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449 Prion Diseases

■ ■SELECTED DISORDERS OF

THE UPPER MOTOR NEURON Primary Lateral Sclerosis This rare disorder arises sporadi cally 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 involve ment of the corticospinal and corticobulbar tracts. Fasciculations, amyotrophy, and sensory changes are absent; neither electromyog raphy 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 dis eases, or adult-onset spastic paraplegia as diagnostic considerations (Chap. 455). A myelopathy suggestive of PLS is infrequently seen with infection with the retrovirus human T-cell lymphotropic virus 1 (HTLV-1) (Chap. 453). The clinical course and laboratory testing will distinguish these possibilities. Hereditary Spastic Paraplegia In its pure form, HSP is usu ally 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. Table 448-3 lists more commonly identified genetic types of HSP. Symptoms usually begin in the third or fourth decade of life, presenting as progressive spastic weakness beginning in the lower extremities; however, 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 distur bance 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 cortico spinal 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 (Table 448-3). 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. This is an example of rather striking allelic variation, as most other mutations in the same gene cause not HSP but Pelizaeus-Merzbacher disease, a widespread disorder of CNS myelin. Another recessive variant is caused by defects in the paraplegin gene. Paraplegin has homology to metalloproteases that are important in mitochondrial function in yeast. A slowly progressive, adult-onset X-linked progressive spastic paraly sis designated adrenomyeloneuropathy is caused by mutations in the ABCD1 gene; these cases are associated with elevated serum levels of very-long-chain fatty acids (Chap. 453). ■ ■FURTHER READING Akçimen F et al: Amyotrophic lateral sclerosis: Translating genetic discoveries into therapies. Nat Rev Genetics 44:642, 2023.

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Prion Diseases Prions are proteins that adopt alternative conformations, which become self-propagating. Some prions cause degeneration of the cen tral 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 neurodegenera tive diseases (NDs) including Alzheimer’s disease (AD) and Parkinson’s disease (PD). While CJD is caused by the accumulation of PrPSc prions (Table 449-1), α-synuclein prions cause multiple system atrophy (MSA) (Chap. 451). Infectious MSA prions have been recovered from human brain samples stored in formalin for up to 20 years. Similar resistance to formalin was demonstrated for brain samples from sheep with scrapie. Increasing data suggest that Aβ and tau prions together may cause AD, α-synuclein prions PD in addition to MSA, and tau prions frontotemporal lobar degeneration (FTLD). CJD typically pres ents as a rapidly progressive dementia accompanied by other motor abnormalities and behavioral changes. The illness is relentlessly pro gressive 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.

TABLE 449-1 Glossary of PrP Prion Terminology Prion Proteinaceous infectious particle that lacks nucleic acid. Prions are 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). PrPSc Disease-causing Scrapie isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions. PrPC Cellular isoform of the prion protein. PrPC is the precursor of PrPSc. PrP 27-30 A fragment of PrPSc, generated by truncation of the NH2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid. PRNP PrP gene located on human chromosome 20. Prion rod An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrPSc. Morphologically and histochemically indistinguishable from many amyloids. PART 13 Neurologic Disorders PrP amyloid Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques. The potential role of prions in the pathogenesis of NDs is reviewed in Chap. 435. CJD is one malady in a group of disorders caused by prions com posed 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 transi tion in PrP is the fundamental event underlying this group of prion diseases. Four new concepts have emerged from studies of PrP prions: (1) 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. (2) 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. (3) Prion diseases result from the accumulation of PrPSc, the conformation of which dif fers substantially from that of its precursor, PrPC. (4) Distinct strains of prions exhibit different biologic properties, which are epigeneti cally inherited. 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. SPECTRUM OF PrP PRION DISEASES The sporadic form of CJD is the most common PrP prion disorder in humans. sCJD accounts for ~85% of all cases of human PrP prion disease, and genetic prion diseases account for 10–15% of all cases (Table 449-2). Genetic prion diseases were historically divided into three forms: familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI). All dominantly inher ited PrP prion diseases are caused by mutations in the PrP gene. Although infectious PrP prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of PrP prions is an impor tant biologic feature. Kuru of the Fore people of Papua New Guinea resulted from the consumption of brains from dead relatives during ritualistic cannibalism. After the cessation of this practice in the late 1950s, kuru nearly disappeared, with the exception of a few recent patients exhibiting incubation periods of >50 years. Iatrogenic CJD (iCJD) results from the accidental inoculation of patients with prions

TABLE 449-2 The PrP Prion Diseases DISEASE HOST MECHANISM OF PATHOGENESIS Human 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? Animal 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 Abbreviations: BSE, bovine spongiform encephalopathy; CJD, CreutzfeldtJakob disease; CWD, chronic wasting disease; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; iCJD, iatrogenic Creutzfeldt-Jakob disease; MBM, meat and bone meal; sCJD, sporadic Creutzfeldt-Jakob disease; sFI, sporadic fatal insomnia; TME, transmissible mink encephalopathy; vCJD, variant Creutzfeldt-Jakob disease. through medical procedures such as cadaver-derived dura mater grafts and human pituitary hormones. Variant CJD (vCJD) that mostly occurs in teenagers and young adults in Europe, predominantly the United Kingdom and France, is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). Although occasional cases of iCJD still occur, this form of CJD is currently on the decline due to public health measures aimed at preventing the spread of PrP prions. More than seven diseases of animals are caused by prions (Table 449-2). Scrapie of sheep and goats is the prototypic PrP prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, exotic ungulate encephalopathy, and nonhuman primate prion dis ease are all thought to occur after the consumption of prion-infected foodstuffs. The BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. The origin of chronic wasting disease (CWD), a prion dis ease endemic in deer and elk in regions of North America, and more recently identified in isolated populations in Scandinavia and Korea, is uncertain. In contrast to other prion diseases, CWD is highly transmis sible among cervids. Bodily excretions, such as feces, urine, and saliva, from asymptomatic, infected cervids contain prions that are likely to be responsible for the spread of CWD. Notably, mink are carnivores and mink encephalopathy is spread from one animal to another. ■ ■EPIDEMIOLOGY CJD is found throughout the world. The incidence of sCJD is ~1–2 cases per million population, although a person’s lifetime risk of dying from CJD is ~1 in 5000 to 6000 deaths. Because sCJD is an agedependent ND, its incidence is expected to increase steadily as older segments of populations in developed and developing countries con tinue 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. 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 surveil lance 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 fol lowing 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 ani mals 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 dis ease 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 desig nated PRNP and is located on the short arm of chromosome 20. Lim ited 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 (Fig. 449-1). PrP 27-30 polymer izes 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 bio logic properties, which are epigenetically heritable. The existence of prion strains raised the question of how heritable biologic informa tion can be enciphered in a molecule other than nucleic acid. Various strains of PrP prions have been defined by incubation times, distribu tion of neuronal vacuolation (i.e., spongiform change) on neuropathol ogy, and stabilities of PrPSc to denaturation. Subsequently, the patterns of PrPSc deposition were found to correlate with the neuroanatomic PrP Polypeptide CHO CHO GPI S S PrPC 209 amino acids PrPSc 209 amino acids PrP 27-30 ~142 amino acids Codon

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 PrPC and PrPSc consist of 209 residues. After limited proteolysis, the NH2 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.

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 PrPSc 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 PrPSc 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 NH2 termini of the two human PrPSc molecules, reflecting different tertiary structures. These

distinct con formations 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 PrPSc, whereas brain extracts from patients with fCJD and sCJD harboring 21-kDa PrPSc resulted in 21-kDa PrPSc in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrPSc can exist in two different conformations as demon strated by the sizes of the protease-resistant fragments, even though the amino acid sequence of PrPSc is invariant. CHAPTER 449 Prion Diseases This analysis was extended when patients with sporadic fatal insom nia (sFI) were identified. Although they did not carry a PRNP muta tion, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrPSc was found in their brains, and on passage of sFI prion disease to mice expressing the chimeric human–mouse PrP transgene, 19-kDa PrPSc was also found. These findings indicate that the disease phenotype is dictated by the conformation of PrPSc and not the amino acid sequence. PrPSc acts as a template for the conversion of PrPC into nascent PrPSc. On the passage of prions into mice expressing a chimeric hamster–mouse PrP transgene, a change in the conformation of PrPSc 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 amy loid fibrils to make “synthetic prions,” which were inoculated into transgenic mice overexpressing high levels of wild-type mouse PrPC. Approximately 500 days later, the mice died of prion disease. The incu bation 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 consis tent 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 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 differ ent 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 “spe cies barrier” to transmission is correlated with the degree of similarity between the amino acid sequences of PrPC in the inoculated host and of PrPSc in the inoculum. The importance of sequence similarity between

TABLE 449-3 Distinct Prion Strains Generated in Humans with Inherited Prion Diseases and Transmitted to Transgenic Micea INOCULUM HOST SPECIES HOST PrP GENOTYPE INCUBATION TIME [DAYS ± SEM] (n/n0) PrPSc (kDa) None Human FFI(D178N, M129)

FFI Mouse Tg(MHu2M) 206 ± 7 (7/7)

FFI → Tg(MHu2M) Mouse Tg(MHu2M) 136 ± 1 (6/6)

None Human fCJD(E200K)

fCJD Mouse Tg(MHu2M) 170 ± 2 (10/10)

fCJD → Tg(MHu2M) Mouse Tg(MHu2M) 167 ± 3 (15/15)

aTg(MHu2M) mice express a chimeric mouse–human PrP gene. Notes: Clinicopathologic phenotype is determined by the conformation of PrPSc in accord with the results of the transmission of human prions from patients with FFI to transgenic mice. Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; SEM, standard error of the mean. the host and donor PrP argues that PrPC directly interacts with PrPSc in the prion conversion process. PART 13 Neurologic Disorders SPORADIC AND INHERITED

PrP PRION DISEASES Several different scenarios might explain the initiation of sporadic 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 activa tion 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 shortterm memory where information storage is thought to occur in the absence of new protein synthesis. More than 40 different mutations resulting in nonconservative substitutions in the human PRNP gene have been found to segregate with inherited human prion diseases. Missense mutations, a dele tion, expansions in the octapeptide repeat region of the gene, called octapeptide repeat insertions (OPRIs), and stop codon mutations are responsible for genetic forms of prion disease. Although phenotypes may vary dramatically, even within families, specific phenotypes observed with certain mutations appear to cause fCJD. More than 20 missense variants—including substitutions at codons 102, 105, 117, 198, and 217, and mid to longer OPRIs—cause the GSS form of PrP prion disease, with prominent parkinsonism and/or cerebellar features and typically onset of dementia later in the course. Regarding OPRI mutations, the normal human PrP sequence contains an unstable section in the N-terminal region comprised of five repeats—a nine-amino-acid sequence or nonapeptide (R1) fol lowed by four octapeptide repeats (R2, R2, R3, R4), which includes two tandem R2 domains. Insertions from 2 to 12 extra octapeptide repeats cause variable phenotypes including conditions

indistinguishable from sCJD, GSS-like presentations, and even a slowly progressive dementing illness of many years' duration to an early-age-of-onset disorder that is similar to AD. A mutation at codon 178 that results in substitution of asparagine for aspartic acid generally causes FFI if methionine is encoded at codon 129 on the same allele. In contrast, a typical CJD

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. ■ ■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 poly morphism (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 progres sive 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 MV2-cortical (MV2C) with significant vacuolation (spongiform change) surrounded by perivacuolar PrPSc staining in all cortical lay ers 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 replica tion 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 poly morphism at codon 127 in PRNP was identified among longtime sur vivors 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.

ACQUIRED (TRANSMITTED)

PrP PRION DISEASES ■ ■IATROGENIC CJD Accidental transmission of CJD to humans through medical proce dures (i.e., iatrogenic) appears to have occurred with cadaver-derived human pituitary hormones, dura mater grafts, and corneal trans plants, 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 contamina tion 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 inocula tions 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. Dura Mater Grafts More than 200 cases of CJD after implanta tion of dura mater grafts (dCJD) have been recorded. Dura mater is normally collected from cadavers, mass sterilized in a heated vat, freeze-dried, and prepared for use in a variety of surgical procedures. Unfortunately, some of the donor cadavers unknowingly had prion disease. All but possibly two of the grafts appear to have been acquired from a single manufacturer. More than two-thirds of the cases occurred in Japan. 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). Two subtypes of dCJD have been identi fied in Japan, a type with PrPSc plaques and a type without plaques (synaptic PrPSc). Human Growth Hormone and Pituitary Gonadotropin Therapy

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. Recombinant hGH is now exclusively used therapeutically so that possible contamination with prions is no longer an issue. 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. ■ ■VARIANT CJD The restricted geographic occurrence and chronology of vCJD raised the possibility that BSE prions had been transmitted to humans through the consumption of tainted beef. 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. 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.

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 stud ies 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 protec tion 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 infec tion 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 second of four RBC recipients did not die from vCJD but was found to have vCJD prions in the lymphoreticular system. 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. Further evidence of the transmissibility of vCJD is that among the two most recent cases of vCJD identified, one in France and one in Italy, both had laboratory exposure to BSE-infected brain tissue. 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. CHAPTER 449 Prion Diseases ■ ■NEUROPATHOLOGY Frequently, the brains of patients with CJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy. On light microscopy, the pathologic hallmarks of CJD are spon giform degeneration (vacuolation), neuronal loss, and astrocytic gliosis. The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative dis orders. 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.

The amyloid plaques of GSS disease are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amy loid fibrils, with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congo philic angiopathy has been noted in some cases of GSS disease.

In vCJD, a characteristic feature is the presence of “florid plaques.” These are composed of a central core of PrP amyloid, surrounded by vacuoles in a pattern suggesting petals on a flower. ■ ■CLINICAL FEATURES 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 cere bellar gait and coordination deficits, referred to as the Heidenhain and Brownell-Oppenheim variants, respectively. Frequently, the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly fol lowed by dementia. Patients with early visual deficits often have a faster decline overall. PART 13 Neurologic Disorders Motor symptoms and signs other than cerebellar ataxia include extrapyramidal dysfunction manifested as rigidity, masklike facies, dystonia, myoclonus, or less commonly choreoathetoid movements and pyramidal signs (usually mild and not actual weakness). Some uncommon features include seizures (usually major motor), hypo esthesia, supranuclear gaze palsy, motor neuron disease, or dysauto nomic signs such as changes in body temperature and sweating. Most patients with the most common subtype of CJD will eventually develop myoclonus. Unlike other involuntary movements, myoclonus usually persists during sleep. Startle myoclonus elicited by loud sounds, bright lights, or a person or object suddenly appearing in a patient’s visual field is frequent. It is important to stress that myoclonus is nei ther specific nor confined to CJD and tends to occur later in the course of CJD. Dementia with myoclonus can also be due to AD (Chap. 442), dementia with Lewy bodies (Chap. 445), corticobasal degeneration (Chap. 443), cryptococcal encephalitis (Chap. 221), or the myoclonic epilepsy disorder Unverricht-Lundborg disease (Chap. 436). Clinical Course Most patients with sCJD and most types of fCJD live ~6–12 months after the onset of clinical signs and symptoms. Life expectancies can be longer, up to a few years, for less common sCJD subtypes, and some mutations causing genetic prion disease can have durations of a decade or longer. ■ ■DIAGNOSIS The constellation of a rapid onset of cognitive impairment over weeks to months, with myoclonus and other motor symptoms, and typical mag netic resonance imaging (MRI) findings (see below) in an afebrile 60- to 70-year-old patient generally indicates CJD—most commonly sCJD. Variations in the typical course appear in genetic and transmitted (i.e., acquired) forms of the disease. As noted above, most mutations

causing fCJD have a slightly earlier mean age of onset, although usu ally an otherwise similar clinical and radiologic presentation as sCJD. In GSS, cerebellar ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS also presents earlier than sCJD (mean age ~43 years) and usually progresses more slowly, leading to death ~5 years after symptom onset. FFI is typically characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness; survival is typically <2 years and sometimes just a few months.

Variant CJD has a different clinical course from most other prion diseases, with an early psychiatric prodrome (most commonly depres sion, 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. ■ ■LABORATORY TESTS 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 cur rent 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 (RTQuIC; 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 dis eases, especially CJD, and can help distinguish CJD from most other conditions. The first reported MRI findings were on T2-weighted MRI and were hyperintensities in the striatum (caudate and puta men) and less commonly in the thalamus (depending on the type of prion disease). Subsequently, with fluid-attenuated inversion recovery (FLAIR) sequences, hyperintensity of the cortex (cortical ribboning) could also be seen. Diffusion MRI, with a combination of diffusionweighted imaging (DWI) and attenuation deficient coefficient (ADC) sequences, greatly improved sensitivity and specificity (to mid to high 90th percentile) of MRI for prion disease, showing hyperintensity (i.e., brightness or high signal) on DWI with corresponding hypointensity (i.e., darkness or low signal) on ADC in the cortex (cortical ribboning) and striatum and less commonly in the thalamus and/or cerebellum (Fig. 449-2). This abnormal signal on DWI and ADC is due to reduced or restricted diffusion of water molecules in these brain regions sec ondary to vacuolation. DWI and FLAIR MRI, however, often show areas of artifactual hyperintensity, particularly in regions where there is air adjacent to brain tissue, such as near sinuses. The true abnormal signal of reduced or restricted diffusion can be distinguished from artifact by (1) acquiring the diffusion MRI in multiple planes (e.g., axial and coronal), (2) looking for corresponding hypointensity in the cor tex or deep nuclei on ADC, and/or increasing the degree of diffusion weighting. T2, FLAIR, and diffusion MRI are often normal, however, particularly in GSS, FFI, sFI, and in some rare genetic prion diseases such as those due to stop-codon mutations. Any prion disease with a long duration (e.g., >1–2 years) often will show nonspecific atrophy on brain MRI or head computed tomography (CT). To a limited extent, the pattern of these MRI abnormalities can also help determine the subtype of sCJD present. For example, MRI findings in the MM1/MV1 subtype are typically located in the cortex (i.e., cortical

ribboning) and deep nuclei (striatum +/– thalamus), MV2K and VV2 involve deep nuclei, and MM2/MV2C are predominantly cortical. These abnor malities may be unilateral or bilateral; when they are bilateral, they may be symmetric or asymmetric. The pattern and type of MRI abnor malities in CJD are not seen with other NDs but can overlap with viral encephalitis, paraneoplastic/autoimmune encephalopathy syndromes, metabolic disorders, or seizures. To establish the diagnosis of either sCJD or familial prion disease, sequencing the PRNP gene must be performed. Finding the wild-type PRNP gene sequence permits the diagnosis of sCJD if there is no history to suggest infection from an exogenous source of prions. The identifi cation of a mutation in the PRNP gene sequence that encodes a non conservative amino acid substitution argues for familial prion disease.

A B C FIGURE 449-2 Brain magnetic resonance imaging (MRI) in a 72-year-old patient with sporadic Creutzfeldt-Jakob disease, MM1 subtype (classic subtype), showing axial (A) fluid-attenuated inversion recovery (FLAIR), (B) diffusion-weighted imaging (DWI), and (C) attenuation deficient coefficient (ADC) sequences at three different levels. There is cortical ribboning indicating restricted diffusion in the left much greater than right temporal (solid white arrow), occipital (solid white arrow), parietal (solid white arrow), insular (no arrow), and posterior cingulate cortices (dashed arrows). There is also restricted diffusion in the left greater than the right caudate head (arrowheads). The corresponding hypointensity (very dark) areas on the ADC sequence confirm that the hyperintensity (bright) areas on DWI and FLAIR are regions of reduced diffusion, not artifacts. Note that the abnormalities are best seen on DWI sequences. Images are radiologic orientation (right side of image is left side of brain). General cerebrospinal fluid (CSF) laboratory testing (i.e., cell count, protein, glucose) is nearly always normal, except that mild and non specific protein elevation and, rarely, mild pleocytosis can be seen in a minority of cases. The first CSF surrogate biomarker used in clinical practice and still incorporated in several diagnostic criteria for sCJD is the 14-3-3 protein, which is elevated in many forms of brain cell injury. Although newer enzyme-linked immunosorbent assays (ELISAs) quantitatively measuring the 14-3-3γ isoform have improved sensitiv ity and specificity, this test is still less accurate diagnostically than some other biomarkers. The sensitivity of 14-3-3 ELISAs in sCJD ranges from ~60% to almost 90% depending on the sCJD subtype (highest in MM1/MV1), whereas the range of specificity has been reported to be as low as 40% to as high as 96% depending on the controls used, making its utility questionable. The level of total tau protein (t-tau), a microtubule-associated protein expressed in neurons and glia, is ele vated in the CSF in many conditions associated with brain cell injury. ELISAs measuring t-tau appear to have a sensitivity and a specificity in the low to mid 90%, which is clinically superior to 14-3-3; however, there is no consensus at this time regarding the best t-tau ELISA or cutoff that should be used to support a diagnosis of sCJD. Assays that amplify PrPSc into amyloid PrPSc fibrils and detect the fibrils by adding thioflavin, which binds amyloid and fluoresces, have greatly enhanced premortem diagnosis of human prion diseases. The first such assay developed was the protein misfolding cyclic ampli fication (PMCA), which was modified into the more user-friendly

 RT-QuIC assay that is now widely used in clinical practice but still primarily performed at national prion surveillance centers. The sen sitivity and specificity of the current CSF RT-QuIC assay (i.e., second generation) for sCJD are about 90–95% and 98–99%, respectively. The advantage of PMCA and RT-QuIC is that they detect prions; however, false positives for RT-QuIC do occur, and as noted by the sensitivity, upward of 10% of sCJD cases are

negative for RT-QuIC. As with other surrogate biomarkers, RT-QuIC is less sensitive for some uncommon sCJD subtypes, for several genetic prion diseases (i.e., GSS and other slower progressing forms), and particularly for vCJD. In contrast, PMCA seems to be more sensitive when applied to CSF and possibly blood and urine from patients with vCJD, but this test is not available for clinical practice in most countries. Improved methods to detect prions in blood, urine, skin, and even tears will be welcomed. EEG can be useful in the diagnosis of CJD, particularly when other ancillary tests are unrevealing, although only ~60% of patients (mostly with the MM1/MV1 subtype of sCJD) show the typical pattern of peri odic sharp wave complexes (PSWCs). PSWCs are usually repetitive, high-voltage, bi- or triphasic sharp discharges that normally appear quite late in the clinical course. Even when PSWCs are seen, they may be transient and might require serial EEGs to detect. During the early phase of CJD, the EEG is usually normal or shows only scattered theta and even delta slow wave activity. The presence of these stereotyped periodic bursts of PSWCs, <200 ms in duration and occurring every

1–2 s, makes the diagnosis of CJD very likely. These discharges are fre quently but not always symmetric; there may be a one-sided predomi nance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

■ ■DIFFERENTIAL DIAGNOSIS Many conditions mimic CJD, including various NDs, autoimmune/paraneoplastic encephalopathies or ataxias, infections, and even psy chiatric conditions. Dementia with Lewy bodies (DLB) (Chap. 445) is one of the most common disorders to be mistaken for CJD, particularly when there is a phase of the illness with a fast decline. It can present rarely in a subacute fashion with delirium, myoclonus, and extrapy ramidal features. Other NDs to consider include AD, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, ceroid lipofuscinosis, and myoclonic epilepsy with Lafora bodies. Usually when these diseases are mistaken for CJD, they have a more slowly progressive and perhaps subtle onset over a few years and then a sudden decline, which makes clinicians consider CJD. A thorough history of the earliest features of the illness—obtained through speak ing with friends, family members, or coworkers—often reveals a slower onset over a few years with a more recent rapid decline, suggesting a non-CJD etiology. There have been, however, rapidly progressive cases of AD with a course of <3 years from first symptom onset, often with ataxia, myoclonus, and other symptoms similar to those seen in CJD. Many of these cases have elevated CSF biomarkers such as 14-3-3. The absence of abnormalities on diffusion MRI (i.e., DWI and ADC) will almost always distinguish these conditions from CJD. CSF RT-QuIC, if positive, can also be helpful. PART 13 Neurologic Disorders Several autoantibody-mediated autoimmune encephalopathies (AEs) (Chap. 99), such as anti-LGI1 (leucine-rich glioma inactivated 1), anti-Crmp5 (collapsin response-mediator protein-5 or anti-CV2), and anti-AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) antibody-mediated AEs, can have significant clinical overlap with CJD. Detection of autoantibodies in the serum and/or CSF, depending on the specific antibody-mediated syndrome, and the absence of brain MRI and CSF prion-specific biomarkers can help distinguish these cases from CJD. In AE with seizures, however, brain MRI may show diffusion MRI abnormalities similar to those in CJD, though this is rare, and these abnormalities disappear soon after sei zures are treated. In contrast, these MRI abnormalities generally persist in CJD, except in very long-lived cases. Intracranial vasculitides (Chap. 375) may produce nearly all the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is uncommon with cerebral vasculitis, but focal seizures may confuse the diagnosis. Prominent headache, absence of myoclonus, stepwise

change in deficits, abnormal CSF, and focal white matter change on MRI or angiographic abnormalities all favor vasculitis. Other diseases that can simulate CJD include neurosyphilis (Chap. 187), AIDS dementia complex (Chap. 208), progressive multifocal leukoencephalopathy (Chap. 142), subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis (Chap. 142), diffuse intracranial tumor (gliomatosis cerebri; Chap. 95), anoxic encephalopathy, dialysis dementia, uremia, hepatic encephalopathy, and lithium or bismuth intoxication. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in CSF should alert the physician to another etiology that explains the patient's CNS dysfunction, although there are rare cases of CJD in which mild CSF pleocytosis or mild elevation in IgG index or oligoclonal bands are observed. ■ ■CARE OF CJD PATIENTS There are no disease-modifying treatments for prion diseases, and treatment is symptomatic. Although CJD is communicable, the likelihood of transmission from one patient to another is remote. The risk of accidental inocula tion by aerosols is minuscule; nonetheless, procedures producing aero sols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended

by the CDC and the National Institutes of Health. The primary concern in caring for patients with CJD is the inadvertent infection of health care workers by needle and stab wounds, although with the possible exception of vCJD (as noted above) in which blood transfusions appear to carry some minimal risk for transmission. When caring for patients with prion disease, standard universal precautions used in the clinical setting (e.g., gloves, gowns, and/or eye protection) are recommended when handling bodily fluids (e.g., blood, urine, and feces). Electroen cephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed. Autopsies on patients whose clinical diagnosis is CJD can be per formed with minimal risk to pathologists or other morgue employees if proper prion-specific precautions are followed. Standard microbio logic practices outlined here, along with specific recommendations for decontamination, are generally adequate precautions for the care of patients with CJD and the handling of infected specimens. ■ ■DECONTAMINATION OF CJD PRIONS Prions are generally resistant to commonly used inactivation procedures, and there is some disagreement about the optimal conditions for ster ilization. Some investigators recommend treating CJD-contaminated materials once with 1 N NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 N NaOH for several hours is recommended for sterilization of prions. The term sterilization implies complete destruc tion of prions; any residual infectivity can be hazardous. Transgenic mouse studies show that sCJD prions bound to stainless-steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation. Recent studies show that α-synuclein prions in brain homogenates prepared from MSA patients bind to stainless-steel wires and that the bound prions can be transmit ted to transgenic mice expressing mutant human α-synuclein. Prion precaution protocols should be used for any patient with known or suspected CJD who is undergoing a surgical procedure that has a high risk of exposure to prions (e.g., neurosurgery). In such protocols, procedures should be implemented to reduce exposure of operating room staff and to isolate surgical equipment until the diag nosis has been definitively determined. If the patient is known to have prion disease, the equipment should be destroyed if possible or, if not possible, then thoroughly cleansed to eliminate risk of prion exposure. Importantly, as human prions appear to be more resistant than many animal prions to denaturation, particularly when bound to metal, prion removal methods used in the clinical setting should be based on data from studies using human

prions. ■ ■PREVENTION AND THERAPEUTICS There is no known effective therapy for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrPSc formation in cultured cells led to clinical studies of quinacrine in CJD patients. Unfortunately, quinacrine failed to slow the rate of cognitive decline in CJD, possibly because therapeutic concentrations of quinacrine were not achieved in the brain. Although inhibition of the P-glycoprotein (Pgp) transport system resulted in substantially increased quinacrine levels in the brains of mice, the prion incubation times were not extended by treatment with the drug. Whether such an approach can be used to treat CJD remains to be established. Like the acridines, anti-PrP antibodies have been shown to elimi nate PrPSc from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate as well as por phyrin and phenylhydrazine derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation. New treatment trials are underway and, based on animal models, hold promise even when treatment is begun close to symptom onset.

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