Prion Diseases

KEY CLINICAL POINTS

1. Prions are proteinaceous infectious particles that lack nucleic acid and consist entirely of alternatively folded proteins that undergo self-propagation.
2. The hallmark of all PrP prion diseases is the aberrant folding of the PrP protein, resulting in the accumulation of PrPSc.
3. Sporadic CJD (sCJD) accounts for ~85% of all cases of human PrP prion disease, while genetic prion diseases account for 10–15%.
4. The most common sporadic CJD subtypes (MM1/MV1) present with rapidly progressive dementia, ataxia, and myoclonus, with a mean survival of ~4–7 months.
5. Variant CJD (vCJD) is associated with bovine spongiform encephalopathy (BSE) and typically affects younger patients (mean age 28 years) with an early psychiatric prodrome.
6. Prion diseases are transmissible via medical procedures (iatrogenic CJD) such as cadaver-derived dura mater grafts, human pituitary hormones, and corneal transplants.
7. The diagnosis of CJD can be established by brain biopsy if PrPSc is detected, though biopsy is rarely indicated with current ancillary testing.
8. PrPSc acts as a template for the conversion of PrPC into nascent PrPSc, and the conformation of PrPSc dictates the disease phenotype, not the amino acid sequence.
9. Chronic Wasting Disease (CWD) is highly transmissible among cervids (deer, elk, moose) via bodily excretions such as feces, urine, and saliva.
10. Recombinant human growth hormone (hGH) is now exclusively used therapeutically to prevent prion contamination.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

Prion diseases are a group of rare CNS disorders caused by prions composed of the human prion protein (PrP). PrP prions reproduce by binding to the normal, cellular isoform of the prion protein (PrPC) and stimulating conversion of PrPC into the disease-causing isoform PrPSc. PrPC is rich in α-helix and has little β-structure, whereas PrPSc has less α-helix and a high amount of β-structure. The α-to-β structural transition in PrP is the

fundamental event underlying this group of prion diseases. Harrison's defines this as: Prions are proteins that adopt alternative conformations, which become self-propagating. Some prions cause degeneration of the central nervous system (CNS). Once relegated to causing a group of rare CNS disorders, such as Creutzfeldt-Jakob disease (CJD), increasing evidence argues that prions also cause more common neurodegenerative diseases (NDs) including Alzheimer's disease (AD) and Parkinson's disease (PD).

1.1 Prion Protein Biology

- Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA.
- Prion diseases may manifest as infectious, genetic, or sporadic disorders.
- Prion diseases result from the accumulation of PrPSc, the conformation of which differs substantially from that of its precursor, PrPC.
- Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable.
- PrPSc can exist in a variety of different conformations, many of which seem to specify disease phenotypes.
- The human PrP gene is designated PRNP and is located on the short arm of chromosome 20.
- Limited proteolysis of PrPSc produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30, whereas PrPC is completely hydrolyzed under the same conditions.
- PrP 27-30 polymerizes into prion rods that are morphologically indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS.

1.2 Classification of Prion Diseases

- Sporadic CJD (sCJD) is the most common PrP prion disorder in humans.
- Genetic prion diseases account for 10–15% of all cases.
- Genetic prion diseases were historically divided into three forms: familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI).
- All dominantly inherited PrP prion diseases are caused by mutations in the PRNP gene.
- Infectious PrP prion diseases account for <1% of all cases.
- Kuru of the Fore people of Papua New Guinea resulted from the consumption of brains from dead relatives during ritualistic cannibalism.
- Iatrogenic CJD (iCJD) results from the accidental inoculation of patients with prions through medical procedures such as cadaver-derived dura mater grafts and human pituitary hormones.

2. EPIDEMIOLOGY

- CJD is found throughout the world.
- The incidence of sCJD is ~1–2 cases per million population.
- A person's lifetime risk of dying from CJD is ~1 in 5000 to 6000 deaths.
- Because sCJD is an age-dependent ND, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand.
- Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation and/or included misdiagnoses.
- Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases.
- Ingestion of scrapie-infected sheep or goats as a cause of CJD in humans has not been demonstrated, and epidemiologic studies do not support this, although speculation about this potential route of infection

continues.

• Whether PrP prion disease in deer, elk, or moose has passed to cows, sheep, or directly to humans remains unknown.

• The U.S. Centers for Disease Control and Prevention (CDC) conducts surveillance of CJD in the United States to ascertain the number and type of cases annually.

• Because up to 90% of culled deer in some game herds have been shown to harbor CWD prions, the CDC also has a study following deer hunters to determine if they have an increased rate of prion disease and whether it is a novel prion disorder.

3. ETIOLOGY & PATHOPHYSIOLOGY

• The prion concept explains how a single disease can manifest as sporadic, heritable (i.e., genetic), and infectious.

• A major feature that distinguishes PrP prions from viruses is the finding that both the normal and disease-causing PrP isoforms are encoded by a chromosomal gene.

• The prion concept explains how a single disease can manifest as sporadic, heritable (i.e., genetic), and infectious.

• The hallmark of all PrP prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant folding of the PrP protein.

• Species Barrier Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have provided new insights into the pathogenesis of these maladies.

• The amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrPSc sequence from the last mammal in which it was passaged.

• While the primary structure (i.e., amino acid sequence) of PrP is likely to be the most important or even the sole determinant of the tertiary structure of PrPC, PrPSc seems to function as a template in determining the tertiary structure of nascent PrPSc molecules as they are formed from PrPC.

• In turn, prion diversity appears to be enciphered in the conformation of PrPSc, and thus prion strains seem to represent different conformers of PrPSc.

• In general, transmission of PrP prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal.

• This "species barrier" to transmission is correlated with the degree of similarity between the host and donor PrP.

• The importance of sequence similarity between the host and donor PrP argues that PrPC directly interacts with PrPSc in the prion conversion process.

• Phenotype generally occurs when there is a valine at codon 129 of the same allele.

• Stop codon (nonsense) mutations are rare and cause a range of phenotypes, including some with a prolonged course of years to decades, GSS- or AD-like presentations, autonomic and sensory peripheral nervous system involvement, chronic gastrointestinal upset, and extensive PrPSc amyloid deposits.

Table 1 TABLE 449-1 Glossary of PrP Prion Terminology

Prion	Definition
Prion	Proteinaceous infectious particle that lacks nucleic acid.

Prion	Definition
Prions	Composed entirely of alternatively folded proteins that undergo self-propagation. Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable.
PrP prions	Cause scrapie in sheep and goats, mad cow disease, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).

Table 2 **TABLE 449-2 The PrP Prion Diseases**

Disease	Host	Mechanism of Pathogenesis
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germline mutations in PRNP
GSS	Humans	Germline mutations in PRNP
FFI	Humans	Germline mutation in PRNP (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrPC into PrPSc?
sFI	Humans	Somatic mutation or spontaneous conversion of PrPC into PrPSc?
Scrapie	Sheep, goats	Infection in genetically susceptible sheep and goats
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk, or moose	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Table 3 **TABLE 449-3 Distinct Prion Strains Generated in Humans with Inherited Prion Diseases and Transmitted to Transgenic Mice**

Inoculum	Host Species	Host PrP Genotype	Incubation Time [Days ± SEM] (n/n)	PrPSc (kDa)
None	Human	FFI(D178N, M129)	19	

Inoculum	Host Species	Host PrP Genotype	Incubation Time [Days ± SEM] (n/n)	PrPSc (kDa)
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)	21	
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

3.1 Pathogenesis of Sporadic and Inherited Prion Diseases

- Several different scenarios might explain the initiation of sporadic and inherited prion disease:
  - (1) A somatic mutation in a single cell may be the cause and thus follow a path similar to that for germline mutations in inherited disease. In this situation, the primary structure of PrPC made from the mutated gene would be more susceptible to misfolding into PrPSc. This mutant PrPSc then must be capable of targeting wild-type PrPC, a process known to be possible for some mutations (i.e., high penetrance) but less likely for others (low penetrance).
  - (2) The activation energy barrier separating wild-type PrPC from PrPSc, preventing conversion to PrPSc, could be crossed on rare occasions in the context of a population. Most individuals would be spared, but presentations in older persons who have had more time for this conversion to occur would be seen.
  - (3) PrPSc may be present at low levels in some normal cells, where it performs an important, but yet unknown, function. The level of PrPSc in such cells is hypothesized to be sufficiently low as not to be detected by routine bioassay. In some altered metabolic states, the cellular mechanisms for clearing PrPSc might become compromised, and the rate of PrPSc formation would then begin to exceed the capacity of the cell to clear it.
  - The third possible mechanism is attractive because it suggests that PrPSc is not simply a misfolded protein, as proposed for the first and second mechanisms, but that it is an alternatively folded molecule with a function.
  - Moreover, the multitude of conformational states that PrPSc can adopt, as described above, raises the possibility that PrPSc or another protein might function in a process such as short-term memory where information storage is thought to occur in the absence of new protein synthesis.

3.2 Human PRNP Gene Polymorphisms

- Polymorphisms influence the susceptibility to sporadic, genetic, and acquired forms of PrP prion disease.
- The methionine [M] or valine [V] polymorphism at codon 129 of human PRNP not only modulates the age of onset of some genetic prion diseases but also can affect the clinical phenotype.
- Sporadic CJD can be divided into six different molecular subtypes, based on the combination of codon 129 polymorphism (MM, MV, or VV) and the prion type (1 or 2), with each subtype having a particular clinical and pathological presentation.
- MM1/MV1 subtypes are the most common (~40–70% of cases) and usually have the most prototypic form of sCJD with rapidly progressive dementia, ataxia, and myoclonus and a mean survival of ~4–7 months.
- The VV2 subtype represents ~15% of sCJD cases, usually starts with ataxia, and has a similar survival as MM1/MV1.
- The MV2 subtype represents ~10% of cases and has a longer mean survival of ~17 months.

• The vast majority of MV2 cases are a form with kuru plaques in the cerebellum, called MV2K, which are clinically similar to VV2 (i.e., early ataxia) but have a slower progression and longer survival.

• A minority of MV2 cases are of a cortical subtype called MV2C with significant vacuolation (spongiform change) surrounded by perivacuolar PrPSc staining in all cortical layers and are usually without kuru plaques or cerebellar involvement.

• The MV2C cases present as a slowly progressive cognitive/dementia syndrome with motor symptoms occurring late in the disease course.

• The MM2 subtype represents ~4% of sCJD cases, has a mean survival of ~15.5 months, and is divided about equally into two subtypes: MM2-thalamic (MM2T, also called sFI) and MM2-cortical (MM2C).

• MM2T is clinicopathologically nearly identical to FFI (see below), whereas MM2C presents similarly to MV2C with a relatively slow progressive dementia and has a mean age of onset in the 50s, about a decade younger than most sCJD.

• VV1 is the least common subtype, representing ~1% of cases, presenting as a progressive dementia with a mean age of onset in the mid to late 40s, about two decades earlier than most other sCJD subtypes.

• Substitution of the basic residue lysine for glutamine at position 218 in mouse PrP produced dominant-negative inhibition of prion replication in transgenic mice.

• This same lysine substituted for glutamine at position 219 in human PrP has been found in 12% of the Japanese population, a group that appears to be resistant to prion disease.

• Dominant-negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine were resistant to scrapie prions but were susceptible to BSE prions that were inoculated intracerebrally.

• A very interesting polymorphism at codon 127 in PRNP was identified among longtime survivors of the kuru epidemic in the Fore people of Papua New Guinea, which when expressed in transgenic mice with humanized PRNP prevented the animals from acquiring prion disease.

4. CLINICAL FEATURES

• CJD typically presents as a rapidly progressive dementia accompanied by other motor abnormalities and behavioral changes.

• The illness is relentlessly progressive and generally causes death within ~7 months from onset.

• Most patients with sporadic CJD (sCJD) are between 50 and 75 years of age, although patients as young as 12 and as old as 96 have been described.

• Nonspecific prodromal symptoms occur in approximately a third of patients with CJD and may include fatigue, sleep disturbance, weight loss, headache, anxiety, vertigo, malaise, and ill-defined pain.

• Most patients with CJD present with cognitive and/or motor deficits.

• Behavioral and psychiatric symptoms, such as depression, anxiety, irritability, apathy, insomnia, appetite changes, psychosis, and visual hallucinations, are very common and often early features.

• These deficits usually progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function.

• A minority of patients present early with either isolated visual impairment or cerebellar gait and coordination deficits, referred to as the Heidenhain and Brownell-Oppenheim variants, respectively.

• Frequently, the cerebellar deficits are rapidly followed by progressive dementia.

• Variant CJD has a different clinical course from most other prion diseases, with an early psychiatric prodrome (most commonly depression, anxiety, apathy, withdrawal, and/or delusions) that persists for several months prior to the appearance of other neurologic symptoms including cerebellar ataxia, painful sensory symptoms, a movement disorder (often myoclonus, dystonia, and/or chorea), and cognitive impairment progressing to dementia.

• The mean age of onset for vCJD is 28 years (median 26, range 12–74), with the majority of patients being <55 years old.

• Patients with dCJD usually present with cerebellar ataxia, visual symptoms, and dementia and have a mean incubation period of 12 years (range 1.3–30 years).

4.1 Sporadic CJD (sCJD)

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• Other neurologic symptoms include cerebellar ataxia, painful sensory symptoms, a movement disorder (often myoclonus, dystonia, and/or chorea), and cognitive impairment progressing to dementia.

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4.3 Iatrogenic CJD (iCJD)

• Accidental transmission of CJD to humans through medical procedures (i.e., iatrogenic) appears to have occurred with cadaver-derived human pituitary hormones, dura mater grafts, and corneal transplants, as well as through contaminated electroencephalogram (EEG) electrode implantation and possibly through other neurosurgical procedures.

• Corneas from donors with unsuspected CJD have been transplanted to apparently healthy recipients who developed CJD after variable incubation periods.

• Two other cases arose due to contamination during epilepsy surgery from depth EEG electrodes previously used in a patient who unknowingly had CJD; these electrodes were subsequently implanted in a chimpanzee, causing CJD 18 months later.

• Surgical procedures may have resulted in other accidental inoculations of patients with prions, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery.

• Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

• Patients with dCJD usually present with cerebellar ataxia, visual symptoms, and dementia and have a mean incubation period of 12 years (range 1.3–30 years).

5. DIFFERENTIAL DIAGNOSIS

• Multiple sclerosis, other demyelinating diseases, or adult-onset spastic paraplegia are diagnostic considerations for a myelopathy suggestive of PLS (Primary Lateral Sclerosis).

• A myelopathy suggestive of PLS is infrequently seen with infection with the retrovirus human T-cell lymphotropic virus 1 (HTLV-1).

• The clinical course and laboratory testing will distinguish these possibilities.

• Prion diseases may manifest as infectious, genetic, or sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations.

5.1 Primary Lateral Sclerosis (PLS)

• PLS is a rare disorder that arises sporadically in adults in mid-to-late life.

• Clinically, PLS is characterized by progressive spastic weakness of the limbs, preceded or followed by spastic dysarthria and dysphagia, indicating combined involvement of the corticospinal and corticobulbar tracts.

• Fasciculations, amyotrophy, and sensory changes are absent.

• Neither electromyography nor muscle biopsy shows denervation.

• On neuropathologic examination, there is selective loss of the large pyramidal cells in the precentral gyrus and degeneration of the corticospinal and corticobulbar projections.

• The peripheral motor neurons and other neuronal systems are spared.

• The course of PLS is usually indolent; infrequently, there is conversion to a more aggressive course with lower motor neuron degeneration as in ALS.

• Early in its course, PLS raises the question of multiple sclerosis, other demyelinating diseases, or adult-onset spastic paraplegia as diagnostic considerations.

5.2 Hereditary Spastic Paraplegia (HSP)

• In its pure form, HSP is usually transmitted as an autosomal trait; most adult-onset cases are dominantly inherited.

• There are >80 genetic types of HSP for which causative mutations in >60 genes have been identified.

• Symptoms usually begin in the third or fourth decade of life, presenting as progressive spastic weakness beginning in the lower extremities.

• There are variants with onset so early that the differential diagnosis includes cerebral palsy.

• HSP typically has a long survival, presumably because respiratory function is spared.

• Late in the illness, there may be urinary urgency and incontinence and sometimes fecal incontinence; sexual function tends to be preserved.

• In pure forms of HSP, the spastic leg weakness is often accompanied by posterior column (vibration and position) abnormalities and disturbance of bowel and bladder function.

• Some family members may have spasticity without clinical symptoms.

• By contrast, particularly when recessively inherited, HSP may have complex or complicated forms in which altered corticospinal and dorsal column function is accompanied by significant involvement of

other regions of the nervous system, including amyotrophy, intellectual disability, optic atrophy, and sensory neuropathy.

• Neuropathologically, in HSP, there is degeneration of the corticospinal tracts, which appear nearly normal in the brainstem but show increasing atrophy at more caudal levels in the spinal cord; in effect, this pathologic picture is of a dying-back or distal axonopathy of long neuronal fibers within the CNS.

• Defects at numerous loci underlie both dominantly and recessively inherited forms of HSP.

• The gene most commonly implicated in dominantly inherited HSP is spastin, which encodes a microtubule interacting protein.

• The most common childhood-onset dominant form arises from mutations in the atlastin gene.

• An infantile-onset form of X-linked, recessive HSP arises from mutations in the gene for myelin proteolipid protein.

• A slowly progressive, adult-onset X-linked progressive spastic paralysis designated adrenomyeloneuropathy is caused by mutations in the ABCD1 gene; these cases are associated with elevated serum levels of very-long-chain fatty acids.

6. INVESTIGATIONS & DIAGNOSIS

• The only highly specific diagnostic tests for CJD and other human PrP prion diseases measure PrPSc.

• The most widely used method involves limited proteolysis that generates PrP 27-30, which is detected by immunoassay after denaturation.

• In humans, the diagnosis of CJD can be established by brain biopsy if PrPSc is detected, although with current ancillary testing available, biopsy is rarely indicated.

• Because PrPSc is not uniformly distributed throughout the CNS, the absence of PrPSc in a limited sample such as a biopsy does not rule out prion disease.

• The use of reverse templated quake-induced conversion assay (RT-QuIC; see below), a method for amplifying prions into amyloid fibrils and detecting them with thioflavin fluorescence, has greatly increased the sensitivity of brain biopsy.

• If no attempt is made to measure or detect PrPSc but pathologic changes typical of CJD are seen in a brain biopsy, then the diagnosis is reasonably secure.

• Brain MRI has become an important diagnostic tool for prion disease.

• On light microscopy, the pathologic hallmarks of CJD are spongiform degeneration (vacuolation), neuronal loss, and astrocytic gliosis.

• Spongiform degeneration is characterized by many 1- to 5-µm vacuoles in the neuropil between nerve cell bodies.

• Generally, the vacuolation occurs in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum.

• Astrocytic gliosis is a constant but nonspecific feature of PrP prion diseases.

• Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions.

• Astrocytic processes filled with glial filaments form extensive networks.

• The degree and location of these pathologic hallmarks vary depending on the type of human prion disease, including between sCJD subtypes described above.

• Amyloid plaques have been found in ~10% of CJD cases.

• Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis.

• On first passage of samples from some human Japanese CJD cases into mice, amyloid plaques were found.

• These plaques stain with antibodies raised against PrP, demonstrating that the amyloid is composed of PrP.

6.1 Laboratory Tests

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7. MANAGEMENT & TREATMENT

• There is no specific cure for prion diseases.

• Recombinant hGH is now exclusively used therapeutically so that possible contamination with prions is no longer an issue.

• The transmission of CJD prions from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been responsible for fatal cerebellar disorders with dementia in >200 patients ranging in age from 5 to 42 years, most occurring in France, the United Kingdom, and the United States.

• These patients received injections of hGH every 2–4 days for ~2–12 years.

• If it is thought that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years.

• Four cases of CJD also occurred in women in Australia receiving human pituitary gonadotropin, with incubation periods of 12–16 years.

• Notably, there is some evidence that deceased patients who received hGH early in life may have inadvertently received Aβ prions also, which can lead to amyloid and even tau pathology.

• Whether iatrogenic propagation of Aβ or tau prions in the human CNS led to an ND, such as AD or cerebral amyloid angiopathy (CAA), in these patients is still controversial.

• The steady decline in the number of vCJD cases over the past decade argues that there will not be a prion disease epidemic in Europe, similar to those seen for BSE and kuru.

• What is certain is that PrP-prion-tainted meat should be prevented from entering the human food supply.

• More than 200 cases of vCJD have occurred, with >90% of these in Britain.

• Variant CJD has also been reported in people either living in or originating from France, Ireland, Italy, the Netherlands, Portugal, Spain, Saudi Arabia, the United States, Canada, and Japan.

• For some of these patients, such as those from North America, evidence suggests they acquired the disease while living or traveling outside their home country.

7.1 Iatrogenic Prevention

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8. PROGNOSIS & COMPLICATIONS

• CJD typically presents as a rapidly progressive dementia accompanied by other motor abnormalities and behavioral changes.

• The illness is relentlessly progressive and generally causes death within ~7 months from onset.

• Most patients with sporadic CJD (sCJD) are between 50 and 75 years of age, although patients as young as 12 and as old as 96 have been described.

• MM1/MV1 subtypes are the most common (~40–70% of cases) and usually have the most prototypic form of sCJD with rapidly progressive dementia, ataxia, and myoclonus and a mean survival of ~4–7 months.

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• The MV2 subtype represents ~10% of cases and has a longer mean survival of ~17 months.

• The vast majority of MV2 cases are a form with kuru plaques in the cerebellum, called MV2K, which are clinically similar to VV2 (i.e., early ataxia) but have a slower progression and longer survival.

• A minority of MV2 cases are of a cortical subtype called MV2C with significant vacuolation (spongiform change) surrounded by perivacuolar PrPSc staining in all cortical layers and are usually without kuru plaques or cerebellar involvement.

• The MV2C cases present as a slowly progressive cognitive/dementia syndrome with motor symptoms occurring late in the disease course.

• The MM2 subtype represents ~4% of sCJD cases, has a mean survival of ~15.5 months, and is divided about equally into two subtypes: MM2-thalamic (MM2T, also called sFI) and MM2-cortical (MM2C).

• MM2T is clinicopathologically nearly identical to FFI (see below), whereas MM2C presents similarly to MV2C with a relatively slow progressive dementia and has a mean age of onset in the 50s, about a decade younger than most sCJD.

• VV1 is the least common subtype, representing ~1% of cases, presenting as a progressive dementia with a mean age of onset in the mid to late 40s, about two decades earlier than most other sCJD subtypes.

• The mean age of onset for vCJD is 28 years (median 26, range 12–74), with the majority of patients being <55 years old.

• Patients with dCJD usually present with cerebellar ataxia, visual symptoms, and dementia and have a mean incubation period of 12 years (range 1.3–30 years).

9. SPECIAL CONSIDERATIONS

• Ingestion of scrapie-infected sheep or goats as a cause of CJD in humans has not been demonstrated, and epidemiologic studies do not support this, although speculation about this potential route of infection continues.

• Whether PrP prion disease in deer, elk, or moose has passed to cows, sheep, or directly to humans remains unknown.

• Studies with mice modified to carry the human PRNP gene demonstrate that oral infection with CWD prions can occur, but the process is inefficient compared to intracerebral inoculation.

• Because up to 90% of culled deer in some game herds have been shown to harbor CWD prions, the CDC also has a study following deer hunters to determine if they have an increased rate of prion disease and whether it is a novel prion disorder.

• The U.S. Centers for Disease Control and Prevention (CDC) conducts surveillance of CJD in the United States to ascertain the number and type of cases annually.

• Four known (and a fifth possible) secondary cases of vCJD infection occurred from blood product transfusions.

• These persons received blood components (non-leukodepleted red blood cells [RBCs] in the four known cases and factor X in the fifth case) from asymptomatic donors who later developed vCJD infection.

• The RBC donors did not develop vCJD infection until ~1.5–3.3 years after donation, and the incubation period for recipients of RBCs ranged from 5 to 8.5 years.

• Thus, vCJD is the only form of human prion disease proven to be transmissible by blood.

• The second of four RBC recipients did not die from vCJD but was found to have vCJD prions in the lymphoreticular system.

• The French patient accidentally stabbed herself with forceps being used on frozen brain sections from a transgenic mouse overexpressing human PrP and inoculated with BSE.

• She developed symptoms 7.5 years later at age 31 and died from definite vCJD after 19 months in 2019.

• The last reported case of vCJD worldwide was in France in 2021, and the prior two cases occurred in the United Kingdom in 2013 and 2016.

9.1 Blood Transfusion Risk

• Four known (and a fifth possible) secondary cases of vCJD infection occurred from blood product transfusions.

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9.2 Occupational Exposure

• The French patient accidentally stabbed herself with forceps being used on frozen brain sections from a transgenic mouse overexpressing human PrP and inoculated with BSE.

• She developed symptoms 7.5 years later at age 31 and died from definite vCJD after 19 months in 2019.

• The last reported case of vCJD worldwide was in France in 2021, and the prior two cases occurred in the United Kingdom in 2013 and 2016.

10. KEY PEARLS & CLINICAL TRAPS

• Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny.

• Prion diseases may manifest as infectious, genetic, or sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations.

• Prion diseases result from the accumulation of PrPSc, the conformation of which differs substantially from that of its precursor, PrPC.

• Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable.

• In other words, PrPSc can exist in a variety of different conformations, many of which seem to specify disease phenotypes.

• How a specific conformation of a PrPSc molecule is imparted to PrPC during prion replication to produce nascent PrPSc with the same conformation is not well understood.

• Additionally, it is unclear what factors determine where in the CNS a particular PrPSc molecule will be created.

• The most compelling evidence that vCJD is caused by BSE prions was obtained from experiments in mice expressing the bovine PrP transgene.

• Both BSE and vCJD prions were efficiently transmitted to these transgenic mice and with similar incubation periods.

• In contrast to sCJD prions, vCJD prions did not transmit disease efficiently to mice expressing a chimeric human–mouse PrP transgene.

• Earlier studies with nontransgenic mice suggested that vCJD and BSE might be derived from the same source because both inocula transmitted disease with similar but very long incubation periods.

• Attempts to determine the origin of BSE and vCJD prions have relied on passaging studies in mice, some of which are described above, as well as studies of the conformation and glycosylation of PrPSc.

• One scenario suggests that a particular conformation of bovine PrPSc was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated meat and bone meal (MBM) were slaughtered and their offal rendered into more MBM.

• Variant CJD cases have virtually disappeared with protection of the beef supply in Europe.

• Interestingly, almost all of the ~238 cases of vCJD reported as of 2024 have been homozygous for methionine (MM) at codon 129 in PRNP.

• However, two cases (one probable and one definite) were codon 129 MV, which is the most common codon 129 polymorphism in most of the world.

• This finding raises the concern that persons with this polymorphism might have a longer incubation period and that another rise in cases might still occur.

• Of particular concern is that four known (and a fifth possible) secondary cases of vCJD infection occurred from blood product transfusions.

• These persons received blood components (non-leukodepleted red blood cells [RBCs] in the four known cases and factor X in the fifth case) from asymptomatic donors who later developed vCJD infection.

• The RBC donors did not develop vCJD infection until ~1.5–3.3 years after donation, and the incubation period for recipients of RBCs ranged from 5 to 8.5 years.

• Thus, vCJD is the only form of human prion disease proven to be transmissible by blood.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S

and familial cases. Ingestion of scrapie-infected sheep or goats as a cause of CJD in humans has not been demonstrated, and epidemiologic studies do not support this, although speculation about this potential route of infection continues. Whether PrP prion disease in deer, elk, or moose has passed to cows, sheep, or directly to humans remains unknown. Studies with mice modified to carry the human *PRNP* gene demonstrate that oral infection with CWD prions can occur, but the process is inefficient compared to intracerebral inoculation. The U.S. Centers for Disease Control and Prevention (CDC) conducts surveillance of CJD in the United States to ascertain the number and type of cases annually. Because up to 90% of culled deer in some game herds have been shown to harbor CWD prions, the CDC also has a study following deer hunters to determine if they have an increased rate of prion disease and whether it is a novel prion disorder.

PATHOGENESIS

The human PrP prion diseases were initially classified as NDs of unknown etiology. Even though the familial nature of GSS and a subset of CJD cases was well described, the significance of this observation became more obscure with the transmission of GSS and CJD to animals since genetic NDs were not considered transmissible. With the transmission of kuru and CJD to nonhuman primates, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Eventually, the true cause of GSS and a minority of CJD cases became clear with the discovery in 1989 of mutations in the *PRNP* gene of these familial patients. The prion concept explains how a single disease can manifest as sporadic, heritable (i.e., genetic), and infectious. Moreover, the hallmark of all PrP prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant folding of the PrP protein.

A major feature that distinguishes PrP prions from viruses is the finding that both the normal and disease-causing PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30, whereas PrP^{C} is completely hydrolyzed under the same conditions **(Fig. 449-1)**. PrP 27-30 polymerizes into prion rods that are morphologically indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. This discovery raised the possibility that many other NDs might be caused by different proteins, all of which can fold into prions.

Prion Strains Distinct strains of PrP prions exhibit different biologic properties, which are epigenetically heritable. The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Various strains of PrP prions have been defined by incubation times, distribution of neuronal vacuolation (i.e., spongiform change) on neuropathology, and stabilities of PrP^{Sc} to denaturation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with the neuroanatomic location and pattern of vacuolation, and these patterns were also used to characterize prion strains.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human–mouse PrP transgene. In most forms of fCJD and the majority of sCJD cases, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 21 kDa (i.e., type 1 prions), whereas in FFI, and a minority of sCJD cases, it is 19 kDa (type 2 prions) **(Table 449-3)**. This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH_2 termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrP fragments differ. Extracts from the brains of patients with FFI transmitted disease to the mice expressing the chimeric human–mouse PrP transgene and resulted in the formation of 19-kDa PrP^{Sc}, whereas brain extracts from patients with fCJD and sCJD harboring 21-kDa PrP^{Sc} resulted in 21-kDa PrP^{Sc} in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrP^{Sc} can exist in two different conformations as demonstrated by the sizes of the protease-resistant fragments, even though the amino acid sequence of PrP^{Sc} is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a *PRNP* mutation, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrP^{Sc} was found in their brains, and on passage of sFI prion disease to mice expressing the chimeric human–mouse PrP transgene, 19-kDa PrP^{Sc} was also found. These findings indicate that the disease phenotype is dictated by the conformation of PrP^{Sc} and not the amino acid sequence. PrP^{Sc} acts as a template for the conversion of PrP^{C} into nascent PrP^{Sc}. On the passage of prions into mice expressing a chimeric hamster–mouse PrP transgene, a change in the conformation of PrP^{Sc} was accompanied by the emergence of a new strain of prions.

Many new strains of prions were generated using recombinant PrP (recPrP) produced in bacteria; recPrP was polymerized into amyloid fibrils to make "synthetic prions," which were inoculated into transgenic mice overexpressing high levels of wild-type mouse PrP^{C}. Approximately 500 days later, the mice died of prion disease. The incubation times (i.e., time to clinical disease onset) of the "synthetic prions" in mice were dependent on the conditions used for polymerization of the amyloid fibrils, which affected the stability of those amyloid fibrils. Highly stable amyloids gave rise to stable prions with long incubation times; low-stability amyloids led to prions with short incubation times. Amyloids of intermediate stability gave rise to prions with intermediate stabilities and intermediate incubation times. Such findings are consistent with earlier studies showing that the incubation times of synthetic and naturally occurring prions are directly proportional to the stability of the prion.

Species Barrier Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have provided new insights into the pathogenesis of these maladies. The amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged. While the primary structure (i.e., amino acid sequence) of PrP is likely to be the most important or even the sole determinant of the tertiary structure of PrP^{C}, PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^{C}. In turn, prion diversity appears to be enciphered in the conformation of PrP^{Sc}, and thus prion strains seem to represent different conformers of PrP^{Sc}.

In general, transmission of PrP prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal. This "spe-

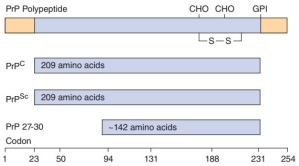
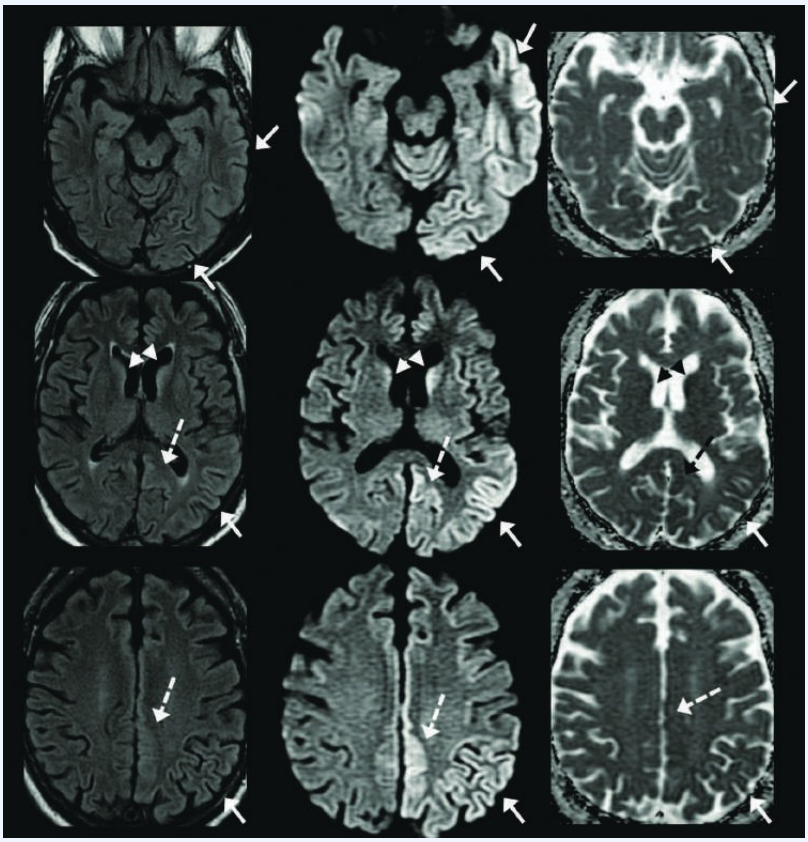


FIGURE 449-1 PrP prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH₂ and COOH termini, both PrP^{C}

Harrison's 22e · Figure 1

FIGURE 449-1 PrP prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH and COOH termini, both PrPC and PrPSc consist of 209 residues. After limited proteoly 2 sis, the NH terminus of PrPSc is truncated to form PrP 27-30 composed of ~142 amino acids. CHO 2 , N-linked sugars; GPI, glycosylphosphatidylinositol anchor attachment site; S–S, disulfide bond. — FIGURE 449-1 PrP prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH and COOH termini, both PrPC and PrPSc consist of 209 residues. After limited proteolysis, the NH terminus of PrPSc is truncated to form PrP 27-30 composed of ~142 amino acids. CHO, N-linked sugars; GPI, glycosylphosphatidylinositol anchor attachment site; S–S, disulfide bond.



Harrison's 22e · Figure 2

FIGURE 449-2 Brain magnetic resonance imaging (MRI) in a 72-year-old patient with (A) fluid-attenuated inversion recovery (FLAIR), (B) diffusion-weighted imaging (DWI), There is cortical ribboning indicating restricted diffusion in the left much greater than arrow), insular (no arrow), and posterior cingulate cortices (dashed arrows). There is The corresponding hypointensity (very dark) areas on the ADC sequence confirm that the not artifacts. Note that the abnormalities are best seen on DWI sequences. Images are — Neuropathologic features of Creutzfeldt-Jakob disease (CJD). The image likely depicts spongiform degeneration (vacuolation), neuronal loss, and astrocytic gliosis in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum, which are the pathologic hallmarks of CJD.