commonly presenting as memory problems, executive dysfunction and/or language impairment).[6,24] Cerebellar symptoms are the initial manifestation in $\sim$ 20% of cases, as are constitutional symptoms (such as dizziness, headaches, sleep or eating changes, or fatigue) and behavioral symptoms (e.g., depression, irritability).[24] Visual changes (blurred vision, diplopia, oculomotor changes, and visual hallucinations) occur as a presenting symptom in 10 to 15% of cases.[6,24,25] Extrapyramidal (i.e., parkinsonism, dystonia, myoclonus, and chorea) and pyramidal symptoms are less frequently seen as presenting manifestation, but are more likely to be seen as the disease progresses. Parkinsonism in sJCD may manifest with supranuclear gaze palsy, early gait problems, and/or alien limb, sometimes resembling atypical parkinsonism.[26] Dystonia can be seen in as much as 20% of JCD cases.[27] Myoclonus is rarely a presenting symptom, but eventually is seen during the clinical course in almost 90% of cases.[6] It is often generalized and associated with periodic sharp wave complexes (PSWCs).[26] Seizures (or even status epilepticus) have only rarely been described as an initial manifestation of sJCD,[28] but seizures can occur later in 8 to 9% of cases.[6,25,28] Clinically evident peripheral neuropathy (including cranial neuropathy) is very uncommon in sJCD,[29] but is seen more commonly in some genetic PrDs.[30–34]

Symptoms follow a rapidly progressive course, and different manifestations are added to the symptomatology throughout the course of the disease. The common final pathway of sJCD in most cases is the development of akinetic mutism.[26]

Median duration of disease is around 4 to 6 months (mean 7 months) and death occurs within 1 year in 90% of cases, and another 5% of patients die in the second year of disease.[6,35] Younger age at onset, female gender, and heterozygosity at *PRNP* codon 129 have been associated with longer survival in sJCD.[35]

Most diagnostic criteria for sJCD have been developed primarily for epidemiological purposes and aim at identifying cases that were not pathologically proven by brain biopsy or autopsy.[36] Because of this, the criteria are not particularly sensitive early in the disease course, and most cases will only fulfill diagnostic criteria later (for example, akinetic mutism is one of the clinical criteria, despite being a very late occurrence). The most commonly used diagnostic criteria are the ones proposed by the World Health Organization in 1998.[36] Those criteria do not take in consideration magnetic resonance imaging (MRI) findings, and so more recently two other sets of criteria have been published (►**Table 1**).[37,38]

Sporadic JCD has been divided into six molecular subtypes based on the polymorphisms in PRNP codon 129 (MM, MV, or VV) and the type of protease-K resistant prion (type 1 or 2).[22,39] This classification, to some extent, sJCD cases based on their clinicopathological features. The MM1 and MV1 variants are quite similar and therefore combined; they comprise the most frequent type (60–70%) with classic features of myoclonus, early dementia, PSWCs on electroencephalogram (EEG), and a faster course with a mean duration of illness $\sim$ 4 months. The VV2 type, comprising $\sim$ 15% of cases, is characterized by early ataxia, uncommon PSWCs, later age of onset, and short disease duration of $\sim$ 6.5 months. The MV2 type comprises $\sim$ 10% of cases, and is clinically similar to the VV2, but has longer disease duration of approximately $\sim$ 17 months. The VV1 type is the least frequent variant, with a duration of $\sim$ 15 months, and is the one associated with the earliest age of onset (mean 43 y).[39] The MM2 type has been further divided into cortical and thalamic types, as will be

Table 1 Diagnostic criteria for sporadic Jakob-Creutzfeldt disease

WHO 1998 revised criteria[36]	UCSF 2007 criteria[37]	MRI-JCD consortium criteria 2009[38]
1. Progressive dementia and/or 2. At least 2 of the following four features: a. Myoclonus b. Visual or cerebellar disturbance c. Pyramidal/ extrapyramidal signs d. Akinetic mutism and 3. PSWCs on the EEG and/or a positive 14–3-3 CSF assay and a clinical duration to death $<$ 2 years 4. No alternative diagnosis on routine investigations	1. Rapidly progressive dementia with at least 2 of the following: a. Myoclonus b. Pyramidal/ extrapyramidal dysfunction c. Visual disturbance d. Cerebellar signs e. Akinetic mutism f. Other higher focal cortical sign[a] and 2. Typical EEG or MRI and 3. Routine investigations should not suggest an alternative diagnosis	1. Progressive dementia 2. At least 2 of the following 4 features: a. Myoclonus b. Visual or cerebellar disturbance c. Pyramidal or extrapyramidal signs d. Akinetic mutism 3. And one of more of the following: a. Periodic discharges on the EEG b. A positive 14–3-3 CSF assay and a clinical duration to death $<$ 2 years c. High signal abnormalities in caudate nuclear and putamen or at least two cortical regions (temporal-parietal-occipital, but not frontal, cingulate, insular or hippocampal) either in DWI or FLAIR MRI d. No alternative diagnosis on routine investigations.

Source: Modified from Geschwind MD, Josephs KA, Parisi JE, Keegan BM. A 54-year-old man with slowness of movement and confusion. *Neurology* 2007;69(19):1881–1887 and Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain* 2009;132(Pt 10):2659–2668.
Abbreviations: CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; JCD, Jakob-Creutzfeldt disease; MRI, magnetic resonance imaging; PSWCs, periodic sharp wave complexes; UCSF, University of California San Francisco; WHO, World Health Organization.
[a]Higher focal cortical signs include such findings or symptoms as apraxia, neglect, acalculia, aphasia, etc.

discussed below. Some refer to the MM2 thalamic type as the sporadic form of fatal insomnia.[40] Since this molecular classification was established, it has been discovered that type 1 and 2 prions coexist in the same brain in about one-third of cases.[41,42] The MM1/2 type seems to fall somewhere between the MM1 and MM2 types in disease duration.[39] Mixed prion types appear to be more common in MM than in MV or VV forms. The precise presentation of these mixed types remains to be determined.[39]

Amid the great variability in clinical presentation, a few sJCD variants are recognized. The Heidenhain variant is observed in $\sim$ 10% of sJCD, and is characterized by visual symptoms at presentation, including visual hallucinations or distortions, cortical visual deficits, and/or oculomotor impairment, with mostly MM1 molecular subtype.[19,43] The Brownell-Oppenheimer variant has ataxia as the presenting and dominant symptom, with a lack of EEG PSWCs and MRI basal ganglia hyperintensities.[43] A thalamic variant, currently known as sporadic fatal insomnia (sFI), is linked to MM2,[44] and a rare amyotrophic form is associated with motor neuron disease findings.[45] There is also a panencephalopathic form, with significant or primary involvement of white matter, which has been described primarily in Japan and only rarely seen in Caucasians.[46,47] Many feel that the panencephalopathic form is not a distinct type, but may be due to Wallerian degeneration as it occurs preferentially in cultures in which patients lives are prolonged with extraordinary life-extending measures.

More recently, a new form of PrD was described, based on the finding that in a small group of cases with similar clinical and neuropathological features, the PrP^{Sc} was more sensitive to proteinase K digestion. Those cases were termed as having variable proteinase-sensitive proteinopathy (VPSPr) and are clinically characterized by having aphasia, ataxia, and parkinsonism as prominent manifestations and a longer disease course than sJCD.[48] As it is usually diagnosed postmortem, the clinical presentation is not entirely characterized, and it might be underdiagnosed due to longer duration of disease.

Neuroimaging

Brain MRI is currently the most accurate method for the diagnosis of sJCD, with sensitivity of 91 to 96% and specificity of 92 to 94%.[39,49,50] Magnetic resonance imaging changes can also be seen very early in the disease course, even though in some cases they will only appear with repeated exams.[51] Magnetic resonance imaging used for the diagnosis of JCD should always include DWI (diffusion-weighted imaging) and ADC (apparent diffusion coefficient) sequences, as DWI findings are more sensitive than FLAIR/T2 sequences abnormalities (►**Fig. 1**).[51] University of California, San Francisco (UCSF) MRI criteria for sJCD have been updated and are detailed in ►**Table 2**.[49]

There are three major patterns of DWI MRI hyperintensities in sJCD: cortical and subcortical (68% of cases), predominantly neocortical (24%) and predominantly subcortical (primarily striatum; with or without thalamic changes; 5%).[52]

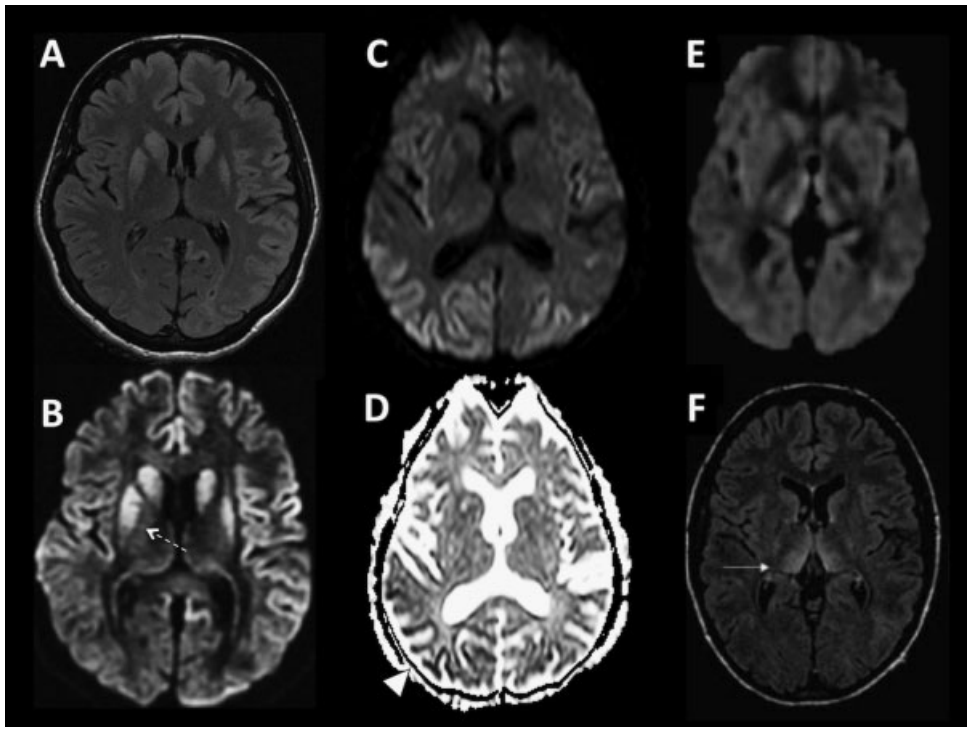

Fig. 1 Brain magnetic resonance imaging (MRI) in sporadic Jakob-Creutzfeldt disease (sJCD). (**A,B**) Axial brain MRI in a patient with JCD. (**A**) Fluid attenuated inversion recovery (FLAIR) sequence showing bilateral striatal hyperintensities and cortical hyperintensities in the bilateral medial frontal regions, left posterior frontal, and anterior parietal regions. Posterior cingulate cortex is also hyperintense. (**B**) Diffusion weighted image (DWI) showing cortical ribboning in the same regions as FLAIR sequence, and also in the right peri-insular cortex. Striatal hyperintensities are also present. Note the anterior-posterior gradient in striatum (*dotted arrow*). (**C,D**) Axial brain MRI in a patient with sJCD. (**C**) Axial DWI showing cortical ribboning in parietal, occipital and frontal regions (right more than left). Caudate and putamen are mildly hyperintense, more on the right side. (**D**) Apparent diffusion coefficient map showing bilateral hypointensities in parietal (*arrowhead*) and occipital cortices (right more than left). (**E,F**) probable variant JCD with MRI showing bilateral thalamic hyperintensity in the mesial pars (mainly dorsomedian nucleus) and posterior pars (pulvinar) of the thalamus, the so-called double hockey stick sign. Also note the "pulvinar sign" (*solid arrow*), with the posterior thalamus (pulvinar) being more hyperintense than the anterior putamen. (Modified from Vitali et al. Semin Neurol 2008;28(4): 467–483).

Cortical hyperintensities (or cortical ribboning) can be seen in almost any neocortical region, but with relative sparing of the precentral cortex.[49] Subcortical hyperintensities usually comprise the striatum bilaterally, with an anterior-posterior gradient (i.e., the anterior caudate being more hyperintense than the posterior putamen).[49] Limbic (i.e., insula, anterior cingulate, hippocampus) hyperintensities may be seen as an additional finding in up to 90% of sJCD cases, but predominant or isolated limbic abnormalities are not characteristic of sJCD and should point to a nonprion diagnosis (particularly encephalitis and seizures).[49]

Whenever an area of hyperintensity is questioned to be a false-positive, adding coronal and sagittal images to the evaluation, as well as searching for correspondent ADC map hypointensities, may be helpful.[49] The DWI hyperintensities have a pattern of water diffusion restriction (probably caused by vacuolation),[53] with corresponding hypointensities in the ADC maps. The ADC hypointensities are more easily identified in subcortical structures, but may also be found in cortical regions.[49] Cortical ribboning can also be seen in viral encephalitis, seizures, status epilepticus, hyperammonemic encephalopathy, acute phase of hypoxic injury, mitochondrial encephalopathy, vasculitis, and other conditions.[51,54] Striatal or thalamic DWI hyperintensities with ADC hypointensities have also been described in extrapontine myelinolysis, Wilson's disease, Wernicke encephalopathy, and hyperglycemia with seizures.[49,54] White matter abnormalities are typically absent in sJCD. With the progression of disease as atrophy progresses, particularly in patients with disease duration of over 1 year, DWI hyperintensities fade away and so might be absent in later MRI scans.[49] Importantly, most MRIs in sJCD are still being misread, with radiologists missing the sJCD diagnosis, even with DWI scans.[55,56]

Cerebrospinal Fluid and Electroencephalography Findings

Cerebrospinal fluid (CSF) analysis is typically normal in sJCD, sometimes with mildly elevated protein concentration (typically less than 75 mg/dL). Cerebrospinal fluid pleocytosis (> 10 WBC cells/mm^3), an elevated immunoglobulin G (IgG) index, and/or the presence of oligoclonal bands are unusual in sJCD and should lead to considering other conditions, particularly infectious or autoimmune disorders.

A few CSF markers have been used in clinical practice (such as 14–3-3 protein and total tau [t-tau]), but due to great variability in accuracy across studies, the clinical value of each marker is still not entirely clear. Recent recommendations

Table 2 UCSF 2011 MRI criteria for sJCD[49]

MRI definitely JCD	DWI > FLAIR hyperintensities in:
	1. Classic pathognomonic: cingulate, striatum, and > 1 neocortical gyrus (often precuneus, angular, superior, or middle frontal gyrus) Supportive for subcortical involvement: - Striatum with anterior-posterior gradient - Subcortical ADC hypointensity Supportive for cortical involvement: - Asymmetric involvement of midline neocortex or cingulate - Sparing of the precentral gyrus - ADC cortical ribboning hypointensity
	2. Cortex only (> 3 gyri); see supportive for cortex (above)
MRI probably JCD	1. Unilateral striatum or cortex ≤ 3 gyri; see supportive for subcortical (above); see supportive for cortex (above)
	2. Bilateral striatum or posteromesial thalamus; see supportive for subcortical (above)
MRI probably not JCD	1. Only FLAIR/DWI abnormalities in limbic areas, where hyperintensity can be normal (e.g., insula, anterior cingulate, hippocampi) and ADC map does not show restricted diffusion in these areas
	2. DWI hyperintensities due to artifact (signal distortion); see other MRI issues (below)
	3. FLAIR > DWI hyperintensities; see other MRI issues (below)
MRI definitely not JCD	1. Normal
	2. Abnormalities not consistent with JCD
Other MRI Issues	1. In prolonged courses of sJCD (> 1 year) brain MRI might show significant atrophy with loss of DWI hyperintensity, particularly in areas previously with restricted diffusion
	2. To help distinguish abnormality from artifact, obtain sequences in multiple directions (e.g., axial and coronal)

Source: From Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, Johnson DY, Miller BL, Geschwind MD. Diffusion-weighted MRI hyperintensity patterns differentiate JCD from other rapid dementias. *Neurology* 2011;76 (20):1711–1719.

Abbreviations: ADC, apparent diffusion coefficient; JCD, Jakob-Creutzfeldt disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; sJCD, sporadic Jakob-Creutzfeldt disease; UCSF, University of California San Francisco.

from the American Academy of Neurology suggest ordering CSF 14–3-3 when there is a strong suspicion of JCD, but the diagnosis is still uncertain (pretest probability of 20–90%).[57] In the systematic review, the sensitivity of 14–3-3 was 92% and specificity 80%.[57]

Thus far, total tau might be the best CSF diagnostic marker for sJCD with sensitivity and specificity higher than 90%,[58,59] although there is still no complete agreement over its cutoff value (usually higher than 1,150 pg/mL). Combining markers also seems to increase their diagnostic value.[60] The 14–3-3 protein is a nonspecific marker for neuronal injury, and can be increased in non-PrD, such as cerebrovascular disease, metabolic, and hypoxic encephalopathies, seizures, brain metastases, and central nervous system infections, or even other neurodegenerative dementias.[61,62]A large multicenter study found that the specificity of 14–3-3 was lower when used to differentiate JCD from acute neurologic disorders (such as vascular, inflammatory, or seizures) in comparison to using it to differentiate JCD from neurodegenerative dementias (82–87% vs. 95–97%. respectively), so taking into consideration the differential diagnoses is fundamental to interpreting the test result.[63]

A typical EEG in sJCD has sharp, or triphasic waves (periodic sharp wave complexes [PSWCs]) occurring about once every second. However, this EEG finding is found in only about two-thirds of sJCD patients, usually after serial EEGs and in later stages of the illness.[64] Often the only EEG finding is focal or generalized slowing. Periodic sharp wave complexes are relatively specific, but they can also be seen in other conditions, including toxic-metabolic and anoxic encephalopathies, progressive multifocal leukoencephalopathy, Alzheimer's disease, Lewy body dementia, and nonvasculitic autoimmune meningoencephalitis.[65,66]

Neuropathology

Atrophy is the only gross anatomical finding in sJCD brains. The typical neuropathological findings are neuronal loss, gliosis, and vacuolation (or spongiform changes), without inflammatory signs. Current diagnostic criteria for definite sJCD also require positive PrP^{Sc} tissue immunoreactivity.[67,68] PrP amyloid plaques (or Kuru plaques) are found in 5 to 10% of sJCD cases, particularly the MV2 subtype.[44]

Genetic Prion Disease

Genetic prion diseases (gPrDs) are often divided according to their genetic, clinical, and pathological characteristics into three forms: gJCD, GSS and FFI. One problem with this

classification is that a single *PRNP* mutation, particularly octapeptide repeat insertions (OPRIs) can be associated with different phenotypes and great variability even within a single family.

Genetic prion diseases are sometimes referred to as familial, but considering that up to 60% of the gPrD cases do not have a positive family history,[18] the term "familial" can be misleading. In those cases with a negative family history, there is often a history of family members being (mis)diagnosed with more common neurodegenerative diseases such as Alzheimer's or Parkinson's disease. Other possible explanations for a negative family history are incomplete or age-dependent penetrance, or incomplete history.

Genetic Jakob-Creutzfeldt Disease

The clinical features of gJCD are highly variable, and inter- and intrafamilial variations may be seen.[44] As a group and in comparison to sJCD, gJCD is associated with a younger age at onset (typically $<$ 55 years; but onset may occur as late as the ninth decade) and longer clinical course.[19,35] Cerebrospinal markers, EEG, and brain MRI may not be as sensitive or specific as in sJCD.[44,69,70]

Gerstmann-Sträussler-Scheinker Disease

Gerstmann-Sträussler-Scheinker disease typically presents as a subacute progressive ataxic and/or parkinsonian disorder with later onset of cognitive impairment; onset most commonly occurs in the fourth to sixth decades.[70] Mean disease duration is around 5 years, ranging from 3 to more than 8 years. Pyramidal signs may also be found; and lower limb dysesthesia and areflexia may be other associated clinical features, particularly in the P102L variant.[71]

There is considerable phenotypic variability within and between mutations and families, and some cases may not have ataxia as a primary feature, presenting instead with early dementia and behavioral abnormalities.[70] At least 15 *PRNP* mutations have been shown to cause GSS. Electroencephalograms in most cases do not show typical JCD findings, and CSF protein 14–3-3 is increased in $\sim$ 50% of cases.[18] The MRI scans are usually normal, and some degree of brain and cerebellar atrophy may be seen with the progression of disease.[71] Cortical ribboning is an uncommon finding in GSS,[71] but limbic DWI or FLAIR hyperintensities can be found in up to 50% of cases.[49] Neuropathologically, GSS is defined by the presence of PrPSc amyloid plaques (Kuru plaques) in the brain.[19,67,68]

Fatal Familial Insomnia

Fatal familial insomnia is a rare disorder that usually presents with progressive, severe insomnia and dysautonomia, with motor and cognitive problems appearing later in the course. Progressive insomnia is eventually associated with hallucinations. Onset usually occurs in the fifth and sixth decade,[19] and the mean duration of disease is around 15 months.[35] Even though brain MRI is usually normal, F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) imaging reveals thalamic and cingulate hypometabolism. Fatal familial insomnia is caused by a single *PRNP* point mutation, D178N, with codon 129 M on the same chromosome (cis; Patients with D178N-129V usually present with gJCD).[72] The neuropathology of FFI is primarily characterized by thalamic gliosis and neuronal loss.[67]

Acquired Prion Disease

Kuru

Kuru ("to shake or tremble" in the Fore language) was a form of PrD confined to the Fore ethnic group of Papua New Guinea and was transmitted through ritualized cannibalism. The clinical presentation was of pure cerebellar ataxia with relatively preserved cognition.[73] The practice of cannibalism stopped in the late 50s; since then the incidence of Kuru decreased dramatically (from the more than 2,700 cases identified between 1957 and 2004, only 11 occurred after 1996).[74]

Iatrogenic Jakob-Creutzfeldt Disease

More than 400 cases of iatrogenic JCD (iJCD) have been reported worldwide, either from the use of cadaveric-derived human pituitary hormones (growth hormones [hGH] and gonadotropic hormones [hPG]), dura mater grafts, corneal transplants, reuse of EEG implanted depth electrodes or other neurosurgical equipment.[75,76] The number of iJCD cases has been decreasing over the past several years, probably due to increased surveillance and use of effective decontamination measures. Continuing surveillance is necessary, as accidental reuse of neurosurgical equipment previously used on patients with JCD continues to occur.[75,77]

Variant Jakob-Creutzfeldt Disease

Variant Jakob-Creutzfeldt Disease (vJCD) was first recognized in 1995 in the United Kingdom (UK),[78] and soon received worldwide attention for its association with bovine spongiform encephalopathy (BSE), or mad cow disease. Bovine spongiform encephalopathy is the only non-human PrD currently believed to be directly transmissible to humans. It is thought that BSE occurred from the practice of feeding scrapie-infected sheep products to cattle. More than 180,000 cattle suffered from BSE, the vast majority in the UK.[79] The incidence of BSE has declined dramatically since 1992.[79] Up until June 2013, 225 cases of vJCD had been reported worldwide; and no new cases were reported in the UK in 2012 or 2013. Codon 129 polymorphism is an important susceptibility factor for the development of vJCD, and nearly every case reported thus far was found to be 129MM.[80]

The clinical presentation of vJCD is different from sJCD in several ways. Patients with vJCD are usually younger, with a median age of onset around 27 (range 12–74).[81] The mean disease duration is longer, $\sim$ 14.5 months (compared with $\sim$7 mo for sJCD). Although psychiatric symptoms often occur early in sJCD,[24] prominent psychiatric symptoms are often the presenting symptoms in vJCD for more than 6 months before obvious neurologic symptoms arise. The EEG rarely shows classic PSWCs, and if so, then only at the end-stage of disease.[82] Brain MRI usually shows the "pulvinar sign," (►**Fig. 1**), in which the pulvinar (posterior thalamus) is

brighter than the anterior putamen on T2-weighted or DWI MRI (found in more than 85% of cases in the first exam)[83]; this finding is extremely rare in other human prion diseases.[84] Posterior thalamus hyperintensities have been reported in gJCD and in sJCD, but in those cases, the basal ganglia are usually brighter than the posterior thalamus.[85]

Definitive diagnosis of vJCD is based on pathologic evidence of the variant form of PrP^{Sc} in brain biopsy or autopsy. Because vJCD is acquired peripherally, PrP^{Sc} can be found in the lymphoreticular system, including tonsillar tissue.[86] Brain pathology of vJCD shows abundant PrP^{Sc} deposition, in particular multiple fibrillary PrP plaques surrounded by a halo of spongiform vacuoles ("florid" plaques) and other PrP plaques and deposits, especially prominent in the cerebellar molecular layer.[67]

It was more recently discovered that vJCD could also be acquired from transfusion of contaminated blood products. It is important to stress that while transmission through blood products has been reported in variant JCD, there are no known cases to date of transmission from sporadic JCD patients through blood transfusion.[87,88] There have been three cases of vJCD[89] of patients who received (contaminated) blood transfusions before 1999 and developed symptoms 6 to 9 years later. Two other patients (both PRNP 129MV) received contaminated blood products and died of nonneurologic causes, but had positive prion testing in their lymphoreticular system. In the UK, vJCD prions were found by immunostaining in 3 of 12,674 anonymized appendix samples,[90,91] leading to assumptions that there are subclinically infected persons in the population. One major concern is the fact that their risk of developing symptomatic vJCD and passing it on to others through medical/surgical procedures or blood products is not known. In light of this concern, additional measures were taken to prevent transmission of vJCD through blood products with donor selection and efforts toward developing methods to detect PrP in blood. Universal leukoreduction of donated blood has also been done since 1999 in the UK, and more recently in the rest of Europe.[79]

Treatment and Management

Despite all active efforts, there are no currently available drugs to change disease progression in PrD, and symptomatic treatment is the only available option. Symptomatic treatment may include the empirical use of SSRIs to treatment depression and agitation, atypical antipsychotics (particularly quetiapine) to treat agitation and psychosis and clonazepam to treat severe myoclonus or agitation.[92]

Two other management points are important. As mentioned before, a significant percentage of genetic PrDs have no clearly evident family history (and sporadic and genetic PrDs may be clinically indistinguishable), and so genetic testing should be considered for every patient with PrD. Genetic counseling is indispensable prior to testing for PRNP mutations. Also, family and caregiver education is paramount in the disease process. In some countries around the world, there are organizations (such as the Creutzfeldt-Jakob Disease Foundation in the United States) specializing in providing the necessary information for the care of patients with PrDs.[93]

Future Directions

The diagnosis of JCD is still challenging for most clinicians, even though it may be significantly augmented with the use of brain MRI and CSF markers. Differential diagnostic considerations are often equally rare when assessing a patient with a rapidly progressive dementia.[92,94] There are efforts to develop assays to detect PrPSc in blood and CSF; while promising, these are not yet available for clinical use.[95,96]

Another area of active research is the development of pharmacotherapy to treat PrDs, despite the difficulties of conducting clinical trials in a rapidly progressive and fatal disease.[97] Clinical trials have been done with flupirtine, pentosan polysulfate, and quinacrine, but unfortunately, all have failed to show consistent benefits.[39] There are ongoing trials with doxycycline in Germany, France, and Italy, and other compounds are under investigation in experimental settings. Immunotherapy against PrP has been studied in animal models and may offer a promising treatment strategy.[39]

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