Prion Disease

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Semin Neurol 2019;39:428–439.

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Abstract

Prion diseases are a phenotypically diverse set of disorders characterized by protease-resistant abnormally shaped proteins known as prions. There are three main groups of prion diseases, termed sporadic (Creutzfeldt–Jakob disease [CJD], sporadic fatal insomnia, and variably protease-sensitive prionopathy), genetic (genetic CJD, fatal familial insomnia, and Gerstmann–Straussler–Scheinker syndrome), and acquired (kuru, variant CJD, and iatrogenic CJD). This article will review the pathophysiology, genetics, clinical presentations, and diagnostic challenges in patients with prion disease. Case discussions, images, and tables will be used to highlight important characteristics of prion disease and prion mimics.

Keywords

- transmissible spongiform encephalopathies
- prion disease
- Creutzfeldt–Jakob disease
- fatal familial insomnia
- variant CJD
- Gerstmann–Straussler–Scheinker syndrome
- kuru
- Wernicke–Korsakoff syndrome
- Bovine spongiform encephalopathy

Human prion diseases, also termed transmissible spongiform encephalopathies, are rare fatal neurological diseases with a unique disease etiology. These diseases can be acquired, sporadic, or genetic, and are characterized by the accumulation and aggregation of prions, or abnormally folded proteins. The abnormally folded proteins, termed PrP^{sc}, have a high number of β-pleated sheets in their posttranslational conformation compared with the typical α-helices seen in the normal form of the protein (PrP^{c}).[1,2] The PrP^{sc} conformation is partially resistant to proteases and acts as a template for further misfolding of the normal PrP^{c} to abnormal PrP^{sc}.[3] Each PrP^{sc} converts a normal protein into an abnormal protein, leading to exponential conversion over a rapid period. The conversion to abnormal protein and subsequent accumulation and aggregation of the PrP^{sc} is associated with neuronal death and the pathognomonic spongiform appearance (nerve cell loss, gliosis, and vacuolation) of the brain observed in prion disease.[4,5]

The most prevalent human prion diseases are sporadic. These include sporadic Creutzfeldt–Jakob disease (sCJD) as well as the rare entities of sporadic fatal insomnia and variably protease-sensitive prionopathy (VPSPr). Genetic forms are the next most common and are caused by autosomal-dominant mutations in the *PRNP* gene that encodes for the prion protein. Genetic CJD (gCJD), Gerstmann–Straussler–Scheinker (GSS), and familial fatal insomnia (FFI) all fall into this category. Although the most notorious, the rarest forms of disease are acquired prion diseases and include kuru, iatrogenic CJD (iaCJD), and variant CJD (vCJD).

Human prion disease can be hard to diagnosis given the variable phenotypic presentations, which we will outline in this article. Fortunately, newer testing techniques such as real-time quaking-inducing conversion (RT-QuIC) and immunohistochemistry/western blot techniques for PrP^{sc} deposition are improving our diagnostic accuracy. When diagnosing human

Issue Theme Neuroinfectious Disease, Part 2; Guest Editor, Anna M. Cervantes-Arslanian, MD

DOI https://doi.org/10.1055/s-0039-1687841.
ISSN 0271-8235.

Table 1 Common mimics of prion disease listed in order of most common to least common

Autoimmune/antibody mediated disorders
Alzheimer disease, frontal temporal dementia
Other dementia (Lewy body, vascular, unclassified)
Encephalitis, not specified
Corticobasal degeneration, multiple systems atrophy
Infection (herpes virus, syphilis)
Neoplastic
Metabolic/toxic

prion disease, it is important to be aware of the broad differential diagnoses that may fall into a rapidly progressive dementia.[5] Please refer to ►**Table 1** for common CJD mimics. This article will review the current information on sporadic, genetic, and acquired human prion diseases and provide clinical vignettes highlighting the need for a thorough investigation to obtain an accurate and timely diagnosis.

Clinical Vignette 1

A 59-year-old Caucasian male presented to the emergency department with 3 months of progressive cognitive decline and gait instability. History was gathered from his wife who reported that over the past 3 months the patient's personality drastically changed from jovial to irritable, impatient, and angry. He also began to make up stories about where he had been and what he was going to do, such as stating he was in another state the day prior. More recently, the wife reported him having vivid hallucinations of people breaking into the house, for which the patient responded by getting out a gun to shoot them. The personality changes were accompanied by a change in sleep pattern, in which his typical 6 hours of sleep per night was replaced with over 12 hours per night. During the 3 weeks prior to presentation, the patient had progressive worsening of his gait with repeated falls. Per his wife, his gait was unsteady and wobbling as seen with intoxication. His neurologic examination was significant for drowsiness, poor recall, decreased attention and concentration, slow speech, and slow reaction time. Cranial nerve examination was significant for disconjugate primary gaze with left eye abduction and decreased bilateral upgaze. There was nonfatiguing direction changing nystagmus. There was severe bilateral appendicular ataxia with a wide-based gait and severe truncal ataxia. Intermittent large-amplitude negative myoclonic jerks were present in the extremities, most evident in outstretched arms.

The patient was admitted to the hospital for neurologic evaluation. Initial magnetic resonance imaging (MRI) brain with and without contrast was normal; however, his electroencephalogram (EEG) was significant for periodic multifocal left-sided sharp waves. Initial laboratory results for HIV, syphilis, Lyme disease, metabolic disorders, toxins, and heavy metals were negative. Lumbar puncture for infectious or neoplastic etiologies was also unremarkable. Vitamin B1 level resulted as undetectable, securing a diagnosis of Wernicke syndrome.

Comments: this case is an example of rapidly progressive dementia with myoclonus, oculomotor abnormalities, and ataxia. The initial history, neurologic examination, and abnormal EEG were suspicious for a diagnosis of CJD. The presentation of progressive cognitive impairment, myoclonus, visual signs, and EEG findings met probable sCJD criteria based on the World Health Organization (WHO) and University of California, San Francisco (UCSF) diagnostic criteria (►**Table 2**). Wernicke–Korsakoff syndrome is a well described CJD mimic, as this case demonstrates. This patient was treated successfully with intravenous (IV) thiamine replacement and had rapid and sustained improvement in his mentation, gait, and movement disorder. His neurologic examination returned to normal at outpatient follow-up in 1 year. This case illustrates the importance of neurologists to consider alternate reversible causes of rapidly progressive dementia. General cerebrospinal fluid (CSF) findings in CJD are normal and clinicians should be clued into a CJD mimic with CSF pleocytosis, presence of oligoclonal bands, or elevated immunoglobulin G synthetic rates.

Clinical Vignette 2

A 79-year-old Caucasian male presented for evaluation of 3 weeks of progressive cognitive decline, dysarthria, and difficulty walking. Prior to presentation, the patient was independent in all activities of daily living without neurologic deficits. Over the course of his hospitalization the patient's mental status rapidly deteriorated and he also developed abnormal movements in the right upper and lower extremity. Neurologic examination was significant for poor attention and concentration, severe deficits in registration and recall, severe dysarthria and dysphagia, and involuntary myoclonus of the right-upper and left-lower extremities.

MRI brain with and without contrast demonstrated gyriform increased T2 fluid-attenuated inversion recovery (FLAIR) signal and restricted diffusion in the gray matter of the left more than the right frontoparietal cortex with involvement of the left insular cortex (►**Fig. 1**). EEG demonstrated left hemispheric intermittent epileptiform discharges. Laboratory and CSF analysis was negative for metabolic, nutritional, toxic, inflammatory, paraneoplastic, or neoplastic causes for his symptoms. CSF analysis was significant for positive 14–3-3 protein and elevated neuron specific enolase (NSE) and tau proteins. The patient's neurologic status continued to rapidly decline, leading to death 3 weeks later.

Comment: this case illustrates a classic presentation of sCJD presenting with rapidly progressive dementia. The diagnosis in this case was supported by the MRI findings of cortical ribboning and the CSF findings of elevated 14–3-3, NSE, and tau proteins. Both the WHO and UCSF probable CJD criteria were met including rapid cognitive decline, myoclonus, pyramidal symptoms, and cerebellar findings with an abnormal EEG and MRI. Extensive workup to evaluate for other causes was negative, leading to a final diagnosis of sCJD.

Table 2 Diagnostic criteria

World Health Organization (WHO) criteria (1998)[a]
Progressive dementia
Two of the following four signs/symptoms: • Myoclonus • Pyramidal/extrapyramidal symptoms • Visual/cerebellar dysfunction • Akinetic mutism
Typical EEG or elevated CSF protein 14–3-3 with total disease duration <2 years
Routine investigations should not suggest an alternative diagnosis
University of California, San Francisco (UCSF) criteria (2007)[a]
Rapid cognitive decline
Two of the following six signs/symptoms: • Myoclonus • Pyramidal/extrapyramidal dysfunction • Visual dysfunction • Cerebellar dysfunction • Akinetic mutism • Focal cortical signs (e.g., neglect, aphasia, acalculia, apraxia)
Typical EEG and/or MRI
Other investigations should not suggest an alternative diagnosis
Amended diagnostic criteria for sporadic CJD[b]
Clinical symptoms
I. Progressive cognitive impairment II. A. Myoclonus B. Visual or cerebellar signs C. Pyramidal or cerebellar signs D. Akinetic mutism
Probable sCJD
I + two of II and typical EEG
OR I + two of II and typical MRI brain scan
OR I + two of II and positive CSF 14–3-3
OR I + one of II and positive CSF RT-QuiC
Possible sCJD
I + two of II + duration <2 years
And exclusion of other causes in complete diagnostic workup
Diagnostic algorithm for fatal familial insomnia[c]
Obligatory organic sleep disturbances. If not yet clinically apparent, a polysomnograph has to be performed.
At least two of the following "CJD-like symptoms/signs": • Psychiatric (visual hallucinations, personality change, depression, aggressiveness, disinhibition, listlessness) • Ataxia • Visual • Myoclonus • Cognitive
At least one with the following "relatively disease-specific symptoms/signs": • Loss of weight with a cutoff point of >10 kg during the last 6 months • Vegetative (hyperhidrosis, newly diagnosed arterial hypertension, tachycardia, obstipation, hyperthermia) • Husky voice
Diagnostic criteria for variant CJD[d]
Definite: IA and neuropathological confirmation of vCJD.
Probable: I and four of the five criteria of II and IIIA and IIIB; or I and IVA.
Possible: I and four of the five criteria of II and IIIA.

Table 2 (*Continued*)

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness >6 mo
	C	Routine investigations do not suggest alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric features
	B	Persistent painful sensory symptoms
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD in the early stages of illness
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy

Abbreviations: CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; RT-QuIC, real-time quaking-inducing conversion; sCJD, sporadic Creutzfeldt–Jakob disease; TSE, transmissible spongiform encephalopathy; vCJD, variant Creutzfeldt–Jakob disease.

[a]Revised from Geschwind MD. Rapidly progressive dementia. Continuum 2016;22:510–37.

[b]Revised from Hermann P, Laux M, Glatzel M, et al. Validation and utilization of amended diagnostic criteria in Creutzfeldt–Jakob disease surveillance. Neurology 2018;91:e331–e338.

[c]Revised from Krasnianski A, Vartl M, Sanchez Juan PJ, et al. Fatal familial insomnia: clinical features and early identification. Ann Neurol 2008;63:658–661.

[d]Revised from Heath CA, Cooper SA, Murray K, et al. Diagnosing variant Creutzfeldt–Jakob disease: a retrospective analysis of the first 150 cases in the UK. J Neurol Neurosurg Psychiatry 2011;82:646–651.

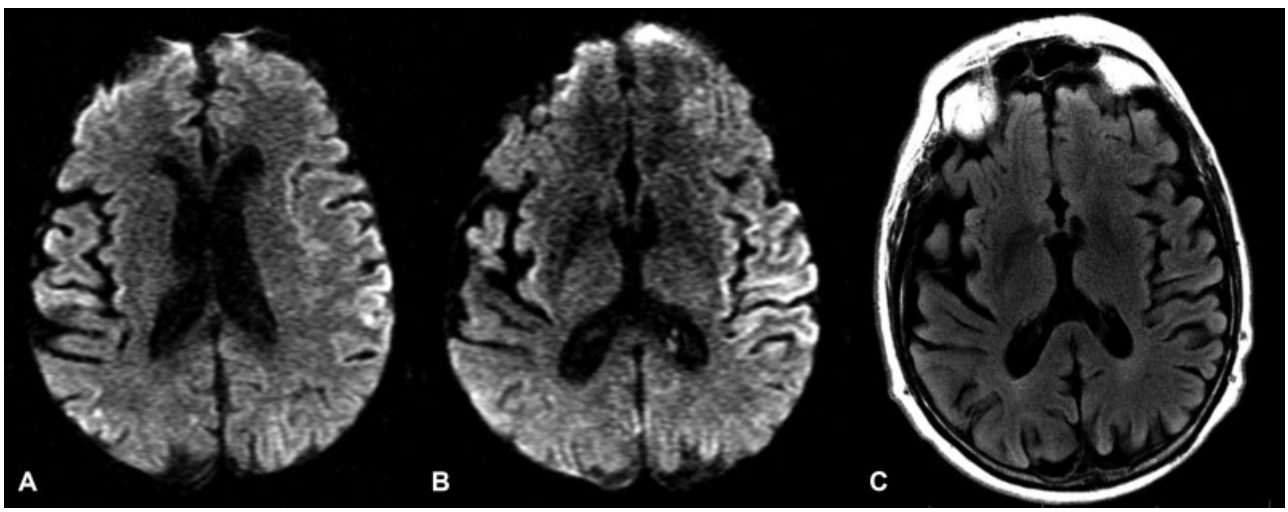

Fig. 1 Case 2: axial MRI brain without contrast. Diffusion-weighted imaging (DWI) demonstrates restricted diffusion within the cortical ribbon of bilateral temporal, parietal, and occipital lobes **(A, B)**. FLAIR imaging demonstrates cortical hyperintensities in the left temporal lobe corresponding with the areas of restricted diffusion **(C)**. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Sporadic Human Prion Disease

Sporadic Creutzfeldt–Jakob Disease

sCJD is the most common human prion disease with an age of onset between 50 and 80 years and has a mean survival of 6 months.[6,7] The typical clinical features are rapidly progressive dementia, ataxia, and myoclonus, but beyond this there is significant phenotypic heterogeneity (►**Table 3**).[8,9] Other clinical symptoms include language disturbances, neuropsychiatric behavioral changes, visual impairment, spasticity, weakness, and akinetic mutism.[10] One notable sporadic variant has been referred to as the "Heidenhain variant" described in the 1950s. This variant of CJD may manifest as disturbed color perception, hallucinations, cortical blindness, or Anton syndrome. With this variant, dementia and other findings of typical CJD do not manifest until late in the disease course.[11]

Attempts to better classify the phenotypes focus on molecular prion types 1 and 2 and the methionine (M) and

Table 3 Sporadic prion subtypes, clinical presentation, imaging findings, and diagnostic testing

	Pathophysiology	Clinical presentation	Imaging characteristics	EEG characteristics	Diagnostic testing	Special notes
Sporadic CJD: polymorphism in the prion gene, *PRNP*, at codon 129, which can be either methionine (M) or valine (V)	MM1/MVI: diffuse cortical, including occipital, and thalamic involvement	Early rapid dementia, myoclonus, ataxia, 25% visual disturbance	Diffusion-weighted images (DWIs) and apparent diffusion coefficient with restricted diffusion in the cortex, caudate, and/or putamen. Abnormal FLAIR hyperintensities in the cortex (cortical ribboning)	1–2 Hz periodic sharp-wave (often biphasic or triphasic) complexes—these appear late in disease	Mild elevation in CSF protein. CSF biomarkers, including NSE, t-tau, and S100β, CSF 14–3-3 protein Real-time quaking-inducing conversion (RT-QuIC) amplification of CSF prion protein Histopathology: nerve cell loss, gliosis, vacuolation (formerly called spongiform change), and PrP^{sc} deposition, protease-resistant PrP^{sc} with immunohistochemistry or western blot	Affects ages 55–75 years; one-third of patients may have constitutional symptoms of fatigue, headache, vertigo, altered sleep or eating patterns. 15% have cortical features of apraxia, neglect.
	MM2: thalamic	Insomnia, psychomotor agitation, ataxia, and cognitive changes				
	MM2 cortical: all cortical layers	Progressive dementia				
	MV2	Early ataxia or cognitive decline—slowly progressive				
	VV1	Progressive dementia				
	VV2: cerebellar	Rapidly progressive ataxia, with later dementia				
Variably protease-sensitive prionopathy	VV polymorphisms	Neuropsychiatric features and later cognitive decline and motor symptoms	MRI with generalized atrophy		Paucity of protease-resistant PrP^{sc} when run on western blot. Neuropathologically: spongiform changes and gliosis.	Affects ages 50–70 years with a longer disease duration (12–78 mo). 50% with ataxia EEG, CSF, and MRI are not helpful for diagnosis
	MM polymorphism	Prominent parkinsonism and myoclonus without psychiatric and cognitive changes				
	MV polymorphism	Neuropsychiatric features and later cognitive decline and motor symptoms				

Abbreviations: CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; NSE, neuron-specific enolase.

valine (V) 129 codon polymorphism.[9,12,13] Researchers have described six subtypes of sCJD: MM1/MV1, MM2 cortical, MM2 thalamic, MV2, VV1, and VV2.[14,15] MM1/MVI is considered the more classical form with diffuse cortical involvement, including occipital and thalamic. Clinical features include early dementia and myoclonus, typical periodic sharp-wave complexes on EEG, and frequent visual disturbances. VV2 has significant involvement of the subcortical structures, including the brainstem nuclei, with earlier clinical signs of ataxia and later dementia. MV2 presents similarly to VV2 with early ataxia progressing to dementia often with a longer disease duration. There is prominent cerebellar involvement in this form. MM2 thalamic has spongiform changes mostly isolated to the thalamus and inferior olives. It is associated with insomnia, psychomotor agitation, ataxia, and cognitive changes. MM2 cortical and VV1 are both characterized by progressive dementia. MM2 cortical features pathological changes throughout all cortical layers, while VV1 features changes in both the cortex and striatum. While these subtypes are useful, it is important to note that they do not fully characterize the broad spectrum of this disease, as up to 35% of subjects can show a mixed phenotypic presentation with two or more PrP^{sc} subtypes colocalized in these individuals.[16,17]

Diagnostic testing including EEG, MRI, and CSF parameters are useful to help secure a diagnosis of sCJD. As described above, EEG may show typical 1 to 2 Hz periodic sharp-wave complexes but are often absent until late in the disease process.[18,19] A helpful diagnostic feature commonly seen in sCJD is the MRI finding of abnormal restricted diffusion in the cortex, caudate, and/or putamen and abnormal FLAIR hyperintensities in the cortical ribbon.[20–22] MRI has variable sensitivity (92–96%) and specificity (93–94%) for the diagnosis of sCJD (►**Fig. 2**).[5] CSF biomarkers including

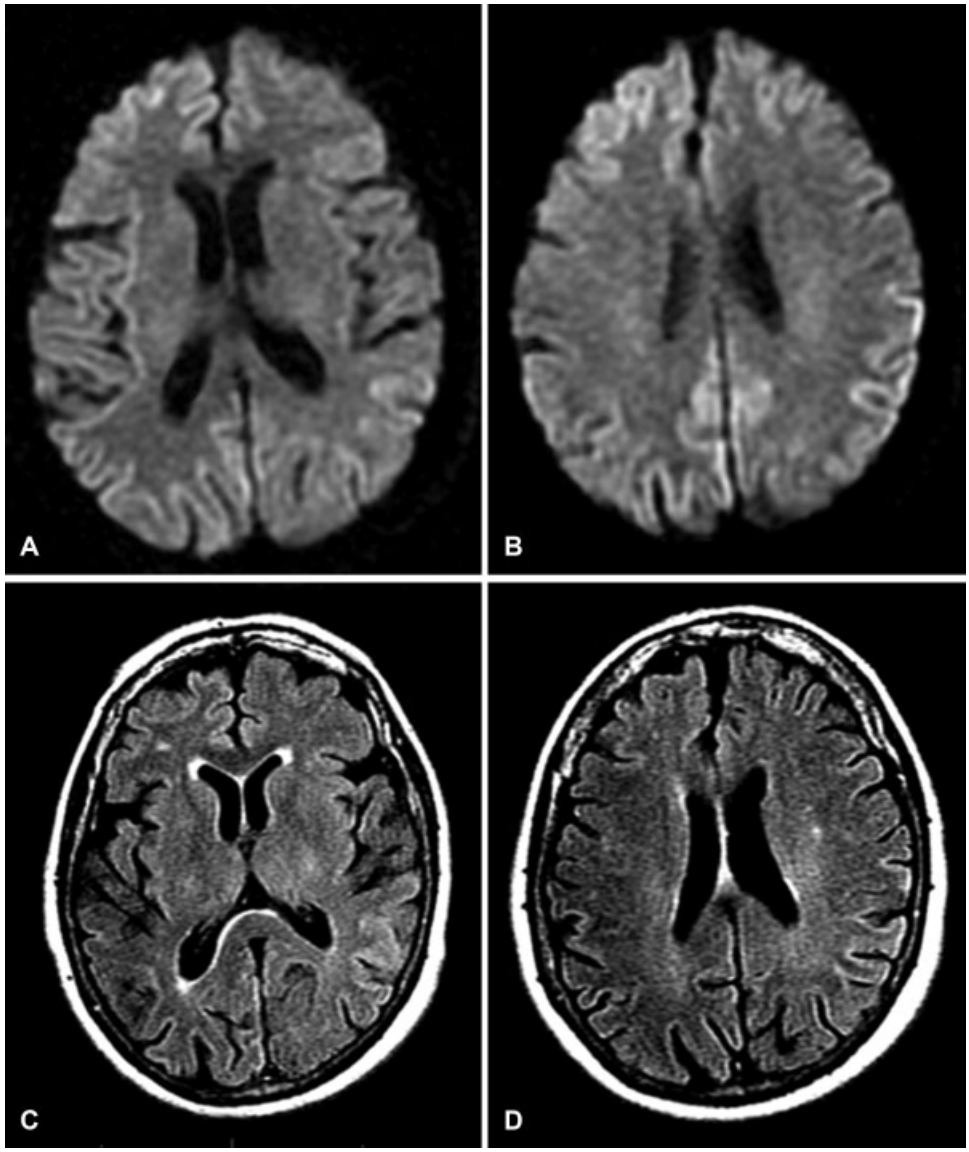

Fig. 2 Axial MRI brain without contrast. Diffusion-weighted imaging (DWI) demonstrates restricted diffusion within the cortical ribbon of bilateral frontal, parietal, and occipital lobes **(A, B)**. FLAIR imaging demonstrates cortical hyperintensities in the right frontal lobe and left parietal lobe which correspond with the areas of restricted diffusion **(C, D)**. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

14–3-3 protein, NSE, and total tau protein can be helpful when taken into clinical context to support the diagnosis of sCJD; however, it is important to note that these are not specific for disease and can be negative in many disease subtypes (►**Tables 3** and **4**).[23–25] The more recently available test of RT-QuIC amplification of CSF prion protein has shown a sensitivity ranging from 77 to 92% and specificity of 99 to 100% for sCJD, and is a promising test for many CJD subtypes.[26–29] ►**Table 2** shows the amended diagnostic criteria for CJD with the use of RT-QuIC amplification.[29–31]

Sporadic Fatal Insomnia

An extremely rare form of fatal insomnia has been described with no mutation identified and no family history to suggest a genetic disorder.[32,33] The clinical symptoms and thalamic pathology are identical to FFI (described below). Clinical presentations include abnormalities in sleep, neuropsychiatric changes, gait abnormalities, and movement disorders. Neuropathological changes are most significant in the thalamus and inferior olives.[34] High levels of type 2 PrP^{sc} were found and all patients identified had MM homozygosity.

Variably Protease-Sensitive Prionopathy

VPSPr, first described in 2008, is the most recent human prion disease to be discovered.[34,35] The initial cohort of patients all contained VV polymorphisms at codon 129 of the *PRNP* gene and were significantly protease-sensitive. The later discovery of patient with MM and MV codon 129 polymorphisms as well as variability in protease sensitivity leads to the current term of variably protease-sensitive prionopathy. The western blot of this prion differs from CJD in size and structure. As the name implies, it is also relatively more sensitive to protease digestion than other prion diseases. Symptom onset is typically in the 50s to 70s with a longer disease duration of 12 to 78 months.[36] The initial clinical description included only MM codon 129 polymorphism patients with predominant neuropsychiatric features and later cognitive decline and motor symptoms.[35] The same authors later described a cohort of 15 patients with other codon 129 polymorphisms, suggesting polymorphic-specific phenotypes in this disease as well.[37] Patients with homozygous MM polymorphism were more likely to have prominent parkinsonism and myoclonus without psychiatric and cognitive changes. On the other hand, the MV and VV patients displayed much more prominent psychiatric and dementia symptoms with less parkinsonism and myoclonus. At least half of the reported patients in all three polymorphism groups also displayed ataxia. EEG, CSF 14–3-3, and MRI testing are less helpful for diagnosis compared with sCJD.[34] Neuropathologically, spongiform changes and gliosis are seen throughout the cerebral cortex, basal ganglia, and thalamus, with smaller changes noted in the cerebellum (►**Table 3**).[35,36]

Genetic Human Prion Diseases

Genetic Creutzfeldt–Jakob Disease

Genetic, or familial, CJD is the most common form of inherited prion disease and is largely indistinguishable from sCJD. While dozens of different mutations in the *PRNP* gene can cause familial CJD, most subjects have either octapeptide insertional mutations or point mutations at codons 102, 178, 200, and 210.[38,39] Compared with sCJD, gCJD subjects present earlier and have a younger age of mortality, though disease duration is not significantly different.[7,14,39] Interestingly, most patients with genetic prion disease have no family history. Common presenting symptoms include dementia, ataxia, myoclonus, parkinsonism, and neuropsychiatric symptoms.[40,41] While periodic complexes on EEG, diffusion-weighted abnormalities on MRI, and elevated 14–3-3 can be helpful in diagnosing gCJD, they are less sensitive than in the diagnosis of sCJD.[15,39] Definitive diagnosis of gCJD requires a clinical diagnosis of CJD with definitive or probable diagnosis of CJD in a first degree relative or neuropsychiatric disorder with a disease-specific *PRNP* gene mutation (►**Table 2**).[31]

Gerstmann–Straussler–Scheinker Syndrome

GSS is the second most commonly inherited prion disorder. It is caused by a variety of missense, nonsense, and octapeptide repeat insertional mutations in the *PRNP* gene, with the most frequently reported being a Pro102Leu mutation.[42,43] The disease has nearly 100% penetrance with clinical signs of cerebellar ataxia, tremor, speech and swallowing abnormalities, pyramidal signs, parkinsonism, sensory dysesthesias, and cognitive changes.[44]

Disease onset and duration are quite broad with onset ranging from 20s to 80s and duration lasting as short as a few months to >10 years.[45] The specific mutation can help narrow onset, duration, and clinical symptoms. Codon 129 polymorphisms can also play a role in the phenotype of this disease. In the Pro102Leu mutation, MM homozygosity is associated with earlier onset compared with MV patients, whereas apolipoprotein E carriers have later onset of symptoms.[46] Neuropathologically, GSS is characterized by prion protein-immunopositive amyloid plaques and tau-immunopositive neurofibrillary tangles with or without spongiform changes.[47] This unique pathology has led to the term "dominantly inherited prion protein cerebral amyloidosis" rather than the historical name of Gerstmann–Straussler–Scheinker disease.[46] Diagnosis requires obtaining a thorough clinical and family history. MRI is not typically helpful· While EEG and 14–3-3 can be helpful, they are neither sensitive nor specific in this disease.[43] RT-QuIC has shown a positive result in 90% of patients when testing in the Pro102Leu mutation population.[39,48] Western blot and genetic testing are the most definitive testing available.[46]

Familial Fatal Insomnia

FFI is the third most common inherited prion disorder. Despite this fact, it is still extremely rare with a risk of one in 30 million people in the general population. It is associated with a missense D178N mutation at codon 178 of the *PRNP* gene.[15,32,49] Interestingly, this same mutation in seen in sCJD. Once again, codon 129 polymorphism plays a role, with the methionine polymorphism leading to an FFI phenotype and valine polymorphism leading to a CJD phenotype.[50–52] Onset of FFI is between the 30s and 60s with a

Table 4 Genetic and acquired subtypes, clinical presentation, imaging findings, and diagnostic testing

	Pathophysiology	Clinical presentation	Imaging characteristics	EEG characteristics	Diagnostic testing	Special notes
Genetic CJD	Autosomal dominant mutations in the *PRNP* gene	Dementia, ataxia, myoclonus, parkinsonism, and neuropsychiatric symptoms	High signal on the diffusion-weighted images (DWIs) localized to the cortex, caudate, and/or putamen	Periodic sharp-wave complexes (late disease finding)	*PRNP* gene mutation 14–3-3, NSE, and t-tau often are elevated; RT-QuIC on CSF	Young age of presentation. Most common *PRNP* mutation worldwide, E200K.
Gerstmann–Straussler–Scheinker syndrome	Autosomal-dominant mutations in the *PRNP* gene: over a dozen mutations	Progressive ataxia, dysarthria, dysphagia, tremor, and motor dysfunction		Generalized slowing	*PRNP* gene mutation	Biomarkers not helpful. Heterozygosity at the *PRNP* codon 129 appears to be protective. Less cognitive symptoms than other subtypes
Fatal familial insomnia	Autosomal-dominant mutations in the *PRNP* gene: a single *PRNP* point mutation, D178N with the cis codon 129M	Abnormalities in sleep, neuropsychiatric changes, gait abnormalities, and movement disorders	FDG-PET hypometabolism in thalamic and cingulate regions	Generalized slowing	*PRNP* gene mutation; sleep studies with reduction in total sleep times, dream enactment, and disorganization of typical sleep cycles	Dysautonomia common. Biomarkers and MRI are not helpful.
Kuru	Acquired form from cannibalism in Papua New Guinea	Progressive ataxia, dysarthria, dysphagia, tremor, and motor dysfunction				*PRNP* polymorphism at codon 127 seems to be protective. Less cognitive complaints
Iatrogenic CJD	Medical devices and transplanted human substances (growth hormone, dura matter grafts) that have been contaminated by PrP^{sc}	Cerebellum with prominent ataxia and later cognitive impairment				Codon 129 polymorphisms seem to effect susceptibility to and incubation timelines of iaCJD (5–42 years)
Variant CJD	Codon 129 polymorphism, methionine homozygous genotype. Transmission directly from animals to humans	Initial neuropsychiatric symptoms that progress to ataxia, abnormal movements, and cognitive decline	MRI diffusion-weighted imaging signal intensity in the pulvinar region of the thalamus (pulvinar sign), which is seen in over 90% of subjects		Brain biopsy, tonsil biopsy	Bovine spongiform encephalopathy prion present in lymphoreticular system. EEG, CSF, and RT-QuIC are not helpful for diagnosis

Abbreviations: CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; iaCJD, iatrogenic CJD; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; RT-QuIC, real-time quaking-inducing conversion.

typical duration of 1 to 2 years.[53] FFI is characterized by abnormal vigilance and sleep patterns. Subjects can initially appear hypersomnolent with psychiatric and mood changes, which are associated with abnormal nocturnal sleep patterns that may not be recognized in the initial stage of the disease.[54–57] As the disease progresses, polysomnography shows reduction in typical sleep transients on EEG, reduction in total sleep times, dream enactment, and disorganization of typical sleep cycles.[58–60] Eventually, subjects experience prolonged periods of abnormal stupor. Autonomic abnormalities with hypertension, pyrexia, and tachycardia as well as movement disorders and gait changes can also be present.[61] Overall metabolic demand is heightened with resultant cachexia. While MRI findings are nonspecific showing diffuse atrophy, positron-emission tomography (PET) scans show prominent thalamic hypometabolism and milder decreases in corpus callosum metabolism.[62,63] CSF 14–3-3 has low sensitivity in FFI. Neuronal loss and gliosis are severe in the anterior ventral and mediodorsal nuclei of the thalamus as well as the inferior olives, with spongiform changes noted very late in the disease course.[54,64,65] While genetic testing is needed for the diagnosis of this disorder, various schema have been proposed to help with the diagnosis and establish which patients should undergo definitive genetic testing. These algorithms, such as the one proposed by Krasnianski et al[66] (►**Table 2**), focus on clinical signs and polysomnography.

Acquired Human Prion Diseases

Kuru

Kuru, first described in the 1950s, was an epidemic disease of the Fore tribe of Papua New Guinea. This spongiform encephalopathy had a typical duration of 1 year characterized by progressive ataxia, dysarthria, dysphagia, tremor, and motor dysfunction with less cognitive dementia symptoms than other human prion diseases. The disease was determined to be caused by ritualistic endocannibalism, with women and children more highly affected as they typically prepared and consumed the brains.[67] Spongiform changes were often severe in the cerebellum, but also seen throughout the cerebral cortex, basal ganglia, and thalamus. Heterozygosity at the *PRNP* codon 129 appears to be protective as it was associated with significantly longer incubation periods.[68] Fortunately, kuru is now extinct following the decline of the Fore endocannibalism ritual in the 1960s.[10]

Iatrogenic Creutzfeldt–Jakob Disease

iaCJD is caused by the use of medical devices and transplanted human substances that have been contaminated by PrP^{sc}. The initial reports occurred in the 1970s in the setting of transplantation of contaminated corneas. Later larger sources of outbreaks occurred due to contaminated growth hormone and dura mater grafts.[69,70] There have even been rare cases of vCJD passed through contaminated blood transfusion.[71,72] With contamination that occurs near the brain due to dura mater grafts and intracranial surgical devices, the clinical presentation is similar to sCJD with rapidly progressive dementia, ataxia, and myoclonus. Presentations related to peripheral growth hormone injection tend to more strongly affect the cerebellum with prominent ataxia and later cognitive impairment.[73] iaCJD is more likely to occur in the younger population.[74] Like the other prion diseases, codon 129 polymorphisms seem to effect susceptibility to and incubation timelines of iaCJD.[6,73,75] Fortunately, the incidence of iaCJD has significantly decreased in the last decade with only rare new diagnoses likely due to long incubation periods.[70] This improvement can be linked to changes in medical practice with better infectivity prevention and use of recombinant growth hormone and autologous or synthetic dura mater grafts (►**Table 4**).

Variant Creutzfeldt–Jakob Disease

The first cases of vCJD were described in 1996.[76] They were eventually found to be transmitted through ingestion of cattle found to have bovine spongiform encephalopathy. To date, over 225 cases have been reported worldwide with the largest number reported in the United Kingdom.[77,78] With regard to codon 129 polymorphism, only the methionine homozygous genotype has been identified in vCJD subjects, suggesting this genotype is susceptible to this disease.[79] vCJD typically presents with initial neuropsychiatric symptoms that progress to ataxia, abnormal movements, and cognitive decline with typical duration of over a year.[70–82] EEG abnormalities and CSF 14–3-3 are not very sensitive.[83,84] CSF RT-QuIC testing has been negative.[10] The most sensitive finding is MRI diffusion-weighted imaging signal intensity in the pulvinar region of the thalamus (pulvinar sign), which is seen in over 90% of subjects.[85,86] While definite diagnosis of vCJD requires brain biopsy, the abnormal prion in vCJD can be found in lymphoreticular tissue, leading to tonsillar biopsy being the location of choice for tissue diagnosis.[87] Diagnostic criteria for definite and probable vCJD using clinical presentation, lack of EEG periodic complexes, and pulvinar high-signal MRI (►**Table 2**) have been shown to have high sensitivity and specificity.[82,88,89] With better food production methods, the initial epidemic of this disease has declined, with only two reported deaths from this disease in the United Kingdom since 2012 (►**Table 4**).[90]

Conclusions

Human prion diseases, while rare, are devastating and fatal neurological diseases with no current treatment options. Despite this fact, they are still important to diagnose given the potential genetic ramifications and risk of acquired transmission. sCJD is by far the most likely to be observed in clinical practice, and recent improvements in diagnostic testing with EEG, MRI, and RT-QuIC have dramatically increased sensitivity and specificity for the diagnosis of this disease. Fortunately, the acquired prion diseases (kuru, iaCJD, and vCJD), which are the rarest yet in many ways the most concerning forms of human prion disease, have become nearly nonexistent thanks to better preventative measures. Nonetheless, it is still important to be vigilant for cases with prolonged incubation periods or new variants of prion

disease transmitted from animals. With regard to the less frequent sporadic and genetic human prior diseases (gCJD, GSS, FFI, VPSPr, etc.), diagnostic testing has variable sensitivity, and RT-QuIC is not validated in these diseases. Hence, it is important to be aware of the typical clinical presentations and maintain a high clinical suspicion. When the more infrequent sporadic and genetic prion diseases are suspected, and mimics have been excluded, either genetic testing or autopsy neuropathological findings will be needed for diagnosis.

Conflict of Interest
None.

References

1 Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science 1982;216(4542):136–144
2 Pan KM, Baldwin M, Nguyen J, et al. Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins. Proc Natl Acad Sci U S A 1993;90(23):10962–10966
3 Prusiner SB. Prions. Proc Natl Acad Sci U S A 1998;95(23): 13363–13383
4 Glatzel M, Stoeck K, Seeger H, Lührs T, Aguzzi A. Human prion diseases: molecular and clinical aspects. Arch Neurol 2005;62(04): 545–552
5 Geschwind MD. Rapidly progressive dementia. Continuum (Minneap Minn) 2016;22(2 Dementia):510–537
6 Ladogana A, Puopolo M, Croes EA, et al. Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology 2005;64(09):1586–1591
7 Takada LT, Kim MO, Metcalf S, Gala II, Geschwind MD. Prion disease. In: Geschwin DH, Paulson HL, Klein C, eds. Handbook of Clinical Neurology, 148. Amsterdam, Elsevier; 2018: 441–464
8 Will RG. Clinical features of human prion diseases. In: Asbury AK, McKhann GM, McDonald WI, et al. eds. Diseases of the Nervous System: Clinical Neuroscience and Therapeutic Principles. 3rd ed. Cambridge: Cambridge University Press; 2002:1716–1727
9 Puoti G, Bizzi A, Forloni G, Safar JG, Tagliavini F, Gambetti P. Sporadic human prion diseases: molecular insights and diagnosis. Lancet Neurol 2012;11(07):618–628
10 Will RG, Ironside JW. Sporadic and infectious human prion diseases. In: Prusiner SB. ed. Prion Biology and Diseases, 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2004:73–93
11 Kropp S, Schulz-Schaeffer WJ, Finkenstaedt M, et al. The Heidenhain variant of Creutzfeldt-Jakob disease. Arch Neurol 1999;56 (01):55–61
12 Parchi P, Castellani R, Capellari S, et al. Molecular basis of phenotypic variability in sporadic Creutzfeldt-Jakob disease. Ann Neurol 1996;39(06):767–778
13 Parchi P, Capellari S, Chen SG, et al. Typing prion isoforms. Nature 1997;386(6622)232–234
14 Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999;46(02):224–233
15 Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. Sporadic and familial CJD: classification and characterisation. Br Med Bull 2003;66(01):213–239
16 Parchi P, Capellari S, Roncaroli F, et al. Co-occurrence of type 1 and type 2 PrPres in sporadic Creutzfeldt-Jakob disease: prevalence, intracerebral variability and phenotypic correlations. Neurol Sci 2001;22:S116
17 Parchi P, Strammiello R, Notari S, et al. Incidence and spectrum of sporadic Creutzfeldt-Jakob disease variants with mixed phenotype and co-occurrence of PrPSc types: an updated classification. Acta Neuropathol 2009;118(05):659–671
18 Steinhoff BJ, Zerr I, Glatting M, Schulz-Schaeffer W, Poser S, Kretzschmar HA. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol 2004;56(05):702–708
19 Collins SJ, Sanchez-Juan P, Masters CL, et al. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. Brain 2006;129(Pt 9):2278–2287
20 Meissner B, Kallenberg K, Sanchez-Juan P, et al. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology 2009;72(23): 1994–2001
21 Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology 2011;76(20):1711–1719
22 Gaudino S, Gangemi E, Colantonio R, et al. Neuroradiology of human prion diseases, diagnosis and differential diagnosis. Radiol Med (Torino) 2017;122(05):369–385
23 Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55(06):811–815
24 Green A, Sanchez-Juan P, Ladogana A, et al. CSF analysis in patients with sporadic CJD and other transmissible spongiform encephalopathies. Eur J Neurol 2007;14(02):121–124
25 Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology 2012;79(06):547–552
26 McGuire LI, Peden AH, Orrú CD, et al. Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. Ann Neurol 2012;72(02):278–285
27 Zanusso G, Monaco S, Pocchiari M, Caughey B. Advanced tests for early and accurate diagnosis of Creutzfeldt-Jakob disease. Nat Rev Neurol 2016;12(06):325–333
28 Foutz A, Appleby BS, Hamlin C, et al. Diagnostic and prognostic value of human prion detection in cerebrospinal fluid. Ann Neurol 2017;81(01):79–92
29 Hermann P, Laux M, Glatzel M, et al. Validation and utilization of amended diagnostic criteria in Creutzfeldt-Jakob disease surveillance. Neurology 2018;91(04):e331–e338
30 Bizzi A, Peoc'h K. Amended diagnostic protocol increases the early diagnosis of sporadic Creutzfeldt-Jakob disease. Neurology 2018; 91(04):155–156
31 Center for Disease Control and Prevention. CDC's diagnostic criteria for Creutzfeldt–Jakob Disease (CJD), 2018. Available at: https://www.cdc.gov/prions/cjd/diagnostic-criteria.html. Updated September 17, 2018. Accessed October 29, 2018
32 Mastrianni JA, Nixon R, Layzer R, et al. Prion protein conformation in a patient with sporadic fatal insomnia. N Engl J Med 1999;340 (21):1630–1638
33 Montagna P, Gambetti P, Cortelli P, Lugaresi E. Familial and sporadic fatal insomnia. Lancet Neurol 2003;2(03):167–176
34 Scaravilli F, Cordery RJ, Kretzschmar H, et al. Sporadic fatal insomnia: a case study. Ann Neurol 2000;48(04):665–668
35 Gambetti P, Dong Z, Yuan J, et al. A novel human disease with abnormal prion protein sensitive to protease. Ann Neurol 2008;63 (06):697–708
36 Head MW, Yull HM, Ritchie DL, et al. Variably protease-sensitive prionopathy in the UK: a retrospective review 1991-2008. Brain 2013;136(Pt 4):1102–1115
37 Zou WQ, Puoti G, Xiao X, et al. Variably protease-sensitive prionopathy: a new sporadic disease of the prion protein. Ann Neurol 2010;68(02):162–172
38 Capellari S, Cardone F, Notari S, et al. Creutzfeldt-Jakob disease associated with the R208H mutation in the prion protein gene. Neurology 2005;64(05):905–907
39 Kovács GG, Puopolo M, Ladogana A, et al; EUROCJD Genetic prion disease: the EUROCJD experience. Hum Genet 2005;118(02): 166–174

40 Meiner Z, Gabizon R, Prusiner SB. Familial Creutzfeldt-Jakob disease. Codon 200 prion disease in Libyan Jews. Medicine (Baltimore) 1997;76(04):227–237

41 Kovács GG, Trabattoni G, Hainfellner JA, Ironside JW, Knight RS, Budka H. Mutations of the prion protein gene phenotypic spectrum. J Neurol 2002;249(11):1567–1582

42 Arata H, Takashima H, Hirano R, et al. Early clinical signs and imaging findings in Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu). Neurology 2006;66(11):1672–1678

43 Webb TE, Poulter M, Beck J, et al. Phenotypic heterogeneity and genetic modification of P102L inherited prion disease in an international series. Brain 2008;131(Pt 10):2632–2646

44 Kong Q, Surewicz WK, Petersen RB, et al. Inherited prion diseases. In: Prusiner SB. ed. Prion Biology and Diseases, 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2004:673–775

45 Piccardo P, Dlouhy SR, Lievens PM, et al. Phenotypic variability of Gerstmann-Sträussler-Scheinker disease is associated with prion protein heterogeneity. J Neuropathol Exp Neurol 1998;57(10): 979–988

46 Ghetti B, Piccardo P, Zanusso G. Dominantly inherited prion protein cerebral amyloidosis – a modern view of Gerstmann-Straussler-Scheinker. In: Pocchiari M, Manson J, eds. Handbook of Clinical Neurology. Amsterdam: Elsevier; 2018:243–269

47 Masters CL, Gajdusek DC, Gibbs CJ Jr. Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Sträussler syndrome with an analysis of the various forms of amyloid plaque deposition in the virus-induced spongiform encephalopathies. Brain 1981;104 (03):559–588

48 Sano K, Satoh K, Atarashi R, et al. Early detection of abnormal prion protein in genetic human prion diseases now possible using real-time QUIC assay. PLoS One 2013;8(01):e54915

49 Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. N Engl J Med 1992;326(07):444–449

50 Goldfarb LG, Petersen RB, Tabaton M, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. Science 1992;258(5083):806–808

51 Monari L, Chen SG, Brown P, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: different prion proteins determined by a DNA polymorphism. Proc Natl Acad Sci U S A 1994;91 (07):2839–2842

52 Johnson RT. Prion diseases. Lancet Neurol 2005;4(10):635–642

53 Harder A, Gregor A, Wirth T, et al. Early age of onset in fatal familial insomnia. Two novel cases and review of the literature. J Neurol 2004;251(06):715–724

54 Lugaresi E, Medori R, Montagna P, et al. Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei. N Engl J Med 1986;315(16):997–1003

55 Gallassi R, Morreale A, Montagna P, Gambetti P, Lugaresi E. "Fatal familial insomnia": neuropsychological study of a disease with thalamic degeneration. Cortex 1992;28(02):175–187

56 Gallassi R, Morreale A, Montagna P, et al. Fatal familial insomnia: behavioral and cognitive features. Neurology 1996;46(04):935–939

57 Krasnianski A, Bartl M, Sanchez Juan PJ, et al. Fatal familial insomnia: clinical features and early identification. Ann Neurol 2008;63(05):658–661

58 Tinuper P, Montagna P, Medori R, et al. The thalamus participates in the regulation of the sleep-waking cycle. A clinico-pathological study in fatal familial thalamic degeneration. Electroencephalogr Clin Neurophysiol 1989;73(02):117–123

59 Portaluppi F, Cortelli P, Avoni P, et al. Progressive disruption of the circadian rhythm of melatonin in fatal familial insomnia. J Clin Endocrinol Metab 1994;78(05):1075–1078

60 Sforza E, Montagna P, Tinuper P, et al. Sleep-wake cycle abnormalities in fatal familial insomnia. Evidence of the role of the thalamus in sleep regulation. Electroencephalogr Clin Neurophysiol 1995;94(06):398–405

61 Cortelli P, Parchi P, Contin M, et al. Cardiovascular dysautonomia in fatal familial insomnia. Clin Auton Res 1991;1(01):15–21

62 Perani D, Cortelli P, Lucignani G, et al. [18F]FDG PET in fatal familial insomnia: the functional effects of thalamic lesions. Neurology 1993;43(12):2565–2569

63 Cortelli P, Perani D, Montagna P, et al. Pre-symptomatic diagnosis in fatal familial insomnia: serial neurophysiological and 18FDG-PET studies. Brain 2006;129(Pt 3):668–675

64 Manetto V, Medori R, Cortelli P, et al. Fatal familial insomnia: clinical and pathologic study of five new cases. Neurology 1992; 42(02):312–319

65 Schmitz M, Dittmar K, Llorens F, et al. Hereditary human prior diseases: an update. Mol Neurobiol 2017;54(06):4138–4149

66 Krasnianski A, Sanchez Juan P, Ponto C, et al. A proposal of new diagnostic pathway for fatal familial insomnia. J Neurol Neurosurg Psychiatry 2014;85(06):654–659

67 Liberski PP, Sikorska B, Lindenbaum S, et al. Kuru: genes, cannibals and neuropathology. J Neuropathol Exp Neurol 2012;71(02): 92–103

68 Collinge J, Whitfield J, McKintosh E, et al. Kuru in the 21st century–an acquired human prion disease with very long incubation periods. Lancet 2006;367(9528):2068–2074

69 Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. Neurology 2000;55(08):1075–1081

70 Brown P, Brandel JP, Sato T, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis 2012;18(06): 901–907

71 Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. Vox Sang 2006;91(03): 221–230

72 Seed CR, Hewitt PE, Dodd RY, Houston F, Cervenakova L. Creutzfeldt-Jakob disease and blood transfusion safety. Vox Sang 2018; 113(03):220–231

73 Rudge P, Jaunmuktane Z, Adlard P, et al. Iatrogenic CJD due to pituitary-derived growth hormone with genetically determined incubation times of up to 40 years. Brain 2015;138(Pt 11):3386–3399

74 Holman RC, Belay ED, Christensen KY, et al. Human prion diseases in the United States. PLoS One 2010;5(01):e8521

75 Brandel JP, Preece M, Brown P, et al. Distribution of codon 129 genotype in human growth hormone-treated CJD patients in France and the UK. Lancet 2003;362(9378):128–130

76 Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996;347(9006):921–925

77 Diack AB, Head MW, McCutcheon S, et al. Variant CJD. 18 years of research and surveillance. Prion 2014;8(04):286–295

78 National CJD Research & Surveillance Unit Data and Reports. Latest NCJDSRU CJD Monthly Statistics. Available at: https://www.cjd.ed.ac.uk/sites/default/files/figs.pdf. Accessed October 15, 2018

79 Pocchiari M, Puopolo M, Croes EA, et al. Predictors of survival in sporadic Creutzfeldt-Jakob disease and other human transmissible spongiform encephalopathies. Brain 2004;127(10):2348–2359

80 Zeidler M, Johnstone EC, Bamber RW, et al. New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 1997;350 (9082):908–910

81 Zeidler M, Stewart GE, Barraclough CR, et al. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet 1997;350(9082):903–907

82 Heath CA, Cooper SA, Murray K, et al. Diagnosing variant Creutzfeldt-Jakob disease: a retrospective analysis of the first 150 cases in the UK. J Neurol Neurosurg Psychiatry 2011;82(06): 646–651

83 Green AJ, Thompson EJ, Stewart GE, et al. Use of 14-3-3 and other brain-specific proteins in CSF in the diagnosis of variant Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001;70(06): 744–748

84 Binelli S, Agazzi P, Giaccone G, et al. Periodic electroencephalogram complexes in a patient with variant Creutzfeldt-Jakob disease. Ann Neurol 2006;59(02):423–427
85 Zeidler M, Sellar RJ, Collie DA, et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. Lancet 2000;355(9213):1412–1418
86 Collie DA, Summers DM, Sellar RJ, et al. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. AJNR Am J Neuroradiol 2003;24(08):1560–1569
87 Hill AF, Butterworth RJ, Joiner S, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. 1999;353(9148):183–189
88 Will RG, Zeidler M, Stewart GE, et al. Diagnosis of new variant Creutzfeldt-Jakob disease. Ann Neurol 2000;47(05):575–582
89 Heath CA, Cooper SA, Murray K, et al. Validation of diagnostic criteria for variant Creutzfeldt-Jakob disease. Ann Neurol 2010;67(06):761–770
90 Will B. Variant CJD: where has it gone, or has it? Pract Neurol 2010;10(05):250–251