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Prion Diseases

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Relationship Disclosure:
Dr Geschwind serves on the board of directors for San Francisco Bay Area Physicians for Social Responsibility, on the editorial board of *Dementia & Neuropsychologia*, and as a consultant for Best Doctors, Inc; the Gerson Lehrman Group, Inc; Guidepoint Global, LLC; Lewis Brisbois Bisgaard & Smith LLP; Lundbeck; MEDACorp; NeuroPhage Pharmaceuticals; and Quest Diagnostics. He receives research support from CurePSP, the Michael J. Homer Family Fund, the National Institute on Aging (R01 AG AG031189), Quest Diagnostics, and the Tau Consortium.

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ABSTRACT

Purpose of Review: This article presents an update on the clinical aspects of human prion disease, including the wide spectrum of their presentations.

Recent Findings: Prion diseases, a group of disorders caused by abnormally shaped proteins called prions, occur in sporadic (Jakob-Creutzfeldt disease), genetic (genetic Jakob-Creutzfeldt disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia), and acquired (kuru, variant Jakob-Creutzfeldt disease, and iatrogenic Jakob-Creutzfeldt disease) forms. This article presents updated information on the clinical features and diagnostic methods for human prion diseases. New antemortem potential diagnostic tests based on amplifying prions in order to detect them are showing very high specificity. Understanding of the diversity of possible presentations of human prion diseases continues to evolve, with some genetic forms progressing slowly over decades, beginning with dysautonomia and neuropathy and progressing to a frontal-executive dementia with pathology of combined prionopathy and tauopathy. Unfortunately, to date, all human prion disease clinical trials have failed to show survival benefit. A very rare polymorphism in the prion protein gene recently has been identified that appears to protect against prion disease; this finding, in addition to providing greater understanding of the prionlike mechanisms of neurodegenerative disorders, might lead to potential treatments.

Summary: Sporadic Jakob-Creutzfeldt disease is the most common form of human prion disease. Genetic prion diseases, resulting from mutations in the prion-related protein gene (*PRNP*), are classified based on the mutation, clinical phenotype, and neuropathologic features and can be difficult to diagnose because of their varied presentations. Perhaps most relevant to this *Continuum* issue on neuroinfectious diseases, acquired prion diseases are caused by accidental transmission to humans, but fortunately, they are the least common form and are becoming rarer as awareness of transmission risk has led to implementation of measures to prevent such occurrences.

Continuum (Minneap Minn) 2015;21(6):1612–1638.

INTRODUCTION

What Are Prion Diseases?

Prion (pree-ahn) diseases are a group of neurodegenerative diseases caused by the conversion of the normal prion protein (PrP^C, prion-related protein, in which C stands for the cellular form of the protein) with a primarily α-helical structure into an abnormal form of the protein called the prion (PrP^{Sc}, in which Sc stands for scrapie, the prion disease of sheep and goats), which stands for *proteinaceous infectious particle*, and has a primarily β-pleated sheet structure. Alfons Jakob described the first cases of human prion disease between 1921 and 1923 and thought his cases were similar to a young woman described by Hans Creutzfeldt in 1920.[1,2] This disease was commonly referred to for many decades as Jakob or Jakob-Creutzfeldt disease until Clarence J. Gibbs, a prominent researcher in the field, started using the term Creutzfeldt-Jakob disease because the acronym was closer to his own initials.[3] It turns out,

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however, that only two of five of Jakob's cases and not even Creutzfeldt's case had what we would now consider prion disease. Thus, the disease should be called Jakob or Jakob-Creutzfeldt disease.[4] In this article, the term Jakob-Creutzfeldt disease is used rather than Creutzfeldt-Jakob disease, and therefore when abbreviated, ''JCD'' is more appropriate than ''CJD.'' (Note, however, that clinicians occasionally mistakenly test for Jakob-Creutzfeldt disease by polymerase chain reaction (PCR) in CSF for the JC virus, the virus that causes progressive multifocal leukoencephalopathy and has nothing to do with prion disease!)

For many years, it was believed that this family of diseases, often referred to as transmissible spongiform encephalopathies, including scrapie and Jakob-Creutzfeldt disease, were caused by ''slow viruses,'' in part because of their transmissibility and the prolonged incubation period between exposure and symptom onset.[5] The infectious agent could not, however, be inactivated by methods that inactivate viruses and other microorganisms. Tikvah Alper, Ian Pattison, and others postulated that the ''scrapie agent'' did not contain nucleic acid and might be a protein.[5,6] Researchers later showed that transmission of the transmissible spongiform encephalopathy causative agent from animal to animal could be prevented by treating the tissue using methods that destroy and denature proteins.[5,6] Stanley Prusiner received the 1997 Nobel Prize in Physiology or Medicine in part for isolating the scrapie agent and confirming it was a misfolded protein, which he called a ''proteinaceous infectious particle,'' or prion.[5] Although Dr Prusiner's ''prion hypothesis'' has been controversial for many years, accumulating evidence over the past several years has confirmed the prion hypothesis beyond any reasonable doubt.[7]

Prion diseases are unique in medicine in that they can occur by three mechanisms: spontaneous (sporadic), genetic (familial), and acquired (infectious/transmitted). The model of prion disease is that the pathologic disease-causing misfolded form of the prion protein, PrP^{Sc} (in which ''Sc'' stands for scrapie, the prion disease of sheep and goats) acts as a template, such that when it comes into contact with a prion protein, PrP^{C} (in which ''C'' stands for the normal, cellular form of the protein), it transforms PrP^{C} into PrP^{Sc}, resulting in two prions. These two prions, in turn, transform two more PrP^{C} into PrP^{Sc}, which then transform four more, and so forth, leading to an exponential transformation and accumulation of prions. Debate still exists as to whether it is the accumulation of PrP^{Sc},[5] or possibly an intermediary form of the prion during the conversion of PrP^{C} to PrP^{Sc} that is responsible for neurodegeneration.[8]

Background on Human Prion Diseases

My experience with human prion diseases stems largely from the University of California, San Francisco's (UCSF's) rapidly progressive dementia clinical research program. Since 2001, we have reviewed records on more than 2500 referred cases of patients with rapidly progressive dementia, many of whom were suspected of or at risk for prion disease. We ultimately evaluated approximately one-quarter (more than 600) of these cases in person at our center, a plurality of whom turned out not to have prion disease. In more than 270 cases, however, we confirmed the diagnosis of human prion disease.[9,10] We have previously published on nonprion causes of, and the diagnostic evaluation for, rapidly progressive dementia[9,10]; this will be updated in the upcoming *Continuum* issue on dementia.

Human prion diseases occur in most of the developed world at a rate of 1 to

KEY POINTS

- Although Stanley Prusiner's ''prion hypothesis'' has been controversial for many years, accumulating evidence over the past several years has confirmed the prion hypothesis beyond any reasonable doubt.
- Prion diseases are unique in that they can occur by three mechanisms: spontaneous (sporadic), genetic (familial), and acquired (infectious/transmitted).
- The model of prion disease is that the pathologic disease-causing misfolded form of the prion protein, PrP^{Sc}, acts as a template, so when it comes into contact with a prion protein, PrP^{C}, it transforms PrP^{C} into PrP^{Sc}, resulting in two prions.

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KEY POINT

- Of human prion diseases, 80% to 95% are sporadic Jakob-Creutzfeldt disease, 10% to 15% are genetic (often familial), and less than 1% are acquired.

1.5 cases per million per year. In the United States, with a population of about 330 million, about 400 cases of prion disease are diagnosed per year, an incidence of 1.2 in 1 million.[11] Of human prion diseases, 80% to 95% are sporadic Jakob-Creutzfeldt disease, 10% to 15% are genetic (often familial), and less than 1% are acquired. Although the latter are the least common, they are probably the most notorious. In sporadic Jakob-Creutzfeldt disease, the conversion of PrP^{C} to PrP^{Sc} is thought to occur spontaneously (or possibly through a somatic mutation of *PRNP*). In genetic prion diseases, it is thought that mutations in the prion protein gene, *PRNP*, make the PrP^{C} more susceptible to changing conformation (misfolding) into PrP^{Sc}. In acquired forms, PrP^{Sc} is accidentally transmitted to a person, causing their endogenous PrP^{C} to misfold.[5,12]

SPORADIC JAKOB-CREUTZFELDT DISEASE

Sporadic Jakob-Creutzfeldt disease reportedly has a mean survival of about 6 months (median about 5 months), with 85% to 90% of patients dying within 1 year. The peak age of onset is 55 to 75 years of age, with median age of onset of about 67 years and mean of 64 years.[13,14] Sporadic forms of prion disease include sporadic Jakob-Creutzfeldt disease and the recently identified variably protease-sensitive prionopathy (discussed later in this article).[13]

Diagnosis of Sporadic Jakob-Creutzfeldt Disease

Histopathologic changes in human prion diseases include nerve cell loss, gliosis, vacuolation (formerly called spongiform change), and PrP^{Sc} deposition (**Figure 4-1**). Classically, pathologic (definite) diagnosis of prion disease requires identification of the protease-resistant PrP^{Sc} with immunohistochemistry or Western blot (**Figure 4-2**).[12,13] Clinical diagnosis of Jakob-Creutzfeldt disease is based on the constellation of symptoms and ancillary tests, including CSF, EEG, and, perhaps most important, brain MRI. The classic clinical phenotype of

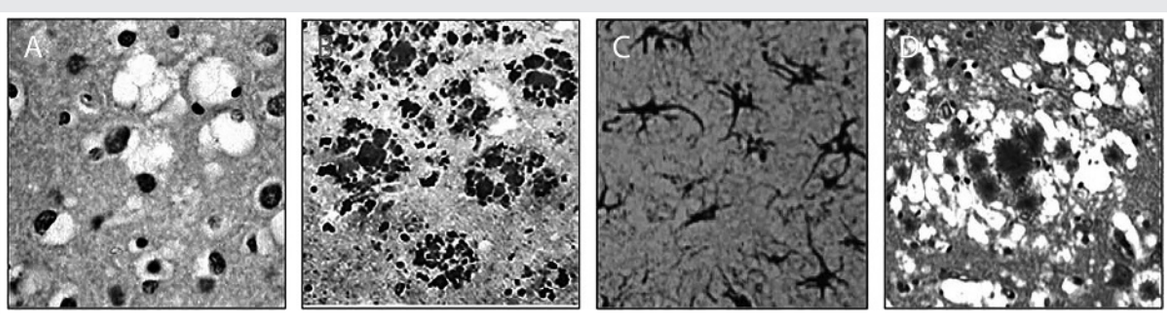

FIGURE 4-1 Pathologic features of prion disease. *A*, Hematoxylin and eosin (H&E) staining demonstrates typical spongiform degeneration (vacuolation) of the gray matter neuropil characteristic of Jakob-Creutzfeldt disease. This feature is less obvious in fatal familial insomnia and Gerstmann-Sträussler-Scheinker syndrome. *B*, Prion protein (PrP)-positive multicentric plaques are pathognomonic for Gerstmann-Sträussler-Scheinker syndrome. These are mostly present within the molecular layer of the cerebellum but may be diffusely present throughout the cerebrum. *C*, Glial fibrillary astrocytic protein (GFAP) antibodies demonstrate hypertrophy and proliferation of astrocytes. This feature is present in all prion subtypes. In fatal familial insomnia, this is often found focally within the anterior nucleus and dorsomedial nucleus of the thalamus and brainstem in combination with neuronal dropout. In Gerstmann-Sträussler-Scheinker syndrome it may parallel PrP plaque pathology. *D*, The florid plaques of variant Jakob-Creutzfeldt disease consist of dense core PrP amyloid deposits surrounded by vacuoles.

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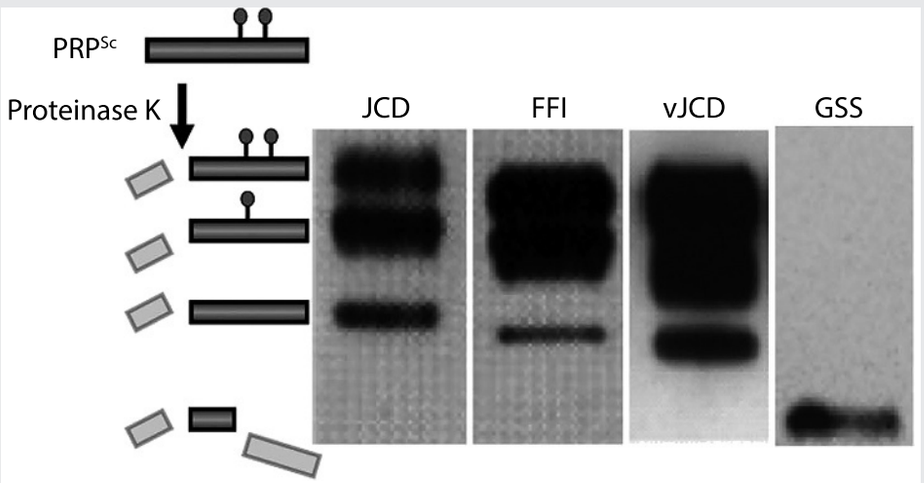

FIGURE 4-2 Western blot comparing the major isoforms observed in the four principal subtypes of prion disease. To the left of the blot displays the prion protein (PrP) segment that is represented in the adjacent blot. The highest molecular weight of PrP is the diglycosylated fraction of PrP, whereas the monoglycosylated and unglycosylated fractions run faster in the gel because of their lower molecular weight. In Jakob-Creutzfeldt disease, fatal familial insomnia, and variant Jakob-Creutzfeldt disease, proteinase-K cleaves approximately the first 67 amino acids of protease-resistant scrapie-related isoform (PrP^{Sc}), leaving the PK-resistant core, PrP90-231. In the Jakob-Creutzfeldt disease case shown, the unglycosylated (lowest) band migrates at 21 KDa, indicating Type 1 prions, whereas the fatal familial insomnia case migrates lower, at 19 KDa, indicating Type 2 prions. In most cases of Gerstmann-Sträussler-Scheinker syndrome, a second C-terminal cleavage that removes the glycosylated segment occurs endogenously, leaving a unglycosylated central segment, which usually runs at 7 to 8 KDa.

FFI = fatal familial insomnia; GSS = Gerstmann-Sträussler-Scheinker syndrome; JCD = Jakob-Creutzfeldt disease; vJCD = variant Jakob-Creutzfeldt disease.

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KEY POINTS

- The classic clinical phenotype of sporadic Jakob-Creutzfeldt disease is a rapidly progressive dementia with behavioral abnormalities, ataxia (usually gait), extrapyramidal features, and, eventually, myoclonus.
- About one-third of patients with sporadic Jakob-Creutzfeldt disease have constitutional early symptoms, sometimes considered prodromal features, many of which are difficult to classify neuroanatomically, such as asthenia/fatigue, headache, malaise, vertigo/dizziness, altered sleep and eating patterns, and unexplained weight loss.
- Behavioral abnormalities are the very first symptom(s) in about one-fifth of patients with sporadic Jakob-Creutzfeldt disease and early symptoms in 20% to 30%; they occur in about half of all patients during the disease course.

sporadic Jakob-Creutzfeldt disease is a rapidly progressive dementia with behavioral abnormalities, ataxia (usually gait), extrapyramidal features, and, eventually, myoclonus (**Case 4-1**).[12,13,19,20] The discussion of symptoms in sporadic Jakob-Creutzfeldt disease in this article is divided temporally into three categories: (1) first symptoms, which are the initial symptoms noted by the patient and his or her family; (2) early symptoms, which are symptoms present or reported at first presentation to a physician; and (3) symptoms that occur at any time during the entire disease course. **Table 4-1** shows the distribution of major categories of both the very first symptom in 114 of our serial sporadic Jakob-Creutzfeldt disease cases and early symptoms in three other large sporadic Jakob-Creutzfeldt disease cohorts.[20] **Table 4-2** shows the distribution of major categories and subcategories of specific first symptoms in our cohort. Cognitive symptoms are the most common first symptom, followed equally by cerebellar, constitutional, and behavioral (each around 20%) symptoms.[20] About one-third of patients with sporadic Jakob-Creutzfeldt disease have constitutional early symptoms, sometimes considered prodromal features, many of which are difficult to classify neuroanatomically, such as asthenia/fatigue, headache, malaise, vertigo/dizziness, altered sleep and eating patterns, and unexplained weight loss.[19,20] Behavioral abnormalities are the very first symptom(s)

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Case 4-1

A 61-year-old right-handed previously very physically active and healthy man was noted by his wife to be mildly apathetic and speaking less. Over the next 2 to 3 weeks, he became confused, frequently forgetting why he had walked into a room, wandering around his house, and opening and closing drawers and doors while looking querulously inside. He also developed trouble making simple decisions. One week later, he realized he could no longer read words on the computer screen (''I can't figure out what it says. The words don't go together.''), an analog clock, or numbers. He developed episodic macropsia, with hands appearing to him as too big. By the end of the first month, he was unable to calculate a tip, he stopped driving and working, and he developed occasional myoclonic jerks. By the second month, he became echolalic, spoke only in short sentences, used utensils incorrectly, and required help to eat and dress. By the third month, he became easily angered and frustrated at his deficits, could no longer be left alone, and developed right arm dystonia. His visual difficulties worsened—he mistook a large bird for a person—but he took long daily walks. His family history revealed that his elderly father was alive with mild dementia for 5 years.

On neurologic examination, he had moderately severe nonfluent aphasia, inability to follow a formal neurologic or cognitive examination, a very strong bilateral grasp reflex, and difficulty counting fingers in primary gaze. He tended to notice objects and respond to threat better in his left visual field, and used his left hand for visual search. He also had right arm dystonia, preferentially used his left hand, had no arm dysmetria, and had an intermittent right arm alien limb. His gait was slightly slow and normal to mildly wide based, but he required no support.

Brain MRI at 3 months (**Figure 4-3**) showed asymmetric, left greater than right, cortical ribboning on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map, and left caudate

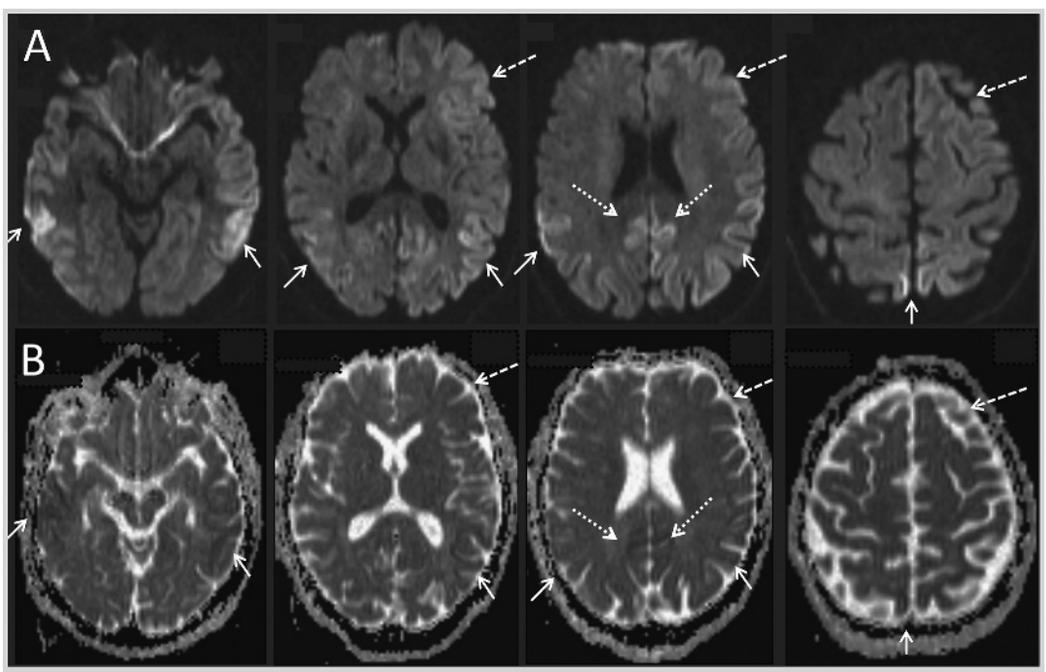

FIGURE 4-3 Imaging of the patient in **Case 4-1**. *A*, Axial diffusion-weighted imaging (DWI) and *B*, axial apparent diffusion coefficient (ADC) map 3 months after onset of sporadic Jakob-Creutzfeldt disease. Bilateral restricted diffusion cortical ribboning is shown in the bilateral temporal (*solid arrows*), parietal (*solid arrows*), posterior cingulate (*dotted arrows*) cortices, and the left frontal cortex (*dashed arrows).*

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Continued from page 1616

head DWI hyperintensity, consistent with prion disease. His EEG showed diffuse slowing, mild disorganization, superimposed left hemispheric slowing, and intermittent sharp-wave complexes, occasionally periodic. Lumbar puncture was declined. He met World Health Organization (WHO),[15] University of California, San Francisco (UCSF),[16,17] and European MRI-CJD Consortium Criteria[18] for probable sporadic Jakob-Creutzfeldt disease. He died of aspiration pneumonia 4 months after onset. Brain autopsy and *PRNP* genetic testing confirmed sporadic Jakob-Creutzfeldt disease, MM1/2 subtype.

Comment. This patient's presentation with prominent early visual symptoms was reminiscent of the Heidenhain variant of sporadic Jakob-Creutzfeldt disease, but this was quickly followed by a rapidly progressive more classic form of sporadic Jakob-Creutzfeldt disease with aphasia, extrapyramidal features, and cognitive impairment. His cognitive and language deficits would be consistent with either MM1 or MM2, whereas his early visual symptoms would be consistent with MM1, but not typically with MM2.[13]

in about one-fifth of patients[20] and early symptoms in 20% to 30%; they occur in about half of all patients during the disease course.[19] Certain focal higher cortical dysfunctions (eg, aphasia, apraxia, neglect, and acalculia) are early features in about 15% and occur throughout the disease course in about half of cases.[19,20] Visual disturbances and oculomotor dysfunction occur early in 7% to 17% of cases and during the clinical course in about 30% to 40% of cases.[19,20] About 5% to 10% of patients with sporadic Jakob-Creutzfeldt disease have initial or early sensory symptoms.[20] Because Jakob-Creutzfeldt disease affects many areas of the brain, its presentations are protean, and it can mimic, particularly early on, many other neurologic or psychiatric conditions, making diagnosis difficult. Many

TABLE 4-1 Comparison of University of California, San Francisco First Symptom Study With a Number of Previous Early Symptom Studies[a]

	Study[b,c]			
Symptom	University of California, San Francisco (UCSF) 2001–2004, n = 114	France 1968–1982,[19] n = 230	United Kingdom 1990–1994,[21] n = 144	Japan 1975–1978,[22] n = 63
Cognitive	40	46	19	29
Cerebellar	22	34	39	41
Constitutional	21	17	NA	5
Behavioral	20	29	15	36
Sensory	9	5	NA	6
Motor	9	NA	6	NA
Visual	7	17	10	13

NA = not available.
[a] Reprinted with permission from Rabinovici GD, et al, Neurology.[20] *www.neurology.org/content/66/2/286.short* © 2006 American Academy of Neurology.
[b] Percentages of patients presenting with each symptom are shown.
[c] The French and British studies reported at clinical presentation, whereas the Japanese study reported ''initial symptoms,'' not further defined. The UCSF study specifically reports first symptom. The British study included symptoms that did not match any of the UCSF categories (eg, ''other'') and are thus not included in this table.

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KEY POINT

- Because Jakob-Creutzfeldt disease affects many areas of the brain, its presentations are protean, and it can mimic, particularly early on, many other neurologic or psychiatric conditions, making diagnosis difficult.

incorrect diagnoses are often considered in patients with Jakob-Creutzfeldt disease, and patients are often about two-thirds of the way through the disease course before the correct diagnosis is made.[23] For this reason, some refer to Jakob-Creutzfeldt disease as ''The Great Mimicker.''

TABLE 4-2 First Symptom in Sporadic Jakob-Creutzfeldt Disease[a,b]

Major Symptom Domain/Subcategory	% of Subjects With First Symptom[c]
Cognitive	**40**
Memory loss	45
Aphasia/dysphasia	13
Frontal/executive	13
Confusion/disorientation	11
Visuospatial	9
Cognitive, unspecified	5
Decreased alertness	2
Apraxia	2
Cerebellar	**22**
Gait	84
Limb ataxia	12
Unspecified	4
Constitutional	**21**
Dizziness/vertigo	41
Fatigue/lethargy	21
Sleep disturbance	10
Headache	7
Urinary incontinence	7
Weight loss	7
Gastrointestinal upset	3
Palpitations	3
Behavioral	**20**
Agitation/irritability	36
Depression	16
Anger/aggression	8
Apathy	8
Personality change	8
Aberrant motor	4
Mania	4
Unspecified	4
Bizarre behavior	4
Social isolation	4
Panic attack	4

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TABLE 4-2 **First Symptom in Sporadic Jakob-Creutzfeldt Disease**[a,b]
Continued from page 1618

Major Symptom Domain/Subcategory	% of Subjects With First Symptom[c]
Motor	**10**
Extrapyramidal	25
Pyramidal	17
Handwriting change	17
Cramps	8
Unspecified	8
Myoclonus, action	8
Tremor, unspecified	8
Fasciculations	8
Sensory	**9**
Paresthesia	60
Pain	20
Special senses	10
Sensory, unspecified	10
Visual	**7**
Unspecified	67
Diplopia	33

[a] Data from Rabinovici GD, et al, Neurology.[20] *www.neurology.org/content/66/2/286.short*.
[b] First symptoms based on 146 first symptoms among 114 subjects with sporadic Jakob-Creutzfeldt disease; as some subjects had more than a single first symptom, the total percentages of major categories total is more than 100%.
[c] Percentages for subcategory refer to percent of patients within the major category symptom and may not total 100% because of rounding.

KEY POINT

■ The major current classification of sporadic Jakob-Creutzfeldt disease is based on a combination of two features: a polymorphism in the prion gene, *PRNP*, at codon 129, which can be either methionine (M) or valine (V), and the size (molecular weight) of PrP^{Sc} after it has been partially digested with protease K and run on Western blot.

Classification of Sporadic Jakob-Creutzfeldt Disease

The major current classification of sporadic Jakob-Creutzfeldt disease is based on a combination of two features: a polymorphism in the prion gene, *PRNP*, at codon 129, which can be either methionine (M) or valine (V) (**Figure 4-4**[24]) and the size (molecular weight) of PrP^{Sc} after it has been partially digested with protease K and run on Western blot (**Figure 4-2**). Type 1 prions, with a more distal cleavage site, are 21 kilodalton (kDa), and type 2, with a more proximal cleavage site, are 19 kDa. These factors result in six possible combinations (MM1, MV1, VV1, MM2, MV2, and VV2), but based on clinical and neuropathologic features, the six original "molecular" subtypes of sporadic Jakob-Creutzfeldt disease proposed actually were MM1/MV1, VV1, VV2, MV2, MM2-cortical, and MM2-thalamic. MM1 and MV1 are clinicopathologically nearly identical, and MM2 has two forms, a cortical and a thalamic form.[13] MM1/MV1 is the most common subtype (about 40%), usually presenting as a very rapidly progressive dementia with myoclonus, ataxia in about one-half of cases, and visual signs and dysphasia in approximately one-fourth of cases. VV2 is the next most common (about 15%), presenting as a rapidly progressive ataxia. MV2 forms are the third most common (about 8%) and usually begin with either ataxia or cognitive decline and are more

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KEY POINTS

- EEG was the earliest diagnostic test for sporadic Jakob-Creutzfeldt disease, showing 1 Hz to 2 Hz periodic sharp-wave (often biphasic or triphasic) complexes found in about two-thirds of cases, depending on their molecular classification, but these usually do not appear until patients are quite advanced and thus require serial testing.
- Brain MRI, particularly diffusion-weighted images and the apparent diffusion coefficient map sequences, showing restricted diffusion in the cortical or deep nuclei gray matter has high diagnostic utility for sporadic Jakob-Creutzfeldt disease, with sensitivity of 92% to 96%, specificity of 93% to 94%, and accuracy of about 97%.

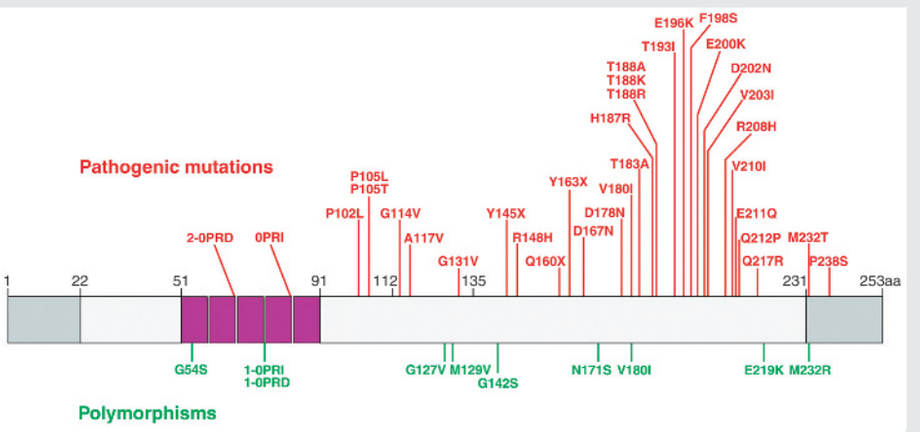

FIGURE 4-4 Prion protein (PrP) mutations and polymorphisms. A schematic representation of full-length human PrP is shown with the cleaved signal sequences shown in gray and the octapeptide repeat region in purple. Disease-associated mutations are shown in red and nonsynonymous nonpathogenic genetic variants (polymorphisms) in green.

OPRD = octapeptide repeat deletion; OPRI = octapeptide repeat insertion.

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slowly progressive than the prior two (mean about 16 months versus 4 to 6.5 months in duration). The MM2-thalamic subtype is sometimes also referred to as "sporadic fatal insomnia," as it has overlapping features with fatal familial insomnia, a form of genetic prion disease.[12,13] To complicate matters, it was later discovered that some patients have both type 1 and type 2 prions, thus giving three additional subtypes (MM1-2, MV1-2, and VV1-2). The clinicopathologic features of these mixed subtypes appear to present based on the relative amounts of type 1 versus type 2 prions.[13] Although this classification scheme is valuable for research purposes, its clinical value is less clear, as it also requires brain tissue to determine the prion type and patients do not always fit the expected clinicopathologic features of their molecular subtype. Therefore, the clinical manifestations of sporadic Jakob-Creutzfeldt disease described above and in the following sections pertain to sporadic Jakob-Creutzfeldt disease in general, unless otherwise stated.

Diagnostic Tests

Ancillary tests, such as CSF, EEG, and brain MRI, each with varying utility, can help with sporadic Jakob-Creutzfeldt disease diagnosis. EEG was the earliest diagnostic test for sporadic Jakob-Creutzfeldt disease, showing 1 Hz to 2 Hz periodic sharp-wave (often biphasic or triphasic) complexes (**Figure 4-5**) found in about two-thirds of cases, depending, in part, on their molecular classification. These abnormalities, however, usually do not appear until patients are quite advanced and, thus, typically require serial testing.[13,25] Brain MRI, particularly diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences, showing restricted diffusion in the cortical or deep nuclei gray matter (**Figure 4-6**) has high diagnostic utility for sporadic Jakob-Creutzfeldt disease, with sensitivity of 92% to 96%, specificity of 93% to 94%,[19] and accuracy of about 97%.[20] Abnormal hyperintensity can be seen on fluid-attenuated inversion recovery (FLAIR) and especially DWI MRI in the cortical gyri (cortical ribboning),

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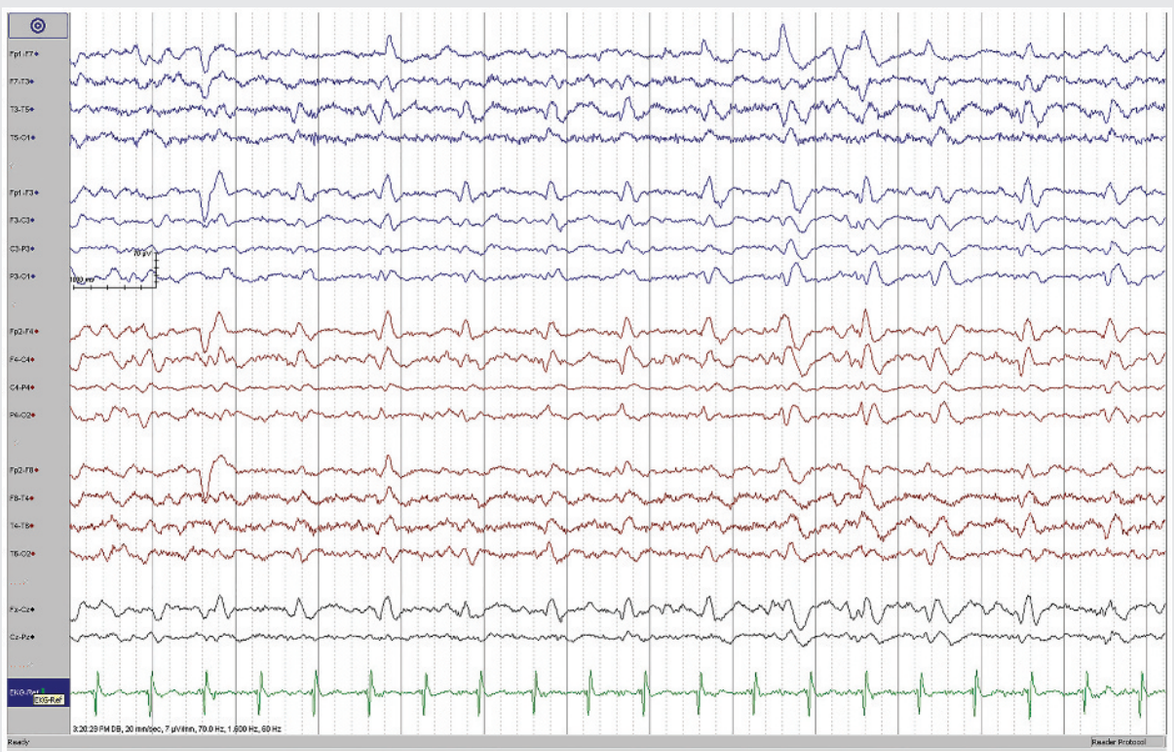

FIGURE 4-5 EEG in a sporadic Jakob-Creutzfeldt disease case. Recordings obtained using a standard international 10- to 20-electrode placement with a singleelectrocardiogram chest electrode (*bottom*). The EEG shows classic 1 Hz to 2 Hz generalized triphasic periodic sharp-wave complexes as well as diffuse background slowing with poor organization (*not shown*), suggestive of Jakob-Creutzfeldt disease.

caudate, putamen, or thalamus. When the striatum is involved, there is usually an anterior to posterior gradient of decreasing hyperintensity.[16] A typical MRI in sporadic Jakob-Creutzfeldt disease, with cortical and basal ganglia restricted diffusion, is shown in **Figure 4-3** and **Figure 4-6**. Usually the abnormalities are more difficult to see on T2/FLAIR sequences than on DWI.[16,26,27] As the DWI hyperintensities are caused by restricted diffusion, often, corresponding hypointense (dark) regions are seen on the ADC map, although this often depends on the quality of the ADC image. Because of the phenomenon of eddy current distortion, sometimes corresponding hypointense cortical ribboning is not found on the ADC map.[16] Not all sporadic Jakob-Creutzfeldt disease cases, such as some of the MM2 and VV2 subtypes, have these typical MRI changes.[13] Various MRI criteria for diagnosing sporadic Jakob-Creutzfeldt disease have been published, including UCSF[16] and European MRI-CJD Consortium Criteria,[27] and are discussed later. If a patient is strongly suspected to have Jakob-Creutzfeldt disease, but the MRI is nondiagnostic and other conditions have been ruled out, consider blood testing for genetic prion disease, particularly before proceeding to brain biopsy, as some forms do not have the classic MRI findings.[12,16] Unfortunately, the majority of MRIs of sporadic Jakob-Creutzfeldt disease cases are misread by radiologists, who sometimes misinterpret findings of Jakob-Creutzfeldt disease for other conditions such as encephalitis,

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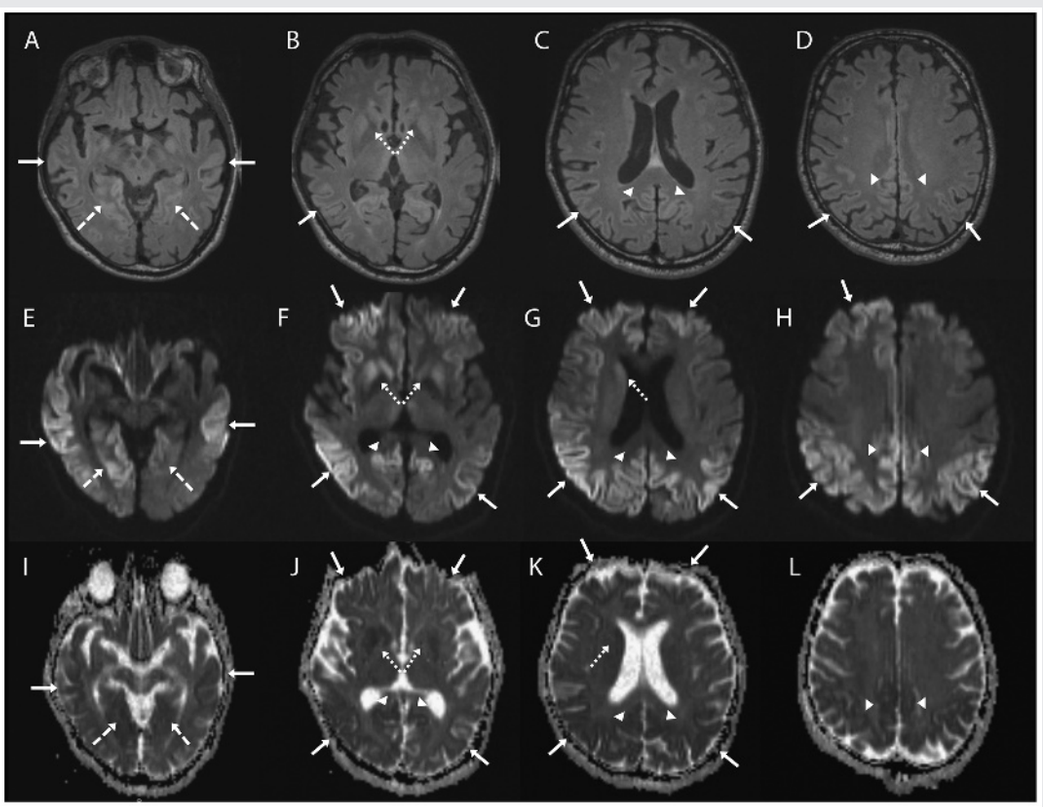

FIGURE 4-6 Axial brain MRI sequences in a patient with sporadic Jakob-Creutzfeldt disease. Note that the axial fluid-attenuated inversion recovery (FLAIR) sequences (*A–D*) are generally much less sensitive than the diffusion sequences, particularly diffusion-weighted imaging (DWI) (*E–H*) and the apparent diffusion coefficient (ADC) map (*I–L*). The DWI and ADC map show cortical ribboning (*solid arrows*) in the bilateral parietal, right greater than left frontal and lingula (*dashed arrows*), and posterior cingulate (*arrowheads*). Asymmetric involvement of the striatum is also shown (*right greater than left*) (*dotted arrows*). Bright regions on DWI are dark on the ADC map, indicating true restricted diffusion of water molecules. This case would meet University of California, San Francisco MRI criteria for sporadic Jakob-Creutzfeldt disease.[16]

stroke, or infection. Unfortunately, more commonly the MRI abnormalities are not even noted in radiology reports.[28,29] Among more than 150 pathology-proven serial sporadic Jakob-Creutzfeldt disease subjects, surprisingly we found no differences in the sensitivity of outside MRI reports for sporadic Jakob-Creutzfeldt disease between academic and nonacademic centers.[28]

General CSF findings in sporadic Jakob-Creutzfeldt disease are usually normal, with the exception of mildly elevated protein (usually less than 100 mg/dL) in a large minority of cases.[12] Although elevated white blood cell count, oligoclonal bands, or IgG index can rarely occur in Jakob-Creutzfeldt disease,[30] their presence probably should prompt an infectious and inflammatory (eg, autoimmune and paraneoplastic) evaluation.[9,10] The utility of CSF biomarkers, such as 14-3-3, S100β, neuron-specific enolase (NSE), and total tau (t-tau), for sporadic Jakob-Creutzfeldt disease diagnosis is somewhat controversial, in part because of the variability in accuracy between studies and across continents. These proteins are not prion specific, and the tests do not identify prions; many consider these proteins to be markers for neuronal injury. The sensitivity of

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the 14-3-3 by Western blot in the literature ranges from 53% to 97%, although it is most commonly reported to be between 85% and 95%, with specificity ranging from 40% to 100%.[14,18,31–36] Recommendations from the American Academy of Neurology in 2012 suggest ordering CSF 14-3-3 when a strong suspicion of Jakob-Creutzfeldt disease exists but the diagnosis is still uncertain (pretest probability of 20% to 90%).[35] Several studies, however, have found other biomarkers, including NSE, t-tau, and S100β, or possibly a combination of biomarkers, to have higher accuracy than 14-3-3 alone.[13,18,31,33,34,36] A 2015 study in a cohort of subjects with sporadic Jakob-Creutzfeldt disease and nonprion rapidly progressive dementia found t-tau to have higher diagnostic accuracy than NSE or 14-3-3, but DWI/ADC MRI to have much higher accuracy than any or all of these three biomarkers (97% for MRI versus 70% to 80% for biomarkers).[18] The author recommends sending these tests as biomarkers of neuronal injury; they may confirm or suggest a history of rapid neuronal injury, and, in some cases in which the MRI findings are absent or ambiguous, they might support a diagnosis of sporadic Jakob-Creutzfeldt disease. Importantly, these tests do not definitively confirm or refute a diagnosis of sporadic Jakob-Creutzfeldt disease. These CSF biomarker tests should only be used for cases of suspected Jakob-Creutzfeldt disease and not as general screening tests.[18,32]

A recent test called real-time quaking-induced conversion (RT-QuIC), which detects prions by amplifying them into amyloid fibrils, has been shown to have modest sensitivity (about 77% to 92%) but very high specificity (99% to 100%) for prion detection in CSF[31]; when applied to olfactory mucosal brushings from affected patients, this test might have even better diagnostic accuracy.[31] Although this work needs to be replicated in larger cohorts with improved controls of nonprion rapidly progressive dementias, RT-QuIC is a very promising premortem diagnostic test.

The accuracy of CSF and other biomarkers in sporadic Jakob-Creutzfeldt disease appears to vary somewhat based on their molecular classification.[13,18,31] Unfortunately, as brain tissue is required for this classification scheme, unless brain biopsy is performed to determine the prion type and molecular classification, one cannot determine the molecular classification to determine premortem accuracy of these tests in an individual. In a similar manner, to some extent, the molecular classification of sporadic Jakob-Creutzfeldt disease can have an effect on the neuroanatomic pattern of MRI involvement.[13]

Currently, the most commonly used clinical diagnostic criteria for probable sporadic Jakob-Creutzfeldt disease are the UCSF[17] and European[18,27] criteria, which are based on the 1998 revised WHO criteria,[15] with various modifications (**Table 4-3**). A major problem with the WHO criteria for clinical diagnostic use is that they were developed for epidemiologic surveillance purposes to help identify through medical record review whether deceased cases of suspected Jakob-Creutzfeldt disease that were not assessed neuropathologically (and therefore not pathologically-proven) had a high likelihood of sporadic Jakob-Creutzfeldt disease (high specificity).[15] Thus, the criteria are not particularly sensitive early in the disease when patients are being evaluated initially; many patients will not fulfill these diagnostic criteria until late in their course (eg, akinetic mutism is one of the clinical symptoms in the criteria, despite being the end stage of disease). The WHO criteria and other criteria do not include many symptoms often found early (prodromal) in Jakob-Creutzfeldt disease, such as psychiatric/behavioral

KEY POINTS

- The utility of CSF biomarkers, such as 14-3-3, S100β, neuron-specific enolase, and total tau, for sporadic Jakob-Creutzfeldt disease diagnosis is somewhat controversial, in part, because of the variability in accuracy between studies and across continents. These proteins are not prion specific, and the tests do not identify prions; many consider these proteins to be markers for neuronal injury. These CSF biomarker tests should only be used for cases of suspected Jakob-Creutzfeldt disease and not as general screening tests.
- A recent test called real-time quaking-induced conversion (RT-QuIC), which detects prions by amplifying them into amyloid fibrils, has been shown to have modest sensitivity (about 77% to 92%) but very high specificity (99% to 100%) for prion detection in CSF; when applied to olfactory mucosal brushings from affected patients, this test might have even better diagnostic accuracy.

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symptoms or constitutional or related concerns (discussed previously in the article).[19,20] The UCSF criteria modified some of the symptom specifications in the WHO criteria, but, perhaps more importantly, added diffusion-weighted MRI (substituting it for the CSF 14-3-3 protein).[16] In 2009, the European MRI-CJD Consortium criteria[27] also added the use of MRI (while keeping in the CSF 14-3-3 protein).[16,18] Two major differences between the UCSF and European MRI-CJD Consortium criteria are that the latter allow FLAIR alone to be abnormal (they do not require DWI) and they do not allow the MRIs to have only involvement of frontal and limbic cortices (because they found too many false positives caused by air-brain artifact).[16,18,27] Using FLAIR without diffusion sequences is problematic for at least two reasons. First, DWI is much more sensitive than FLAIR for detecting Jakob-Creutzfeldt disease abnormalities,[16,18] and second, several nonprion rapidly progressive dementias have T2/FLAIR hyperintensities (particularly in the deep nuclei) that overlap with those seen in Jakob-Creutzfeldt disease. Although some non-Jakob-Creutzfeldt disease conditions with T2/FLAIR hyperintensities can have restricted diffusion on DWI/ADC sequences, most do not.[13,16] The likelihood of misinterpreting artifact can be reduced by obtaining sequences in both axial and coronal views and confirming restricted diffusion by reviewing the ADC map.[16]

Over the past few years, a novel form of sporadic Jakob-Creutzfeldt disease

TABLE 4-3 Commonly Used Diagnostic Criteria for Sporadic Jakob-Creutzfeldt Disease

- **World Health Organization Criteria (WHO) (1998)[a]**
  1. Progressive dementia
  2. Two of the following four signs/symptoms:
     - Myoclonus
     - Pyramidal/extrapyramidal symptoms
     - Visual/cerebellar dysfunction
     - Akinetic mutism
  3. Typical EEG or elevated CSF protein 14-3-3 with total disease duration <2 years
  4. Routine investigations should not suggest an alternative diagnosis
- **University of California, San Francisco Criteria (UCSF) (2007)[b]**
  1. Rapid cognitive decline
  2. Two of the following six signs/symptoms:
     - Myoclonus
     - Pyramidal/extrapyramidal dysfunction
     - Visual dysfunction
     - Cerebellar dysfunction
     - Akinetic mutism
     - Focal cortical signs (eg, neglect, aphasia, acalculia, apraxia)
  3. Typical EEG and/or MRI[b]
  4. Other investigations should not suggest an alternative diagnosis

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TABLE 4-3 Commonly Used Diagnostic Criteria for Sporadic Jakob-Creutzfeldt Disease *Continued from page 1624*

▶ **European MRI-CJD Consortium Criteria (2009)[c]**

1. Progressive dementia
2. One of the following signs/symptoms:
   - Myoclonus
   - Pyramidal/extrapyramidal symptoms
   - Visual/cerebellar dysfunction
   - Akinetic mutism
   - AND
3. Either
   - Typical EEG
   - Elevated CSF protein 14-3-3 (with total disease duration <2 years)
   - OR
   - Typical MRI[d]
4. Routine investigations should not suggest an alternative diagnosis

CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; EEG = electroencephalography; MRI = magnetic resonance imaging.

[a] WHO revised criteria allow either a positive EEG or a positive CSF 14-3-3 protein provided the disease duration to death is <2 years.[15,16,27]

[b] See Table 1 in Vitali P, et al, Neurology.[16] Briefly, UCSF MRI criteria require diffusion-weighted imaging (DWI) brighter than fluid-attenuated inversion recovery (FLAIR) hyperintensity in the cingulate, striatum and/or greater than one neocortical gyrus, ideally with sparing of the precentral gyrus and apparent diffusion coefficient map supporting restricted diffusion.

[c] Of note, there were typographical errors in the symptom criteria in Zerr 2009 article Figure 1; progressive dementia was not required and dementia was substituted for myoclonus as one of four possible clinical symptoms in the criteria. In fact, European MRI-CJD Consortium clinical symptom criteria are unchanged from WHO 1998 criteria.[15,27]

[d] High-signal intensity on either FLAIR or DWI in both the putamen and the caudate nucleus or in at least two cerebral cortical regions (from either the temporal, occipital, or parietal cortices, not including frontal or limbic regions).

KEY POINTS

- Genetic prion diseases historically have been divided into three forms based on clinicopathologic features: familial Jakob-Creutzfeldt disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia.
- Most *PRNP* mutations causing genetic prion disease are caused by missense mutations, but several octapeptide repeat insertion (OPRI) mutations exist, and at least five stop codon mutations.
- In more than 60% of patients found to have genetic prion disease, there was no known family history of prion disease; often, however, there was a family history of neurologic or psychiatric disease that likely had been misattributed to other etiologies.

has been identified, called variably protease-sensitive prionopathy, in which there is a paucity of protease-resistant PrP^{Sc} when run on Western blot. Presentation is usually of an a typical dementia, with initial features being psychiatric, dysphasic, or cognitive, followed by progressive parkinsonism or ataxia. The codon 129 polymorphism appears to have a significant effect on phenotypic presentation. The age of onset is usually the late sixties to seventies, with disease durations of 18 months to more than 40 months. EEG and CSF biomarkers are often nondiagnostic, with MRI just showing atrophy. Just over 30 cases of variably protease-sensitive prionopathy have been identified since 2008.[13]

GENETIC PRION DISEASES

Genetic prion diseases historically have been divided into three forms based on clinicopathologic features: familial Jakob-Creutzfeldt disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. This division occurred, however, before the identification of the human prion protein gene, *PRNP* (**Figure 4-4**). Most *PRNP* mutations causing genetic prion disease are caused by missense mutations, but several octapeptide repeat insertion (OPRI) mutations and at least five stop

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KEY POINT

- Diagnosis of genetic prion disease can be very difficult as incredible diversity exists in the range of age of onset (from childhood to the very elderly), duration (from a few months to decades), symptoms, and neuropathologic features. Some genetic prion diseases can present similarly to Alzheimer disease, Huntington disease, early-onset psychiatric illness, frontotemporal dementia, progressive supranuclear palsy, severe insomnia, dysautonomia, or even gastrointestinal disorders with neuropathy.

codon mutations exist.[12,24] It is thought that mutations make the prion protein, PrP^{C}, more susceptible to transformation into PrP^{Sc}.[5,12] Importantly, in more than 60% of patients found to have genetic prion disease, there was no known family history of prion disease; often, however, there was a family history of neurologic or psychiatric disease that likely had been misattributed to other etiologies.[37] Diagnosis of genetic prion disease can be very difficult as incredible diversity exists in the range of age of onset (from childhood to the very elderly), duration (from a few months to decades), symptoms, and neuropathologic features. Some genetic prion diseases can present similarly to Alzheimer disease, Huntington disease, psychiatric illness, frontotemporal dementia, progressive supranuclear palsy, severe insomnia, dysautonomia, or even gastrointestinal disorders with neuropathy.[12,24,38]

Familial Jakob-Creutzfeldt Disease

The most common forms of genetic prion disease are the familial Jakob-Creutzfeldt diseases, which are caused by more than 20 different *PRNP* mutations. Familial Jakob-Creutzfeldt disease typically presents as a rapidly progressive dementia with ataxia and other motor features, with onset usually between ages 30 and 55 years. The most common *PRNP* mutation worldwide, E200K, presents as familial Jakob-Creutzfeldt disease.[12] At least four founders of this mutation exist, with the two largest groups being of Sephardic Jewish origin (often Libyan-Tunisian background) and Slovakians.[12]

Patients with familial Jakob-Creutzfeldt disease typically show clinical, MRI, and neuropathologic features that are indistinguishable from sporadic Jakob-Creutzfeldt disease. For example, familial Jakob-Creutzfeldt disease due to E200K mutations typically presents as a rapidly progressive dementia with ataxia and myoclonus, with MRI showing symmetric prominent striatal T2-weighted/DWI hyperintensities, often with less-prominent cortical ribboning (**Case 4-2**).[39] EEG may also vary according to familial Jakob-Creutzfeldt disease mutation, but, in general, periodic sharp-wave complexes tend

Case 4-2

A 47-year-old woman with an unremarkable past medical history saw a neurologist and noted she had interrupted sleep, persistent fatigue, diffuse tingling numbness, and weight loss without loss of appetite for the past 2 months as well as difficulty focusing and forgetfulness for the past 2 weeks. Her bedside cognitive tests and neurologic examination were normal; she scored 30/30 on the Mini-Mental State Examination (MMSE), with normal results on the Frontal Assessment Battery (17/18) and normal animal fluency (19 per minute). Her cognition and gait rapidly deteriorated over the next month, however, and she could not answer questions at a meeting. Two months after onset, she asked to take time off work. By the end of the third month, she could not drive, she spoke less, had word-finding difficulties, and developed an unsteady gait. An antidepressant had no benefit. On neurologic examination, she was quiet, was intermittently unable to produce audible words with quivering lips, had an occasional rest and action tremor in the extremities, and had cautious gait on tandem walking and mild reduction in temperature sensation in her feet, but no myoclonus. Her Montreal Cognitive Assessment (MoCA) score was 22/30, losing one point each with the trails, verbal fluency, and abstraction, and five points for recall. Her animal fluency was 14 per minute (low normal). Brain MRI showed restricted diffusion and, to a lesser extent, fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensity involving the bilateral striatum, left more than right with anterior to posterior gradient, and cortical ribboning of the left greater than right insular, orbitofrontal, frontal, and temporoparietal

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cortices (**Figure 4-7**), consistent with Jakob-Creutzfeldt disease. Her EEG showed focal slowing, but no periodic sharp-wave complexes, and CSF 14-3-3 was elevated. She met World Health Organization (WHO) 1998, University of California, San Francisco, and European MRI-CJD Consortium 2009 criteria for probable sporadic Jakob-Creutzfeldt disease.[16,27] Upon further questioning, however, it was found she had a family history of Jakob-Creutzfeldt disease; her father died of familial Jakob-Creutzfeldt disease at age 63 after a several-month course. Her paternal grandmother died of natural causes in her eighties, but the patient's father's maternal uncle was diagnosed with Jakob-Creutzfeldt disease by brain biopsy at age 56, and the uncle's son died at age 62 of a rapidly progressive dementia. *PRNP* genetic testing of the patient's blood revealed an E200K mutation.

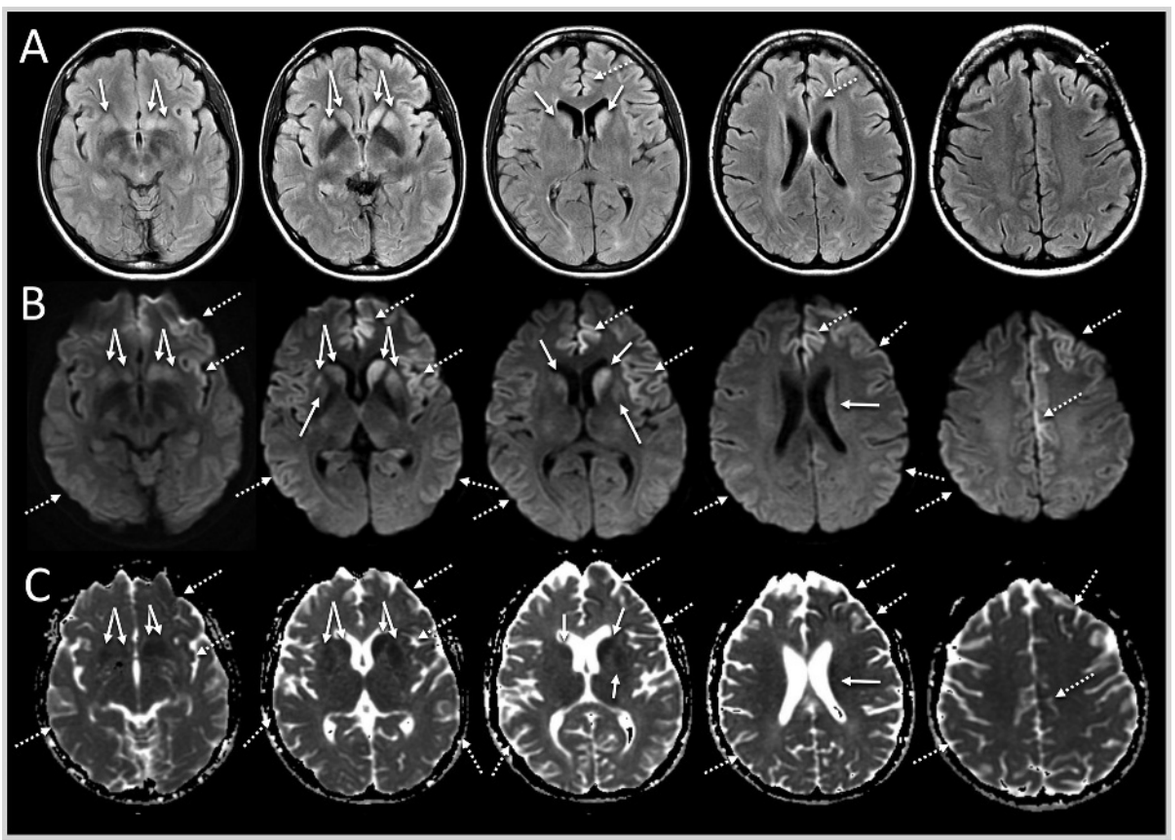

FIGURE 4-7 Imaging of the patient in Case 4-2. Fluid-attenuated inversion recovery (FLAIR) (*A*), diffusion-weighted imaging (DWI) (*B*), and apparent diffusion coefficient (ADC) map (*C*) axial MRI of the patient with a *PRNP* E200K mutation. Restricted diffusion is seen in the striatum (*solid arrows*) and several cortical regions (*dotted arrows*), including left anterior, medial, and posterior cingulate and frontal, insular, and right temporal-parietal cortices. Patients with this mutation typically have prominent striatal restricted diffusion, often with patchy areas of cortical ribboning.

Comment. This history and brain MRI are classic for genetic prion disease due to an E200K mutation. The clinical history and MRI could also be consistent with sporadic Jakob-Creutzfeldt disease, however. As shown in this case, E200K and some other genetic prion diseases are not always 100% penetrant,[12] the family history might not always suggest prion disease, and *PRNP* genetic testing should always be considered in all suspected prion cases.

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KEY POINTS

- Patients with familial Jakob-Creutzfeldt disease typically show clinical, MRI, and neuropathologic features that are indistinguishable from sporadic Jakob-Creutzfeldt disease.
- Gerstmann-Sträussler-Scheinker syndrome typically presents as a slowly progressive ataxic or motoric (eg, parkinsonian) disorder with late-onset dementia, although rapid and amyotrophic cases occur as well.

to appear late. The CSF biomarkers, such as 14-3-3, NSE, and t-tau, often are elevated in familial Jakob-Creutzfeldt disease, but less commonly than they are in sporadic Jakob-Creutzfeldt disease.[12,40] One study found RT-QuIC on CSF to have much higher sensitivity than 14-3-3 or t-tau in familial Jakob-Creutzfeldt disease.[41]

Gerstmann-Sträussler-Scheinker syndrome typically presents as a slowly progressive ataxic or motoric (eg, parkinsonian) disorder with late-onset dementia, although rapid and amyotrophic cases occur as well. Approximately a dozen *PRNP* mutations can cause Gerstmann-Sträussler-Scheinker syndrome, including P102L, P105L, P105T, A117V, Q145X, F198S, Q217R, as well as several OPRI mutations.[12] Median age of onset is often in the fifties (general range twenties to seventies), although phenotypic variability is common even within families (**Case 4-3**). In some families, some of the phenotypic variability between family members appears to be due to codon 129 polymorphisms,[43] whereas, in others, other unidentified

Case 4-3

A 63-year-old right-handed man without significant past medical history presented with about 4 years of progressive gait difficulty, followed by slowed speech and, over the past year, some word-finding problems and cognitive decline.

On neurologic examination, he had moderate dysarthric, slowed, and hypometric saccades, particularly vertically, with saccadic visual pursuit, slow and irregular rapid alternating hand movements and right limb dysmetria, and a positive Romberg sign. His gait, although cautious, was normal based, but he was unable to tandem walk. His Mini-Mental State Examination (MMSE) was 27/30, and more extensive neuropsychological testing revealed impairment of verbal memory, language, abstract reasoning, and executive tasks.

Brain MRI showed bilateral superior parietal atrophy and ventral vermian cerebellar atrophy, more than expected for his age, but no significant white matter disease or diffusion abnormalities. There were no hot-cross bun or putaminal signs suggestive of multiple system atrophy (MSA).[42] His EEG showed mild background slowness. His CSF was normal except for slightly elevated protein (53 mg/dL, normal 15 mg/dL to 50 mg/dL), and his CSF 14-3-3 protein enzyme-linked immunosorbent assay (ELISA; not Western blot) was negative. Serum folate, vitamin E, homocysteine, and paraneoplastic antibodies (anti-Hu, anti-Yo, and anti-MaTa) were normal or negative. He was diagnosed tentatively with multiple system atrophy–cerebellar type (MSA-C) or an idiopathic late-onset cerebellar disorder, despite the lack of MRI findings or dysautonomia. His father had been diagnosed with idiopathic Parkinson disease and was enrolled in treatment trials, but died without autopsy at age 67 after about a 10-year course. Careful review of his father's records, however, revealed an atypical parkinsonian dementia syndrome. *PRNP* testing in the patient revealed an F198S mutation, diagnostic for Gerstmann-Sträussler-Scheinker syndrome. Over the next 18 months, he became wheelchair dependent, and his cognitive function deteriorated significantly (MMSE 11/30). Five years after onset, CSF revealed a

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neuron-specific enolase (NSE) of 40 ng/mL (greater than 30 is consistent with Jakob-Creutzfeldt disease), and at 6 years, CSF showed an NSE of 25 (intermediate) and very elevated t-tau (1689 pg/mL; greater than approximately 1200 pg/mL is consistent with Jakob-Creutzfeldt disease) and phosphorylated tau (151 pg/mL), with an inconclusive 14-3-3 by Western blot. He died 7 years after onset, with brain autopsy confirming Gerstmann-Sträussler-Scheinker syndrome.

Comment. Gerstmann-Sträussler-Scheinker syndrome can present as an ataxic or parkinsonian syndrome progressing over years. Even within the same family, there can be variable phenotypic presentations of symptoms, ages of onset, and disease duration. CSF biomarkers are elevated much less commonly than in sporadic Jakob-Creutzfeldt disease, and, depending on the mutation causing Gerstmann-Sträussler-Scheinker syndrome, there is not usually restricted diffusion, only atrophy. A thorough family history often is necessary to raise suspicion for Gerstmann-Sträussler-Scheinker syndrome, prompting testing for *PRNP* mutations.

factors likely play a role.[12] The youngest known cases of Gerstmann-Sträussler-Scheinker syndrome had onset at age 10, with a course of at least 6 years (unpublished), and age 13, with at least a 2- year course.[44]

Brain MRI, EEG studies, and CSF biomarker tests are usually not helpful in ''ruling in'' the disease. EEG in patients with Gerstmann-Sträussler-Scheinker syndrome usually reveals nonspecific slowing, CSF biomarkers (protein 14-3-3, NSE, and tau) are typically not elevated,[40,41] and some cases have typical brain MRI findings of those seen in sporadic Jakob-Creutzfeldt disease, although most cases do not.[16,43] One study suggests that the RT-QuIC test might have relatively high sensitivity, around 90%, for the P102L mutation.[41]

Fatal Familial Insomnia

Fatal familial insomnia is a very rare form of genetic prion disease associated with a single *PRNP* point mutation, D178N with the cis codon 129M. Onset is typically in the late forties, and patients usually present with severe progressive insomnia over several months, followed by dysautonomia (eg, tachycardia, hyperhidrosis, and hyperpyrexia). Motor and cognitive manifestations tend to occur late. The average survival is about 18 months, slightly longer than most patients with classic sporadic Jakob-Creutzfeldt disease.[12] One of the strongest effects of the codon 129 polymorphism on the clinicopathologic presentation of a prion disease is seen with this mutation. Patients with cis methionine at codon 129 predominantly present as fatal familial insomnia, whereas those with valine at codon 129 usually present as Jakob-Creutzfeldt disease,[12] although this effect of codon 129 polymorphism on the D178N phenotype is not absolute, as Jakob-Creutzfeldt disease and fatal familial insomnia can even both occur within the same family.[45] The trans (on the opposite allele to the one with the mutation) codon 129 can also have an effect on D178N-129M patients, with patients having trans M typically having a shorter course than those who are V trans at codon 129.[46]

Similar to patients with Gerstmann-Sträussler-Scheinker syndrome, EEGs in patients with fatal familial insomnia usually show generalized slowing, without periodic sharp-wave complexes. CSF biomarkers are equally nondiagnostic, with very low sensitivity.[12,40] Although

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KEY POINT

- Because of the diversity of presentation of genetic prion diseases as well as the potential clinical overlap with sporadic Jakob-Creutzfeldt disease, in all suspected cases of prion disease, the author strongly encourages *PRNP* genetic testing, with appropriate counseling protocols, including a discussion of preimplantation genetic diagnosis as appropriate.

limited published data exist on diffusion MRI, there does not appear to be restricted diffusion, and in fact reduced thalamic diffusion due to gliosis may occur.[47] Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, on the other hand, may reveal thalamic and cingulate hypometabolism[12] and, in some cases, even 1 year before clinical onset.

Other *PRNP* Mutations

OPRI mutations consist of 24 base pair repeats of an octapeptide sequence. Generally, repeats of three or more are pathogenic and can present as either a classic Jakob-Creutzfeldt disease phenotype or as Gerstmann-Sträussler-Scheinker syndrome, depending to some extent on the size of the OPRI (more than four OPRI mutations often present as Gerstmann-Sträussler-Scheinker syndrome).

Stop codon mutations have very unusual clinicopathologic presentations as dementias progressing over years, often mimicking Alzheimer disease, frontotemporal dementia, or other neurodegenerative diseases, with prion amyloid angiopathy and tauopathy.[12] Novel, likely pathogenic, mutations causing genetic prion disease, such as E200G and A224V, are continually being identified.[12,48,49] Because of the diversity of presentation of genetic prion diseases as well as the potential clinical overlap with sporadic Jakob-Creutzfeldt disease, in all suspected cases of prion disease, the author strongly encourages *PRNP* genetic testing, with appropriate counseling protocols, including a discussion of preimplantation genetic diagnosis as appropriate.[50]

ACQUIRED PRION DISEASES

Acquired forms of human prion disease are rare and fortunately declining in incidence. Kuru was the first known form of acquired prion disease, identified among the Fore people of Papua New Guinea. It has largely been eradicated through the elimination of the practice of endocannibalism, although because of incubation periods of longer than 50 years, rare cases occasionally still occur. Some fascinating research recently identified a *PRNP* polymorphism at codon 127 in the Fore population that survived the kuru epidemic. This polymorphism appears to be protective against prion disease in mice models.[51] Excitingly, understanding the mechanism of the effect of this polymorphism might lead to treatments for prion diseases.

Variant Jakob-Creutzfeldt Disease

First identified in the United Kingdom in 1994–1995, variant Jakob-Creutzfeldt disease is the only form of human prion disease known to be transmitted directly from animals to humans, in most cases through exposure to bovine spongiform encephalopathy.[12] The bovine spongiform encephalopathy epidemic might have occurred because of the practice of feeding sheep products, some of which were unfortunately contaminated with the prion disease scrapie, to cattle, mostly in the United Kingdom but in other countries as well.[12,52] Food products derived from these infected cattle were consumed by humans, a portion of whom developed variant Jakob-Creutzfeldt disease. The bovine spongiform encephalopathy epidemic peaked around 1992–1993 and was controlled by the late 1990s to early 2000s. There was a temporal relationship between bovine spongiform encephalopathy and variant Jakob-Creutzfeldt disease cases in the United Kingdom (**Figure 4-8**), with the variant Jakob-Creutzfeldt disease onset peaking in 1999–2000, about 6 to 7 years after the bovine spongiform encephalopathy peak in 1993. Since 2000, variant Jakob-Creutzfeldt disease cases have steadily declined, with no new cases with onset after 2012. As of June 2015,

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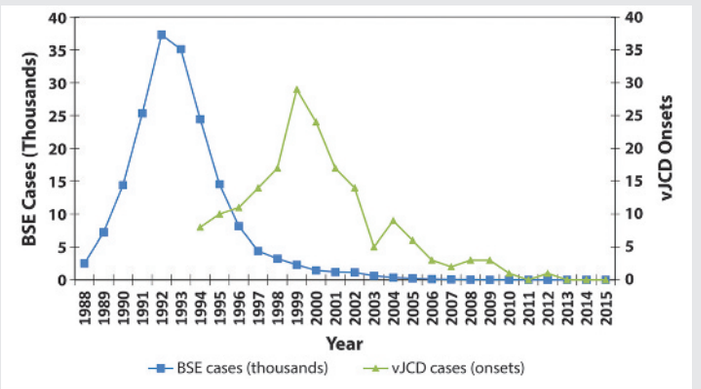

FIGURE 4-8 Number of reported UK bovine spongiform encephalopathy cases (by year of restriction) 1988–2015 and UK variant Jakob-Creutzfeldt disease onsets 1994–2015 showing relationship between UK bovine spongiform encephalopathy and variant Jakob-Creutzfeldt disease cases by year of onset. Note that a temporal relationship exists between the two curves; as the bovine spongiform encephalopathy cases declined, so have the variant Jakob-Creutzfeldt disease cases.

Courtesy of the National CJD Research and Surveillance Unit, Edinburgh, UK.

a total of 229 cases of variant Jakob-Creutzfeldt disease have been reported worldwide (**Figure 4-9**). Most cases of variant Jakob-Creutzfeldt disease have occurred in the United Kingdom and France. At least 10 other countries have reported cases, but some of these cases likely were exposed while residing in the United Kingdom (**Figure 4-9**). Four cases of variant Jakob-Creutzfeldt disease have been identified in the United States and two in Canada, all of whom

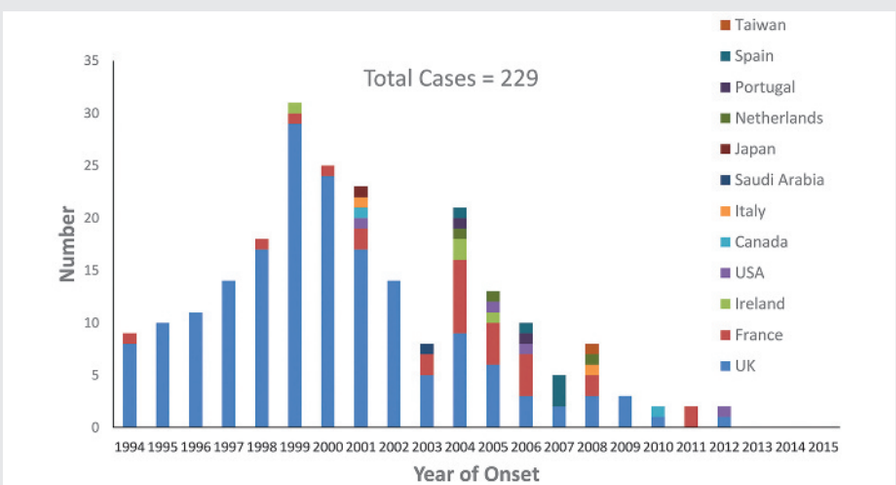

FIGURE 4-9 Variant Jakob-Creutzfeldt disease cases by year and by country 1994–2015. Box blot showing variant Jakob-Creutzfeldt disease case onset by country. Most cases have been in the United Kingdom and France. In the Western Hemisphere, there have been two cases in Canada and four in the United States. No new-onset cases have been identified after 2012.

Courtesy of the National CJD Research and Surveillance Unit, Edinburgh, UK.

KEY POINT

- Most cases of variant Jakob-Creutzfeldt disease have occurred in the United Kingdom and France. At least 10 other countries have reported cases, but in some cases they likely had their exposure while residing in the United Kingdom. Four cases of variant Jakob-Creutzfeldt disease have been identified in the United States and two in Canada, all of whom likely acquired the disease in the United Kingdom or Gulf States.

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KEY POINTS

- The clinical presentation of variant Jakob-Creutzfeldt disease usually begins with a psychiatric prodrome, often at least 6 months before the onset of traditional neurologic symptoms; cognitive dysfunction, dysesthesia, cerebellar dysfunction, and involuntary movements (eg, dystonia, myoclonus, or chorea) usually appear several months after psychiatric onset.
- Unlike all other known forms of human prion disease, in variant Jakob-Creutzfeldt disease, PrP^{Sc} is present not only in the central nervous system, but also the lymphoreticular system, probably because this disease is acquired through oral or blood product exposure.
- One radiologic feature that helps to distinguish variant Jakob-Creutzfeldt disease from other human prion diseases is the ''pulvinar sign,'' in which the pulvinar is brighter than the anterior putamen on T2-weighted images, and probably also diffusion-weighted images.

likely acquired the disease in the United Kingdom or Gulf States.[12,52,53]

The clinical presentation of variant Jakob-Creutzfeldt disease usually begins with a psychiatric prodrome, often at least 6 months before the onset of traditional neurologic symptoms; cognitive dysfunction, dysesthesia, cerebellar dysfunction, and involuntary movements (eg, dystonia, myoclonus, or chorea) usually appear several months after psychiatric onset. Compared to sporadic Jakob-Creutzfeldt disease, the median age of onset of patients with variant Jakob-Creutzfeldt disease is much younger than most sporadic Jakob-Creutzfeldt disease cases, about 27 years (range 12 to 74 years), with a longer median disease duration of 14.5 months.[52] All known neurologic cases of variant Jakob-Creutzfeldt disease have been homozygous for methionine at *PRNP* codon 129, except for one probable variant Jakob-Creutzfeldt disease case who was MV at codon 129, suggesting codon 129 heterozygosity also is a susceptibility factor for the disease.[52] It is not known if persons with codon 129 MV or VV will develop the disease after a longer incubation period or just have a much lower risk of ever developing clinical disease.

The neuropathologic features of variant Jakob-Creutzfeldt disease and Western blot features of proteinase K PrP^{Sc} are distinct from other human prion diseases.[12] Unlike all other known forms of human prion disease, in variant Jakob-Creutzfeldt disease, PrP^{Sc} is present not only in the central nervous system (CNS), but also the lymphoreticular system, probably because this disease is acquired through oral or blood product exposure.[12,52]

EEG usually shows slowing, but periodic sharp-wave complexes have only been reported in very rare cases at the end stage of disease. CSF biomarkers are less sensitive than for sporadic Jakob-Creutzfeldt disease. MRI often shows thalamic involvement. One radiologic feature that helps to distinguish variant Jakob-Creutzfeldt disease from other human prion diseases is the "pulvinar sign," in which the pulvinar is brighter than the anterior putamen on T2-weighted,[54] and probably also DWI, sequences. This finding is present in at least 75% of variant Jakob-Creutzfeldt disease cases using T2-weighted MRI[54] and probably much more frequently when DWI is used. Importantly, it rarely can be seen in sporadic Jakob-Creutzfeldt disease.[54] The so-called ''double-hockey stick sign,'' with bilateral hyperintensity of the medial and posterior (pulvinar) thalamus, is seen in several forms of prion disease, including sporadic Jakob-Creutzfeldt disease and variant Jakob-Creutzfeldt disease.[55] Several studies have suggested the possibility of detection of PrP^{Sc} in the urine of patients with variant Jakob-Creutzfeldt disease,[31] although these tests are not yet clinically available to the author's knowledge.

Because of the lymphoreticular involvement, tonsillar biopsy also can be useful for diagnosis.[56] Diagnostic criteria are divided into possible, probable, and definite categories and based on the presence of certain symptoms, EEG and MRI findings, and evidence of PrP^{Sc} in the lymphoreticular system or CNS.[54]

Despite the successful reduction of the variant Jakob-Creutzfeldt disease epidemic, in part because of the decrease of bovine spongiform encephalopathy, there remains the risk of acquiring variant Jakob-Creutzfeldt disease through the transfusion of blood products derived from donors infected with variant Jakob-Creutzfeldt disease. At least three cases acquired through blood product transfusion have been reported, with symptom onset dating from 6.5 to 7.8 years after transfusion. At the time of donation, donors were several years from onset of variant Jakob-Creutzfeldt disease

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symptoms when their blood was infective.[57,58] Furthermore, based on anonymous tonsil and appendix surveys in the United Kingdom, upward of 1 in 2000 persons in the United Kingdom are believed to be harboring latent variant Jakob-Creutzfeldt disease in their lymphoreticular system. It is not known if these persons might eventually develop the disease or be capable of transmitting it.[59–61] It is for this reason that people having spent a certain amount of time in bovine spongiform encephalopathy–infected countries, particularly during the peak period of the bovine spongiform encephalopathy epidemic, are not allowed to donate blood in the United States and that the United Kingdom primarily uses blood products obtained from the United States.

Iatrogenic Jakob-Creutzfeldt Disease

Aside from kuru, human-to-human transmission of prion disease has been known only to occur iatrogenically through infected corneal transplants, EEG depth electrodes, blood product transfusion, and most commonly cadaveric human pituitary hormone extracts and dura mater graft transplants.[62–64]

Approximately 226 cases of human growth hormone–associated iatrogenic Jakob-Creutzfeldt disease cases have been reported worldwide, mostly in patients who received cadaveric human growth hormone from the US National Hormone and Pituitary Program (NHPP) prior to 1977 (approximately 2700 recipients),[65] but at least two cases occurred through commercial (private) human growth hormone programs.[66] These patients often present with cerebellar or brainstem signs, with cognitive dysfunction occurring later. Brain imaging may show findings overlapping with sporadic Jakob-Creutzfeldt disease or restricted diffusion in the cerebellum.[66–68] Interestingly, one recent study from the United Kingdom on eight brain autopsies from human growth hormone iatrogenic Jakob-Creutzfeldt disease cases found more β-amyloid than expected for the patient's ages, suggesting that β-amyloid might also have been transmitted to these subjects.[69] An alternative possibility, however, is that prion pathology drives β-amyloid synthesis or accumulation, as was suggested from a large, sporadic Jakob-Creutzfledt disease autopsy series.[70] The incubation period thus far for human growth hormone–associated iatrogenic Jakob-Creutzfeldt disease varies widely, from 5 to 42 years (mean 17 years).[65] Although procedures were put in place after 1977 to reduce exposure from pituitary hormones, cases continue to be identified because of long incubation periods. In Europe, mostly in France, cases continue to appear at a rate of approximately two per year, with the most recent case to the author's knowledge published in 2011.[65] Codon 129 methionine homozygosity is present in about 55% of US and French cases (compared to 40% methionine homozygosity in the general population), suggesting this polymorphism is a genetic susceptibility factor.

About 228 cases of dura mater–associated iatrogenic Jakob-Creutzfeldt disease have been reported to date. One hundred forty-two cases, two-thirds of the global total, have occurred in Japan, followed by France, Spain, Germany, Italy, and the United Kingdom (8 to 14 cases each) and a handful of cases in each of a dozen other countries, including the United States.[63,71] Most cases have been linked to grafts manufactured by a German company, which marketed dura mater grafts globally in the 1980s. The disproportionately large number of cases occurring in Japan is believed to be because of dura mater being used in younger patients and in more types of procedures than other countries.[72] Although patients received these grafts

KEY POINT

- Despite the successful reduction of the variant Jakob-Creutzfeldt disease epidemic, in part because of the decrease of bovine spongiform encephalopathy, there remains the risk of acquiring variant Jakob-Creutzfeldt disease through transfusion of blood products derived from variant Jakob-Creutzfeldt disease–infected donors.

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until 1993,[63] the mean incubation period of dura mater–associated iatrogenic Jakob-Creutzfeldt disease is at least 12 years (range of 16 months to 30 years)[63]; hence, new cases are likely to continue to occur. The clinical phenotype and MRI findings of dura mater–associated iatrogenic Jakob-Creutzfeldt disease overlap with those of sporadic Jakob-Creutzfeldt disease.[63]

The incidence of human growth hormone–associated and dura mater–associated iatrogenic Jakob-Creutzfeldt disease has declined steadily since peaking in the 1990s, thanks to the introduction of recombinant growth hormone extracts and synthetic dura mater grafts.[12] Still, given the long incubation times reported for both modes of transmission, additional cases are likely to occur in the future.

Future iatrogenic cases are perhaps most likely to occur when ocular or neurosurgical procedures, such as a brain biopsy, are performed on patients with prion disease. Transmission may occur when the diagnosis is either not suspected or is suspected but not properly communicated to the operating room staff, and, consequently, proper cleaning and decontamination procedures to remove prions from the surgical tools are

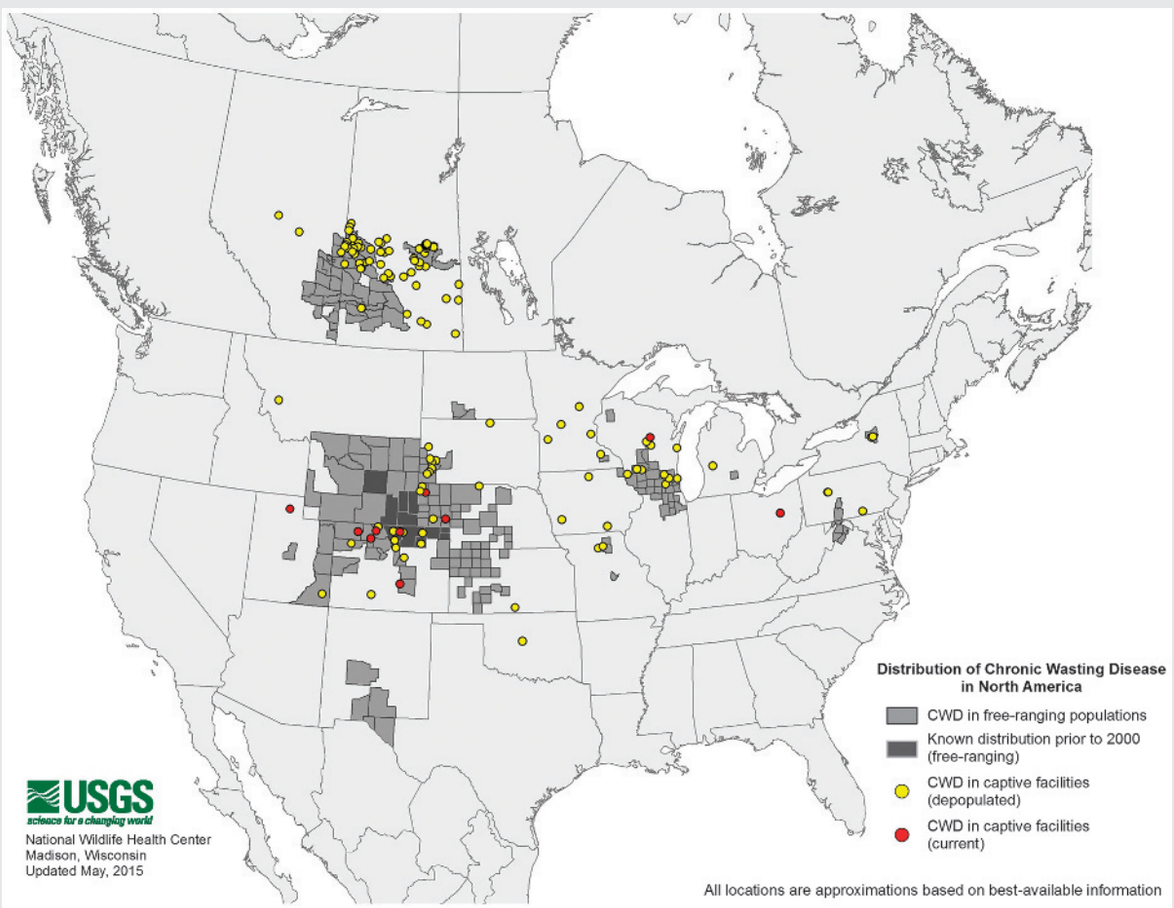

FIGURE 4-10 Map of the distribution of chronic wasting disease in North America.

Reprinted from US Geological Survey.[73] *www.nwhc.usgs.gov/disease_information/chronic_wasting_disease/*.

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not performed. Furthermore, additional cases of iatrogenic Jakob-Creutzfeldt disease acquired from remote exposure to infected human growth hormone extracts and dura mater grafts, as well as from variant Jakob-Creutzfeldt disease blood as noted above, are likely to be identified.

Chronic wasting disease, a prion disease of white-tailed and mule deer, elk, and moose found in both captive and wild ranging animals, is of some concern for animal-to-human transmission in North America (**Figure 4-10**[73]).[74] Affected animals have large concentrations of prions in lymphoid as well as CNS tissue,[71] and prions might also be shed in feces and bodily fluids, such as urine and saliva, indicating a possible route of transmission.[75,76] Studies thus far have not shown that chronic wasting disease is transmissible to humans,[77] but it has been shown to be transmissible to other species via intracerebral inoculation, and chronic wasting disease might be transmitted orally in laboratory animals.[75] Although hunters are advised not to interact with animals that appear sick, to wear rubber gloves when dressing and processing animals, and to avoid handling or consuming brain and spinal tissues, in practice it has been difficult to have hunters follow recommendations that are based solely on a theoretical risk.[78] The Centers for Disease Control and Prevention (CDC) and some state health departments are monitoring for potential new forms of human prion disease that might arise from chronic wasting disease.

TREATMENTS

Although some of the symptoms of human prion disease can be temporarily treated,[12] unfortunately, three randomized double-blinded placebo-controlled trials have failed to modify disease outcome, and currently no cures are available, although many laboratories are working in this area.[12,31]

CONCLUSION

Prion diseases are a fascinating area of medicine. Although classic presentations are often easy to diagnose, the breadth of clinical presentation is extremely broad, and thus, clinicians must have a low threshold for considering a prion diagnosis. MRI and improved CSF tests should greatly aid diagnosis of these conditions. The diagnostic workup of other rapidly progressive dementias will be presented in an upcoming *Continuum* Dementia issue article on rapidly progressive dementias. Finally, the recent discovery that other neurodegenerative diseases might spread within the brain (although not likely to be as transmissible as prion disease) in a prionlike manner should greatly advance our understanding and, it is hoped, the search for treatments for these disorders.[79]

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KEY POINTS

- The incidence of human growth hormone–associated and dura mater–associated iatrogenic Jakob-Creutzfeldt disease has declined steadily since peaking in the 1990s, thanks to the introduction of recombinant growth hormone extracts and synthetic dura mater grafts. Still, given the long incubation times reported for both modes of transmission, additional cases are likely to occur in the future.
- Chronic wasting disease, a prion disease of white-tailed and mule deer, elk, and moose found in both captive and wild-ranging animals, is of some concern for animal-to-human transmission in North America.
- Although some of the symptoms of human prion disease can be temporarily treated, unfortunately three randomized double-blinded placebo-controlled trials have failed to modify disease outcome.

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