Transmissible Spongiform Encephalopathies in Humans

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■ **Abstract** Creutzfeldt-Jakob disease (CJD), the first transmissible spongiform encephalopathy (TSE) to be described in humans, occurs in a sporadic, familial, or iatrogenic form. Other TSEs in humans, shown to be associated with specific prion protein gene mutations, have been reported in different parts of the world. These TSEs compose a heterogeneous group of familial diseases that traditionally have been classified as familial CJD, Gerstmann-Sträussler-Scheinker syndrome, or fatal familial insomnia. In 1996, a newly recognized variant form of CJD among young patients (median age, 28 years) with unusual clinical features and a unique neuropathologic profile was reported in the United Kingdom. In the absence of known CJD risk factors or prion protein gene abnormalities, the UK government concluded that the clustering of these cases may represent transmission to humans of the agent causing bovine spongiform encephalopathy. Additional epidemiologic and recent laboratory data strongly support the UK government's conclusion.

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INTRODUCTION

Transmissible spongiform encephalopathies (TSEs) are a group of rapidly progressive, invariably fatal, neurodegenerative diseases that affect both humans and animals. Most TSEs are characterized by a long incubation period and a neuropathologic feature of multifocal spongiform changes, astrogliosis, neuronal loss, and absence of inflammatory reaction. TSEs in humans include Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and new variant CJD (nvCJD). Kuru has been described only in the Fore population of New Guinea. For many years after its first recognition in 1957, kuru was the most common cause of death among women in the affected population, but it is disappearing because of the cessation of ritualistic cannibalism that had facilitated disease transmission (52, 54, 79, 94). TSEs described in animals include scrapie in sheep and goats, transmissible mink encephalopathy, chronic wasting disease in deer and elk, bovine spongiform encephalopathy (BSE, commonly known as "mad-cow" disease), exotic ungulate spongiform encephalopathy, and feline spongiform encephalopathy in cats, albino tigers, pumas, and cheetahs. The reported ungulate and feline spongiform encephalopathies appear to represent transmission of the BSE agent to these animals.

After descriptions of the transmissibility of scrapie, several theories were suggested to explain the causative agent of TSEs. For years, many researchers proposed that TSEs were caused by "slow viruses"; however, no viruses could be isolated. In the mid-1960s, the possibility that the agent causing scrapie was devoid of nucleic acids or could simply be a protein was suggested (2, 122). Griffith proposed three possible mechanisms by which such an infective protein lacking nucleic acids could support its own replication (65). Subsequent studies demonstrated

that the scrapie agent has many chemical properties in common with protein molecule, supporting the protein hypothesis (127, 131). In 1982, Prusiner introduced the term prion to describe the small proteinaceous infectious particle that he showed was an essential component of the scrapie agent (127). Based on what has now become the prion theory, TSEs result from accumulation, in the neurons, of an abnormal isoform of a cellular glycoprotein known as the prion protein (142). The formation of the abnormal isoform is believed to be triggered by mutations in the prion protein gene, a chance error during prion protein gene expression, or transmission of the pathogenic prions. Once the abnormal isoform is formed or acquired, it is believed to promote the conversion of the cellular prion protein in neighboring neurons through an autocatalytic process (132).

Recently, TSEs attracted considerable public attention because of a 1996 report in the United Kingdom that BSE may have spread to humans and caused a newly recognized variant form of CJD (153). BSE was first recognized in 1986 in Great Britain where a total of 173,952 cases (111) were confirmed during 1988–1998 in over 34,500 herds.

This review article describes the clinical and epidemiologic characteristics of TSEs in humans and summarizes the available scientific evidence for a causal link between nvCJD and BSE.

THE ETIOLOGIC AGENT OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Characteristics of the Agent

Many studies have been done to identify the agent causing TSEs. The success in experimentally transmitting scrapie to rodents facilitated etiologic studies focused on characterizing the agent that causes scrapie. The potential transmissibility of the scrapie agent, its proliferation in the animal host, and the retention of scrapie infectivity after filtration led to the suggestion that scrapie might be caused by "slow viruses" or viroids (52, 128). However, efforts to identify viruses or scrapie-specific nucleic acids by using conventional laboratory techniques were unsuccessful (1, 109, 127). Studies have demonstrated the extreme resistance of scrapie infectivity to radiation, nucleases, and other reagents damaging to nucleic acids (7, 127). These findings, coupled with those of other studies that showed diminution of scrapie infectivity with procedures that modified proteins and linkage of inherited TSEs with point genetic mutations, suggested that the TSE agent is neither a virus nor a viroid (128).

The Prion Theory

Because of the unusual properties of the agent that causes TSEs, the term prion (**pro**teinaceous **in**fectious particles) was introduced to differentiate it from conventional infectious agents (127). Several studies have identified a protease-resistant polypeptide in subcellular fractions of hamster brain enriched with scrapie

infectivity (10, 51, 104, 129). Absence of the protease-resistant polypeptide in the brains of healthy control animals indicated that this protein is required for scrapie infectivity (10). The molecular characteristics of this protein were shown to be similar to those of a cellular glycoprotein that is most commonly found in neurons (117, 120) but also in other cells of mammals and birds. The pathogenic form of the protein, designated PrP-res or simply prion, is primarily distinguished from its cellular isoform, designated PrP-C, in its three-dimensional structure (75, 76, 119). Spectroscopic measurements of PrP-C from purified fractions of hamster brain demonstrated that 42% of PrP-C is composed of α-helix and is almost devoid of β-sheet (3%) (119). In contrast, PrP-res purified from hamster brain infected with the scrapie agent is composed of 43% β-sheet and 30% α-helix (119). PrP-C is found attached on the surface of neurons with a glycoprotein molecule (138). It is encoded by a group of genes located on the short arm of chromosome 20, and its function is unknown. PrP-res, however, is found in the cytoplasm of affected cells (142) and is resistant to heat, radiation, proteolytic enzymes, and conventional disinfectants such as alcohol, formalin, and phenol (6, 7, 127).

The fundamental event in the occurrence of TSEs seems to be a conformational change in PrP-C (25). Animal studies have suggested that conformational change results from biochemical interaction between PrP-C and PrP-res (132, 145). Although the nature of this interaction is poorly understood, it has been postulated that infecting PrP-res may serve as a template in directing the formation of new PrP-res (145). Ablation of the prion protein gene in mice renders them resistant to infection with the scrapie agent, indicating that the presence of PrP-C is essential for propagation of the infectious agent (24, 130). Intracerebral grafting of PrP-C-expressing neuroectodermal tissue in mice devoid of PrP-C allows the replication of inoculated PrP-res (12).

The prion theory clearly challenges our biological understanding of infectious diseases. Some researchers regard the mere thought that a protein devoid of nucleic acids could dictate its own replication as heretical. Others point out that the existence of different prion "strains" in scrapie and other TSEs indicates the presence of a tightly bound, hitherto unrecognized RNA or DNA molecule in the prion particle (151). Suggestions have also been made that the biological properties of prion "strains" may be encrypted within the conformation of PrP-res (128, 145). However, additional studies are required to substantiate these claims or explain the strain diversity of prions, including the variable phenotypical disease expression of some TSEs within the same species.

CREUTZFELDT-JAKOB DISEASE

History

Patients with rapidly progressive neurodegenerative illnesses were first reported by the German neurologists Creutzfeldt and Jakob in the early 1920s (134). The first patient described by Creutzfeldt was a 22-year-old woman with progressive

dementia, tremors, spasticity, ataxia, and possibly myoclonus. Subsequently, Jakob reported five patients, the first three of whom were described as having neuropathologic features similar to Creutzfeldt's case, with a diffuse non-inflammatory disease process and foci of tissue destruction (134). Retrospective review of brain sections of four of Jakob's patients indicated that two of them had the typical neuropathologic features of CJD; neuropathologic review of Creutzfeldt's case was inconclusive (85, 134).

Incidence

CJD is the most common form of TSEs in humans and occurs worldwide, with an estimated incidence of one case/1 million population per year. CJD is reported in almost equal ratios between the sexes, although older males (≥60 years of age) appear to have a higher incidence of disease (69). Brown and co-workers have reported a peak age of onset between 55 and 75 years (mean: 61.5 years) (15). Analysis of the multiple cause-of-death data compiled by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), from 1979 through 1994, showed an average annual CJD death rate of 0.95 deaths/1 million population and a median age at the time of death of 68 years in the United States (69); CJD death rates remained stable during this 16-year period (Table 1). The age-adjusted CJD death rate for whites was significantly higher than that for blacks (69).

Clinical Features

CJD has been recognized to occur sporadically, or through iatrogenic transmission, or as a familial form. Affected patients usually present with a rapidly progressive dementia, visual abnormalities, or cerebellar dysfunction, including muscle incoordination and gait and speech abnormalities. During the course of the disease, most patients develop pyramidal and extrapyramidal dysfunction with abnormal reflexes, spasticity, tremors, and rigidity; some patients may also show behavioral changes with agitation, depression, or confusion. These symptoms often deteriorate very rapidly, and patients develop a state of akinetic mutism during the terminal

TABLE 1 Creutzfeldt-Jakob disease (CJD) deaths and death rates[a] by age group and 4-year periods in the United States, 1979–1994

Age groups (years)	1979–1982		1983–1986		1987–1990		1991–1994	
	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
0–44	22	0.04	10	0.02	21	0.03	27	0.04
45–59	160	1.17	170	1.26	148	1.06	174	1.13
≥60	584	4.04	703	4.52	796	4.84	827	4.83

[a]Death rates are expressed per million persons.

stages of the illness. Myoclonus, the most constant physical sign, is present in nearly 90% of CJD patients (85). CJD is invariably fatal, with a median illness duration of 4 months (mean: 7.6 months); death occurs within 12 months of illness onset in ~85–90% of patients (15). Although a nonspecific, diffusely abnormal electroencephalogram (EEG) tracing is seen in all patients, serial EEG recordings will demonstrate the typical diagnostic pattern in ~75–85% of patients toward the latter part of the illness (15). The diagnostic EEG tracing shows one-cycle to two-cycles per second triphasic sharp-wave discharges (13, 15), which in conjunction with the clinical picture is considered to be diagnostic of CJD. Recently, a new immunoassay has been developed to detect the presence in the cerebrospinal fluid of 14-3-3 protein, which appears to be a marker for CJD. The 14-3-3 protein is a highly conserved protein found in insects, plants, and mammals. In humans and other mammals, 14-3-3 is a normal neuronal protein consisting of several isoforms. Antibodies against the 14-3-3 protein do not cross-react with PrP-res, confirming that these two proteins are different. In patients with dementia, the sensitivity of the 14-3-3 immunoassay in detecting CJD patients was reported to be 96%; the specificity varied from 96% to 99% (74). However, confirmatory diagnosis of CJD requires demonstration of the typical neuropathology or the presence of PrP-res in brain tissue obtained at biopsy or autopsy. The typical neuropathology consists of a microscopic picture of spongiform changes, gliosis, and neuronal loss in the absence of inflammatory reaction (6, 87). The presence of amyloid plaques can be demonstrated in ~5% of CJD patients (39). The presence of PrP-res in biopsy or autopsy brain samples can be demonstrated by immunodiagnostic tests, such as immunohistochemical staining, histoblot, or Western blot techniques (87).

SPORADIC CREUTZFELDT-JAKOB DISEASE

Possible Causes

The sporadic form of CJD accounts for ~85% of all CJD cases. Brown and co-workers reported a mean age at onset of 60 years after their analysis of 232 experimentally transmitted cases of sporadic CJD; the mean duration of illness was 8 months (Table 2) (17). Although the exact cause is unknown, two hypotheses have been suggested to explain the occurrence of sporadic CJD (128). The first one is the possibility of an age-related somatic mutation of the prion protein gene that might result in the formation of PrP-res. Such mutations can randomly occur in the population at a rate of nearly one per million, which roughly corresponds to the incidence of sporadic CJD. The second suggested explanation is the spontaneous conversion of PrP-C into PrP-res in a single neuron or a group of neurons, possibly after a chance error during prion protein gene expression. The PrP-res is then believed to initiate a chain reaction resulting in the spread of disease to other susceptible neurons. The surprisingly stable and uniform incidence of nonfamilial forms of CJD in many different countries and the absence of recognizable transmission patterns to account for a substantial proportion of cases have been strong arguments favoring the spontaneous occurrence of sporadic CJD.

Search for Risk Factors

Consumption of meat and other organs, including animal brain, liver, and kidney, and exposure to blood and blood products have been examined as possible sources of infection in sporadic CJD patients. Several case-control studies done to examine these and other possible modes of transmission have not provided conclusive results (9, 37, 83). A re-analysis of pooled data from previous three case-control studies did not show a statistically significant association of CJD with employment as a health professional, including medical doctors, nurses, dentists, laboratory workers, and ambulance personnel (152). The analysis also found no association of CJD with head trauma, blood transfusion, history of surgery, or consumption of organ meat, including brain, liver, and kidney. The largest case-control study to date conducted in six European countries by the European Union Collaborative Study Group of CJD showed no significant association of CJD with a history of blood transfusion, consumption of beef, veal, lamb, or pork, or occupational exposure to animals or animal products, including butchers and slaughterhouse and farm workers. None of the health professions evaluated in the study were associated with a significant risk of CJD, including physicians, neuropathologists, nurses, laboratory technicians, and dentists. Although raw meat and brain consumption were shown to be significantly associated with an increased risk of CJD, after a conditional regression analysis, brain consumption that would be expected to pose a greater risk was no longer significantly associated (150).

Blood and Blood Products

Experimental transmission of CJD to laboratory animals intracerebrally inoculated with blood obtained from CJD patients indicated the possible presence of the CJD agent in human blood in low concentrations (100, 143). However, review of the experimental studies has raised questions about the validity of these transmissions. In contrast to studies of human blood, three studies have clearly confirmed the infectivity of blood derived from experimentally infected guinea pigs or mice after intracerebral inoculation of healthy animals (89, 99, 144). Recently, the infectivity in rodent models of fractionated blood, including buffy coat, plasma, and plasma fractions I, II, and III derived from experimentally infected animals, has been reported (137). Whether the results of these animal studies provide any conjectural knowledge on blood-borne transmission of the CJD agent in humans is unknown. Several epidemiologic studies indicate that the risk, if any, of CJD transmission through blood or blood products in the human population must be low (137). No convincing evidence exists for any transmission of CJD to a human recipient of blood or blood products (69, 137).

In 1995, a long-term follow-up German study indicated no evidence of CJD transmission either to 27 patients who definitely or to 8 patients who probably received a blood unit from a donor who died of CJD (67). The donor was a 62-year-old man who died from CJD in 1991, and donated 55 units of blood between 1971 and 1991. At least seven of the patients who definitely received a blood unit

TABLE 2 Clinical and neuropathologic features of transmissible spongiform encephalopathies (TSE) in humans

TSE in humans	Mean age at onset (years)	Mean duration of illness (months)	Distinctive clinical features	Presence of typical EEG	Neuropathology
Sporadic CJD (17)	60	8[a]	Dementia, myoclonus, cerebellar dysfunction	75–85% of patients	Spongiform changes, gliosis, neuronal loss; amyloid plaques in 5% of patients
Familial CJD					
codon 178 (21)	46	23	Resembles sporadic CJD	Extremely rare	Resembles sporadic CJD
codon 183 (115)	45	50	Personality change, dementia, Parkinsonism	Rare	Spongiform change, neuronal loss, mild gliosis mainly in frontal and temporal lobes
codon 200 (20, 108)	55	8	Resembles sporadic CJD	64–74% of patients	Resembles sporadic CJD
Iatrogenic CJD					
hGH-associated (126)	30[b]	—	Onset with gait abnormalities and ataxia	5% of patients	Resembles sporadic CJD; but more frequent amyloid plaques
dura-associated	39[c]	10[d]	Resembles sporadic CJD	Resembles sporadic CJD	Resembles sporadic CJD
nvCJD (153, 160, 161)	29	16	Onset with psychiatric symptoms, parasthesia or dysesthesia; delayed development of neurologic signs	None	Numerous amyloid plaques surrounded by vacuoles ("florid" plaques); spongiform changes most evident in basal ganglia and thalamus

FFI (98)	49	13	Sleep disturbances and autonomic dysfunction	Rare	Marked neuronal loss and mild gliosis predominantly in the thalamus; rare spongiform changes or plaques
GSS					
codon 102 (18, 53)	48	60	Predominantly have gait abnormalities and ataxia	Extremely rare	Numerous amyloid plaques usually multicentric; spongiform changes severe to absent; gliosis and neuronal loss
codon 105 (80, 81, 156)	44	106	Spastic paraparesis and dementia	None	Numerous amyloid plaques; variable neurofibrillary tangles; absent spongiform changes; gliosis and neuronal loss
codon 117 (116, 149)	38[e]	41	Dementia, pyramidal and extrapyramidal signs; Parkinsonism (in the US family)	Extremely rare	Numerous multicentric or unicentric plaques; occasional neurofibrillary tangles; variable spongiform changes, gliosis and neuronal loss
codon 198 (47, 56, 71)	52	72	Ataxia, Parkinsonism, and dementia	Extremely rare	Numerous amyloid plaques and neurofibrillary tangles; spongiform changes, gliosis, neuronal loss

[a] Brown and coworkers have reported a median illness duration of 4 months after their analysis of 232 neuropathologically verified CJD cases (15).

[b] Based on the age at onset of 12 US patients; younger ages at onset have been reported in nine UK patients (mean age: 22 years) and 24 French patients (mean age: 19 years) (126).

[c] Based on the age at onset of 64 dura mater graft-associated CJD cases, 43 in Japan (32) and 21 in other countries (see Table 3).

[d] Based on 24 dura mater graft-associated CJD cases with known illness duration (see Table 3).

[e] A mean age at onset of 41 years was reported for a French–Alsatian family with GSS associated with a prion protein gene mutation at codon 117 (148).

from this donor survived 10 years or longer; one of these patients survived for at least 20 years. Analysis of CDC's national multiple cause-of-death data also showed that none of the 4,164 patients with CJD who died from 1979 through 1996 were reported to have hemophilia A, hemophilia B, thalassemia, or sickle cell disease, diseases in which patients have increased exposure to blood products (69, 137). If CJD were transmitted through blood products, these groups of patients would be expected to have been at increased risk. In 1995, CDC alerted over 120 US hemophilia treatment centers about the importance of CJD surveillance among hemophilia patients. This alert and subsequent surveillance of deaths of hemophilia patients, including neuropathologic examination of brain tissues from at least 30 hemophilia patients who died of non-CJD conditions, did not detect any evidence of CJD among the hemophilia population (137). Also in 1995, CDC and the American Red Cross initiated a long-term follow-up study of recipients of blood components derived from donors who subsequently develop CJD. As of June 1998, none of the 196 persons who received blood components derived from 15 donors with CJD were reported to have died of CJD. Forty-two of these recipients were reported to have lived for ≥5 years after receipt of a blood component (137), including four recipients who had survived for 13, 14, 16, and 25 years. In addition, several case-control studies have indicated that the proportion of CJD patients with a history of blood transfusion was not significantly different from that of controls (46, 66, 150, 152), indicating that blood transfusion is not a major risk factor for CJD.

Novel Classification

A recent analysis of the clinicopathologic profile, the prion protein gene polymorphism at codon 129, and the molecular characteristics of PrP-res in several hundred sporadic CJD patients indicated that the haplotype at codon 129 and the size of the PrP-res fragment correlate with distinct clinical and pathologic phenotypes. Based on these correlations, Parchi & co-workers proposed a novel classification scheme for sporadic CJD composed of six groups (121). The majority of sporadic CJD patients were classified in the first group: Met/Met or Met/Val at codon 129 and PrP-res fragment type 1; clinically, these patients had prominent dementia and myoclonus, frequent diagnostic EEG, a mean illness duration of 4.4 months, and a pathologic picture that mainly affected the cerebral cortex, deep nuclei, and the cerebellum. In contrast, sporadic CJD patients classified in the third group, for example, Met/Val at codon 129 and PrP-res fragment type 2, mostly had ataxia and dementia, no diagnostic EEG, and a pathologic picture with widespread distribution and the presence of PrP-res–positive amyloid plaques. One of the groups with the least number of patients was a group with val/val at codon 129 and PrP-res fragment type 1. Sporadic CJD patients classified in this group had an illness characterized by prominent dementia, longer duration, absence of the diagnostic EEG picture, and young age at onset (121).

FAMILIAL CREUTZFELDT-JAKOB DISEASE

The familial form of CJD accounts for 5–15% of CJD patients. Because of its autosomal dominant inheritance pattern, there is commonly a family history of CJD in these patients. Familial CJD is most frequently associated with mutations at codon 200 and less frequently with mutations at codon 178, 208, or 210 of the prion protein gene (19, 50, 53, 55, 60, 61, 125). A CJD patient with a double mutation at codons 180 and 232 was reported in Japan (68). Familial CJD with codon 200 mutation has been reported in geographical clusters among Libyan Jews in Israel (62, 108), Spanish families in rural Chile (53, 61), and in central Slovakia (61, 63). Isolated familial cases have been reported in Canada, France, Japan, the United Kingdom, and the United States (53, 61). In families with codon 200 mutations, ~56% of the carriers develop CJD (61). This form of familial CJD occasionally exhibits "generational skip" and occurs in a seemingly sporadic pattern. The age at onset (mean, 55 years), the frequent occurrence of the diagnostic EEG, and the duration of illness (mean, 8 months) in familial CJD patients with codon 200 mutation closely resemble those of sporadic CJD patients (Table 2) (20, 108).

Familial CJD with codon 178 mutation has been reported in families originating from England, Finland, France, Hungary, and the Netherlands (60). A pedigree analysis of the original Finish family indicated that codon 178 mutation could have a disease penetration rate of ~100% (59). This form of familial CJD occurs when the mutant allele coding for asparagine at codon 178 also codes for valine at codon 129 (53, 64). Compared with sporadic CJD patients, familial CJD patients with codon 178 mutation tend to have illness onset at an earlier age (mean, 46 years), longer duration of illness (mean, 23 months), and a nondiagnostic EEG tracing (Table 2) (21).

Recently, a novel prion protein gene mutation at codon 183 with atypical clinicopathologic features was reported in a Brazilian family (115). Seventeen family members over three generations may have been affected, including six patients whose clinical data were consistent with the disease and three patients confirmed by pathologic examination of the brain. Most patients presented with personality changes followed by progressive dementia and a Parkinsonian syndrome. The mean age at onset of the nine patients was 44.8 years, and the mean duration of illness was 4.2 years. In two of the three patients in whom brain tissues were examined, spongiform changes, neuronal loss, and mild gliosis were predominantly seen in the frontal and temporal lobes.

IATROGENIC CREUTZFELDT-JAKOB DISEASE

The transmissible nature of CJD was first described in 1968, after intracerebral inoculation of a brain biopsy tissue from a CJD patient into a chimpanzee (57). However, a possible person-to-person transmission of the CJD agent was not reported

until 1974, when Duffy & co-workers described a 55-year-old patient who developed CJD 18 months after receiving a corneal transplant obtained from a donor with CJD (44). Subsequently, other modes of iatrogenic transmission of the CJD agent were reported, including the use of contaminated EEG depth electrodes (8), neurosurgical instruments (154), cadaveric pituitary-derived gonadotropin (34) and human growth hormone (hGH) (26), and dura mater grafts (27, 146).

Human Growth Hormone-Associated Creutzfeldt-Jakob Disease

Recognition in the United States of the first three hGH-associated CJD cases (26, 58, 82, 147) raised concern in many other countries because of a potentially large number of patients who may have received contaminated hGH. All three US patients had growth failure secondary to growth hormone deficiency and received hGH treatment between 1963 and 1980. Investigation of these and additional CJD cases who received hGH through the National Hormone and Pituitary Program did not identify a single lot of product common to all patients (26, 48). Although the production of discrete lots of hGH involved processing of a batch of ~5000–20,000 pituitary glands, combining fractions rich in hGH derived from several batches was a common practice (48). Fradkin & co-workers estimated that, between 1963 and 1985, at least 140 infected pituitary glands may have been processed and randomly distributed among many hGH lots (48). In 1985, the use of hGH was discontinued in the United States, and a follow-up study of ~8000 patients who received hGH through the National Hormone and Pituitary Program between 1963 and 1985 was initiated (110); the study cohort of hGH recipients included 6,282 patients for whom the hGH treatment was confirmed. As of April 1999, 20 of the ~8000 hGH recipients had died of CJD (LB Schonberger, personal communication). Worldwide, >84 hGH-associated CJD cases have been reported, including cases who received imported US products in Brazil and New Zealand, and cases who received locally produced hGH in Australia, France, and the United Kingdom (14, 77). Although hGH has now been replaced by a hormone synthesized with recombinant technology, additional hGH-associated CJD cases are expected because of the long incubation period.

Dura Mater Graft–Associated Creutzfeldt-Jakob Disease

In February 1987, the first recognized dura mater graft-associated CJD case was reported in a 28-year-old woman who developed CJD 19 months after a neurosurgical procedure involving implantation of Lyodura, a brand of dura mater graft produced by B Braun Melsungen AG of Germany (27, 146). A telephone survey conducted by CDC investigators indicated that the procedures used by US processors of dura mater grafts were different from those of B Braun Melsungen AG (28); the US processors avoided batch processing of dura mater grafts obtained from different donors and maintained records that allowed identification and tracing of donors of each graft. Because of these differences between the processing of

Lyodura and of other similar products, CDC cautioned that the use of Lyodura might carry an increased risk of CJD transmission (28). In June 1987, representatives of B Braun Melsungen AG reported that, as of May 1, 1987, their procedures for collecting and processing dura were revised to reduce the risk of CJD transmission (29, 78).

Subsequent case reports of Lyodura-associated CJD patients in Germany (91), Italy (103), Japan (112, 158), New Zealand (29), Spain (30, 101), the United Kingdom (155), and the United States (90) suggested that Lyodura processed before May 1987 was in fact associated with a substantial risk of CJD transmission. The epidemiologic characteristics of dura mater graft-associated CJD patients reported in journals published in English and unpublished US cases investigated by CDC are summarized in Table 3; most of the patients were reported to have received Lyodura processed before 1987. A 1996 nationwide CJD survey in Japan identified 43 dura mater graft-associated CJD patients with illness onset from September 1985 to May 1996; at least 41 of these patients received Lyodura processed before May 1987 (32). The latency period between receipt of a dura mater graft and onset of CJD in the 43 patients ranged from 16 to 193 months (mean, 89 months); the mean age at onset of the patients was 53 years (32). Worldwide, as of September 1998, at least 64 dura mater graft-associated CJD cases have been reported; 57 of these patients were reported to have received Lyodura. Four patients most likely received a non-Lyodura graft, and the type of dura in three patients was unknown (Table 3). In addition, as of June 1998, ~21 unpublished Lyodura-associated CJD cases have been identified, including cases in Argentina, Australia, Canada, Japan, and the United Kingdom (159). The mean age at onset of the 64 dura mater graft-associated CJD cases was 38.5 years; the mean incubation period was 5.8 years.

Stringent donor selection procedures, including exclusion of donors at high risk for CJD and avoidance of batch processing of dura mater grafts, are essential in ensuring the safety of dura mater grafts. Neuropathologic screening of donors to detect asymptomatic TSEs and institution of a sodium hydroxide inactivation step would further minimize the risk of CJD transmission. Because complete inactivation of the CJD agent in an intact tissue such as dura mater may not be achieved, treatment with sodium hydroxide should not be regarded as a substitute for careful clinical and neuropathologic screening of donors. Even the most stringent donor screening and dura mater processing may not totally eliminate the potential for an infectious graft. Surgeons should be aware of this possibly inherent risk of CJD transmission by dura mater grafts and may want to consider the alternative use of autologous fascia lata, temporalis fascia, or synthetic substitutes (32, 78).

Route of Infection in Iatrogenic-Creutzfeldt-Jakob Disease

The length of incubation period and the clinical presentation in iatrogenic CJD patients seem to vary depending on the portal of entry. In hGH-associated CJD cases where infection is through the peripheral route, the mean incubation period

TABLE 3   Dura mater graft-associated Creutzfeldt-Jakob disease (CJD) cases with known epidemiologic characteristics[a]

Country	Age at onset (years)	Sex	Time of dura implantation	Time of CJD onset	Latency period (months)	Illness duration (months)	Pathologic confirmation	Dura mater graft used
Australia (139)	26	M	1982	1994	144	9	No[b]	Lyodura
	61	M	1982	1987	58	—	Yes	Lyodura
France (3, 40, 84)	25	M	Jul. 17, 1986	Dec. 1993	89	8	Yes	Lyodura[c]
	52	F	1984	Mar. 1995	132	5	Yes	Unknown
	59	M	Jan. 16, 1989	Jul. 1992	42	5	Yes	Unknown[c]
Germany (91)	26	F	1984	—	84	2	No[b]	Lyodura
Italy (103, 124)	27	M	May 1985	Jan. 1989	44	—	Yes	Lyodura
	32	F	Nov. 1981	—	111	8	Yes	Non-Lyodura
Japan (32, 112, 137a, 141, 157, 158)	25	F	Mar. 15, 1984	Dec. 1986	33	18	Yes	Lyodura
	35	F	Feb. 20, 1985	Sep. 1989	56	27	Yes	Lyodura
	47	F	Sep. 1985	Nov. 1994	110	17	Yes	Lyodura
	52	M	Dec. 24, 1984	Mar. 1993	99	10	Yes	Lyodura
	65	F	Sep. & Oct. 1991	Feb. 1994	28	20	No[b]	Non-Lyodura[d]
	68	M	Dec. 1985	May 1996	125	8	Yes	Lyodura
	68	F	Sep. 1986	1996	120	—	Yes	Lyodura
New Zealand (29)	25	M	1985	May 1988	31	2	Yes	Lyodura

Spain (30, 33a, 101)	18	M	Apr. 18, 1983	1991	79	3	Yes	Lyodura
	19	M	Nov. 22, 1983	1985	16	21	Yes	Lyodura
	34	M	Dec. 5, 1983	1992	105	—	Yes	Lyodura
	41	F	May 1989	Oct. 1992	41	4	Yes	Lyodura
	57	F	Jun. 24, 1984	1987	43	25	Yes	Lyodura
United Kingdom (45, 155)	30	M	Oct. 1985	Aug. 1989	46	4	Yes	Lyodura
	44	F	1983	1991	96	4	Yes	Lyodura
	51	F	1969	1978	84	6	No[b]	Unknown
United States (5, 27, 90, 146)	28	F	Apr. 1985	Nov. 1986	19	4	Yes	Lyodura
	28	F	Sep. 1985	1990	60	18	Yes	Lyodura
	39	F	Jul. 13, 1992	Jun. 1998	72	3	Yes	Non-Lyodura
	72	M	Nov. 21, 1990	May 1995	54	2	No[b]	Non-Lyodura

[a] Additional dura mater graft-associated CJD cases not included in this table have been reported (see text for details).

[b] The CJD diagnosis in these patients was based on clinical data and a CSF test positive for protein 130/131 (in the Australian patient) or the presence of the diagnostic EEG tracing (in the other four patients).

[c] The Lyodura in the 25-year-old patient was used for embolization of the external carotid artery for a nasopharyngeal angiofibroma (3) and the unknown dura mater graft in the 59-year-old for embolization of the fourth and fifth left posterior intercostal arteries (40).

[d] Although the brand of dura mater graft used in this patient could not be determined, the use of Lyodura processed before May 1987 was reported to be unlikely (32).

has been estimated to be as long as 12 years or longer (14). These patients commonly present with gait abnormalities and ataxia (22, 48). Dementia, a common presenting symptom in sporadic CJD patients, is a late manifestation and is mild (49). Because of the resemblance of this clinical presentation with kuru, it was suggested that the peripheral route of infection may be responsible for a predominantly cerebellar dysfunction at the time of clinical presentation. In contrast, in dura mater graft-associated CJD cases, where the infective tissue is directly placed in the cranium, the mean incubation period was shown to be around 6 years. Although patients with dura mater graft-associated CJD tend to be younger than sporadic CJD patients (mean age, 38.5 and 60.0 years, respectively), their symptomatology is almost identical (45).

POLYMORPHISM AT CODON 129

The human prion protein gene has been shown to exhibit polymorphism for methionine or valine at codon 129. A number of studies have indicated that this polymorphism may play a significant role in determining host susceptibility and the phenotypical disease expression of familial, iatrogenic, or sporadic CJD. Three different studies involving analysis of the prion protein gene of 41 hGH and gonadotropin-associated CJD cases showed that 38 (92.7%) of the cases were homozygous for either methionine (21 cases) or valine (17 cases), and 3 (7.3%) cases were heterozygous for methionine and valine (Met/Val) (16, 35, 41). In addition, Brown and co-workers reported that 12 dura mater graft-associated CJD cases tested for codon 129 polymorphism were found to be homozygous for methionine (16). In comparison, among the 261 healthy controls used in the same studies, 126 (48.3%) were shown to be homozygous for either methionine (97 controls) or valine (29 controls), and 135 (51.7%) were heterozygous with Met/Val. Previously, Palmer & co-workers had shown that, among the 22 sporadic CJD cases they tested, 21 (95.5%) cases were homozygous for either methionine (16 patients) or valine (5 patients), and 1 case (4.5%) was heterozygous with Met/Val (118). Hence, persons who are homozygous for either methionine or valine at codon 129 seem to be predisposed to developing sporadic or iatrogenic CJD. In contrast, heterozygosity with Met/Val at codon 129 seems to be protective against both sporadic and iatrogenic CJD.

In addition, the methionine and valine polymorphism at codon 129 when combined with a mutation at codon 178 has been shown to influence the phenotypical disease expression of inherited TSEs in humans (64). When the mutant allele of the prion protein gene coding for asparagine at codon 178 also codes for valine at codon 129, it produces a clinical picture consistent with CJD rather than FFI. In contrast, when the mutant allele coding for asparagine at codon 178 also codes for methionine at codon 129, it produces a clinical picture consistent with FFI rather than CJD.

A study in Britain suggests that polymorphism at codon 129 may influence the pattern of PrP-res deposition and astrocytosis in sporadic CJD patients (97). Patients with valine homozygosity appeared to be associated with greater PrP-res

deposition and astrocytosis in deep gray matter areas. In contrast, patients with methionine homozygosity showed greater PrP-res deposition and astrocytosis in cortical areas. Patients with Met/Val heterozygosity had a mixed deep gray matter and cortical brain pathology. The distribution of spongiform change was not associated with any particular polymorphism at codon 129.

GERSTMANN-STRÄUSSLER-SCHEINKER SYNDROME

GSS, a familial disease with autosomal dominant inheritance, was first described in 1936 by Gerstmann, Sträussler, & Scheinker (134). Since then, the name GSS has been used to describe a heterogeneous group of neurodegenerative disorders with a familial origin, infrequent myoclonus and diagnostic EEG, and a neuropathologic feature of numerous amyloid plaques. GSS is considered a variant of the familial form of CJD, but it is primarily associated with mutations at codon 102 and less frequently with mutations at codon 105, 117, 145, 198, or 217 of the prion protein gene (43, 53). It occurs at an estimated annual incidence of 5 cases/100 million population. Neurologic signs and symptoms that are commonly reported in GSS patients include cerebellar ataxia, gait abnormalities, dementia, dysarthria, ocular dysmetria, and hyporeflexia or areflexia in the lower extremities (85). However, the different prion protein gene mutations in GSS patients are associated with a widely variable clinical presentation, age at onset, and duration of illness (Table 2). The relatively frequent prion protein gene mutations associated with GSS and their clinicopathologic features are briefly described here.

Codon 102

The prion protein gene mutation at codon 102, the most frequently seen mutation in GSS, is associated with a predominantly cerebellar dysfunction at the time of clinical presentation, early age at onset (mean, 48 years), and a prolonged duration of illness (mean, 5 years) (18, 53); patients commonly present with slowly progressive gait abnormalities and ataxia. This form of GSS has been reported in families from Austria, Britain, Canada, France, Germany, Israel, Italy, Japan, and the United States (18, 53, 55, 70, 88). Pedigree and genetic analyses of a 39-year-old woman with GSS indicated that the original Austrian family reported by Gerstmann and co-workers carries a prion protein mutation at codon 102 (86).

Codon 105

A prion protein gene mutation at codon 105 with an unusual clinical picture consisting of spastic paraparesis, cerebellar dysfunction, and dementia has been reported in three Japanese families (80, 81, 156). The age at onset of the patients ranged from 38 to 48 years (mean, 44 years), with a median illness duration of 7 years (mean, 8.8 years). The neuropathology of these patients showed the presence of numerous amyloid plaques and variable degrees of neurofibrillary tangles in the absence of spongiform changes (80, 81).

Codon 117

GSS patients with a prion protein gene mutation at codon 117 predominantly present with dementia associated with extrapyramidal and pyramidal signs (72). Although some patients may develop ataxia, it is relatively a minor feature. This form of GSS has been reported in a large US family of German descent (73, 116) and a French-Alsatian family (43, 149). A 22-year follow-up of the US family indicated that at least 24 family members over five generations might have been affected with a similar disease (116). The neuropathologic profile of the proband of this family was consistent with GSS. The mean age at onset of 20 affected family members was 38 years (range, 22–58 years); the mean duration of illness was 3.4 years (range, 1.5–7 years) (116). Hsiao & Prusiner have described this form of GSS as "dementing GSS" and the codon 102 variant as "ataxic GSS" (72). A second US family with GSS associated with a prion protein gene mutation at codon 117 with early onset gait dysfunction, prominent ataxia, and pseudobulbar and Parkinsonian signs has been reported (102).

Codon 198

The largest and probably most studied family with GSS is the Indiana kindred. A pedigree analysis of this kindred with 1230 members identified 67 affected patients over six generations (47). Most of these patients had symptoms of cerebellar ataxia, dementia, and Parkinsonian features. The mean age at onset of 16 affected members of the kindred was 52 years (range, 34–71 years) (47). Several affected members had neuropathologic findings consistent with GSS (4, 42, 56). Subsequent studies demonstrated the presence of a mutation at codon 198 of the prion protein gene in at least 11 well-documented affected members of the Indiana kindred (42, 71).

FATAL FAMILIAL INSOMNIA

Patients with severe dementia and bilateral symmetrical degeneration of the thalamus have been reported since 1939 (140). Whether these earlier cases shared a similar neuropathology with cases later described as FFI is less clear. The name FFI was first used in 1986 by Lugaresi and co-workers to describe a 52-year-old man who presented with progressive insomnia and autonomic dysfunction, followed by dysarthria, tremor, and myoclonus; the patient's two sisters and many other relatives over three generations had died of a similar disease (96). Neuropathologic examination of the patient and one of his sisters showed neuronal degeneration and reactive astrocytosis confined to the anterior and dorsomedial nuclei of the thalamus; no spongiform changes or inflammatory infiltrates were noted (96). Subsequent study of other affected family members of these siblings, with a total of 22 probable and 7 neuropathologically confirmed cases over five generations, showed a pattern consistent with autosomal dominant inheritance (98); the presence of a mutation at codon 178 of the prion protein gene was later

demonstrated in some of these patients (107). Before Lugaresi and co-workers' description of FFI, a US kindred with an illness that had some features consistent with FFI was reported. At least two of the seven affected members had a neuropathologic picture that included marked gliosis and neuronal loss in the dorsomedial and midline thalamic nuclei and a mutation at codon 178 of the prion protein gene (95, 123).

To date, 24 kindreds with FFI associated with a mutation at codon 178 of the prion protein gene were reported worldwide, including cases in Australia, Austria, Britain, France, Germany, Italy, Japan, and the United States (11, 54a, 105, 106, 114, 123, 133, 135). The mean age at onset of affected family members of nine of the FFI kindreds was 49.3 years (range, 25–72 years); the mean duration of illness was 12.5 months (range, 5–25 months). The predominant feature in most FFI patients is involvement of the thalamus associated with severe sleep disturbances, often with intractable insomnia, and autonomic dysfunction (98). The sleep disorder is characterized by loss of the slow-wave and rapid-eye-movement phases of the sleep cycle (98, 107). The autonomic dysfunction commonly seen in FFI patients includes hyperhidrosis, hyperthermia, tachycardia, and hypertension (98, 107). Cerebellar dysfunction, enacted dream states, myoclonus, and pyramidal signs are also reported in affected patients. A loss of circadian rhythm in the production of growth hormone, prolactin, and melatonin can occur. The diagnostic EEG seen in a majority of CJD patients is rarely seen in FFI patients. The neuropathology shows marked neuronal loss in the thalamus and mild gliosis; spongiform changes or plaques are rarely demonstrated (98). Minimal to mild gliosis has been demonstrated in both the cerebrum and cerebellum. The absence of spongiform changes and the unusual clinical presentation had raised questions about whether FFI should be classified as one of the TSEs. Demonstration of the presence of PrP-res in the brain of affected patients has since resolved this dilemma (107). The proteinase K–treated PrP-res fragment associated with FFI is distinguished by a different pattern of glycosylation and size (113). Although rare sporadic cases are reported, FFI is primarily associated with an allele that has a specific prion protein gene mutation at codon 178 in combination with methionine at the polymorphic codon 129 (64, 113). The polymorphism at codon 129 of the non-mutant allele in FFI patients influences the duration of the disease. The illness duration has been reported to be significantly shorter in FFI patients with methionine homozygosity at codon 129 (mean 12 ± 4 months) compared with patients with methionine and valine heterozygosity (mean 21 ± 15 months). The age at onset was not significantly different in the two groups of patients (54a).

NEW VARIANT CREUTZFELDT-JAKOB DISEASE

Clinicopathologic Features

New variant CJD (nvCJD) was first reported on March 20, 1996, when the UK government's expert advisory committee announced its conclusion that the agent causing BSE might have spread to humans, based on recognition of 10 persons with

a newly recognized variant form of CJD during February 1994 to October 1995. In April 1996, Will & co-workers described the detailed clinical and neuropathologic features of these 10 patients, who ranged in age from 16 to 39 years (median age, 28 years) (153). Their proposal that nvCJD was a new disease entity was based on a cluster of these young patients with unusual clinical features in the absence of known recognizable CJD risk factors or prion protein gene abnormalities and the unique but uniform neuropathologic profile observed in all the patients. The unusual clinical features of the 10 nvCJD patients included prominent behavioral changes at the time of clinical presentation, with subsequent onset of neurologic abnormalities, including ataxia within weeks or months, dementia and myoclonus late in the illness, an illness duration of at least 6 months, and nondiagnostic EEG changes (31, 153). The unique neuropathologic findings included spongiform changes most evident in the basal ganglia and thalamus with sparse distribution throughout the cerebral cortex, and widespread kuru-type amyloid plaques in both the cerebellum and cerebrum. The morphology of the plaques, with a pale periphery and surrounding spongiform lesions, was different from that generally seen in patients with classic CJD but resembles the "florid" plaques described in scrapie. Immunohistochemical analysis showed accumulation of PrP-res in high densities in both the cerebellum and cerebrum. Intensified CJD surveillance in other European countries did not identify cases with similar clinicopathologic profile, except one case in France (33).

As of February 28, 1999, a total of 38 confirmed cases and 2 probable cases of nvCJD had been reported in the United Kingdom (Figure 1). The age at onset of the nvCJD patients ranged from 16 to 52 years (median age, 28 years) (161). A report of the first 21 nvCJD patients indicated that they all had early onset behavioral change symptoms and a nondiagnostic or normal EEG tracing (161). The median
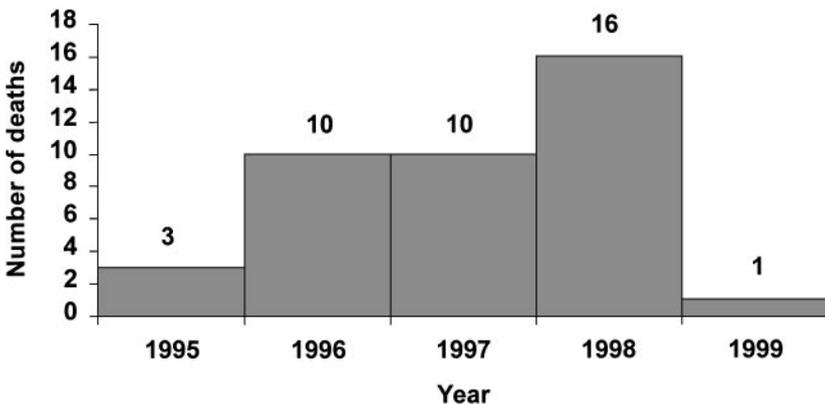

Figure 1 New variant Creutzfeldt-Jakob disease deaths in the United Kingdom, January 1995 to February 1999. Data from Department of Health, United Kingdom, Monthly Creutzfeldt-Jakob disease figures, April 12, 1999, London.

illness duration of these patients was 14 months. An analysis of the first 14 nvCJD patients revealed that nine of them presented with behavioral change symptoms, such as agitation, aggression, anxiety, apathy, depression, emotional lability, insomnia, poor concentration, paranoid delusion, recklessness, or withdrawal; 5 of these patients had a combination of at least two of the behavioral change symptoms (160). Four of the 14 nvCJD patients presented with dysesthesia or parasthesia, and one patient presented with forgetfulness. All the other patients who did not present with behavioral changes developed the behavioral change symptoms early in the illness. None of the 14 patients developed overt neurologic signs within the 4-month period after illness onset. The time interval from illness onset to development of overt neurologic signs ranged from 4- to 24.5 months (median, 6.3 months) (161). The first neurologic sign was usually ataxia with rapid progression of the illness, including development of global cognitive impairment, involuntary movements, incontinence of urine, progressive immobility, unresponsiveness, and mutism. Almost at the same time as the appearance of clear neurologic signs, 12 of the 14 nvCJD patients had delusions, such as a belief that snipers were in the kitchen, patient's baby had recently died, or microscopic people were inside a patient's body. These delusional beliefs were usually fleeting, lasting for hours or days. Magnetic resonant imaging results of some of the nvCJD patients showed typical abnormalities, including high signals in the posterior thalamic areas on T2-weighted images. Interestingly, protein 14-3-3 in the cerebrospinal fluid was detected in only 2 of the 5 patients tested (161). Detection of this protein has been reported to be highly specific and sensitive for the diagnosis of classic CJD (40). In one study, the 14-3-3 protein was detected in the cerebrospinal fluid of all 10 BSE-infected cattle tested and in only 1 of 6 healthy controls (93). All nvCJD patients so far tested for codon 129 polymorphism were homozygous for methionine (161).

Very strong epidemiologic and laboratory evidence is accumulating for a causal association between BSE and nvCJD. The epidemiologic evidence is mainly based on the geographic clustering of nvCJD patients in the United Kingdom where the overwhelming majority of BSE cases were reported. The laboratory evidence was provided by experimental data from (*a*) a French study that involved inoculation of macaques with brain tissues obtained from BSE-infected cattle (92); (*b*) a Western blot analysis of infecting prions obtained from BSE-infected animals and nvCJD patients (36); and (*c*) an ongoing animal model study involving panels of inbred mice that is being conducted in Scotland (23).

Geographic Clustering

The occurrence of unexplained spongiform encephalopathy in at least 13 UK decedents <30 years of age between 1995 and 1997 is extraordinary. In the United States, for a population ~4 times greater than that of the United Kingdom, from 1990 through 1994, mortality data analysis identified one CJD death in a person <30 years of age, a patient who received hGH injections (31). The absence of similar cases in other BSE-free countries despite intensive surveillance efforts

supports the link between the nvCJD outbreak and the BSE outbreak in the United Kingdom. The interval between the initial widespread exposure to potentially contaminated food (1984–1989) and illness onset of the initial nvCJD patients (1994–1996) is consistent with known incubation periods for CJD.

Experimental Study Using Macaques

In June 1996, French researchers reported an experimental study of three cynomologous macaques (two adults and one neonate) that were intracerebrally inoculated with brain homogenates obtained from BSE-infected cattle (92). The adult macaques developed a neurologic disease 150 weeks postinoculation that was characterized by behavioral changes, including depression, edginess, and voracious appetite, followed by ataxia, gait abnormalities, tremors, and late onset myoclonus. Neuropathologic examination revealed numerous "florid" plaques in all the three macaques with plaque morphology and distribution indistinguishable from that seen in nvCJD patients. Two other macaques inoculated with the sporadic CJD agent showed a different neuropathologic picture with numerous lesions in the cortex and no plaques. Because cynomologous macaques represent the nearest available experimental model to humans, the findings of this study provided significant laboratory evidence for a possible link between nvCJD and BSE.

Western Blot Analysis

In October 1996, Collinge and co-workers reported that PrP-res obtained from sporadic, iatrogenic, and nvCJD patients can be distinguished by different banding patterns on Western blot analysis (36). Types-1 and -2 Western blot banding patterns were seen in PrP-res obtained from sporadic CJD patients, a predominantly type-3 pattern in iatrogenic CJD patients, and a type-4 pattern in all 10 nvCJD patients tested. Western blot analysis of PrP-res obtained from cattle and domestic cats naturally infected with BSE and mice and a macaque with experimental BSE showed the type 4 pattern, indicating that PrP-res obtained from BSE-infected cattle has similar molecular properties as PrP-res obtained from the nvCJD patients. The type-4 pattern was distinguishable from the type-3 pattern mainly in the band intensity or glycoform ratio.

Experimental Study Using Inbred Mice

The strongest and most compelling evidence for a causal association between BSE and nvCJD was provided by an ongoing study that is being conducted in Scotland by Bruce and co-workers (23). In this elaborate study, the authors reported that a panel of inbred mice inoculated with the agent causing BSE or nvCJD exhibited indistinguishable patterns of incubation periods and "lesion profile." In previous studies, three panels of inbred mice (RIII, C57BL, and VM) and a panel of crossbred mice (C57BL × VM) were challenged with brain homogenates obtained from eight cattle with BSE and three domestic cats and two exotic ruminants with TSEs.

A uniform pattern of incubation periods was observed in these mice; the shortest incubation period was for RIII mice (range of mean incubation period, 302–335 days), followed sequentially by C57BL, VM, and C57BL × VM mice (23). A similar lesion profile, a vacuolation score on a scale of 0 to 5 in nine areas of the brain, was also observed in the mice. Subsequently, the authors challenged similar panels of mice with brain homogenates obtained from three nvCJD and six sporadic CJD patients. All the surviving RIII mice injected with nvCJD brain homogenates developed neurologic disease with a strikingly uniform pattern of incubation periods (range, 288–351 days) and lesion profile as the RIII mice experimentally infected with BSE of cattle and TSEs of cats and exotic ruminants. In contrast, all the mice that were inoculated with brain homogenates obtained from the six sporadic CJD patients did not show any signs of neurologic disease after 600–800 days (23). However, a large majority of the mice that survived beyond 500 days had neuropathologic evidence of disease transmission; the lesion profile of two of these RIII mice was distinct from that seen in RIII mice infected with the agents causing BSE and nvCJD. A longer period of observation is required to determine whether the non-RIII mice inoculated with the nvCJD agent will develop neurologic disease within the predicted pattern of incubation periods. If the nvCJD agent continues to behave in a similar fashion as the BSE agent, the next panel of mice that would develop neurologic disease should be the C57BL strain, followed sequentially by the VM and C57BL × VM strains. Some of the C57BL are reported to have already shown signs of neurologic disease (23).

CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UNITED STATES

CDC conducts CJD surveillance through periodic review of the national multiple cause-of-death data compiled by the National Center for Health Statistics. Mortality data analysis is an efficient way of conducting CJD surveillance because CJD is invariably fatal, >85% of patients die within a year of onset, and its diagnosis is better ascertained at the time of death. Studies have shown that death certificate reviews identify ≥80% of CJD deaths in the United States (31, 38).

After the occurrence of nvCJD was announced in the United Kingdom, CDC conducted an active CJD surveillance in its four established Emerging Infections Program sites and the Atlanta Metropolitan Active Surveillance Project in Georgia (31, 136). This active CJD surveillance involved review of available death certificate data during 1991–1995 and contact by phone, mail, or fax of neurologists, neuropathologists, and pathologists to identify patients who died from CJD during 1991–1995. Between 90–100% of these specialists in the surveillance areas were contacted. In addition, clinical and neuropathologic records for each CJD patient aged <55 years were sought for review. The annual number of CJD deaths was stable in the five areas during 1991–1995, and the average annual CJD death rate was 1.2/1 million population. No nvCJD cases were identified.

In addition to regular epidemiologic reviews of the National Center for Health Statistics multiple cause-of-death data, since 1996 CDC has augmented surveillance for the nvCJD by conducting follow-up investigation of CJD decedents <55 years of age. This surveillance was initiated with the support of the Council of State and Territorial Epidemiologists. Since April 1996, review of clinical records of 76 of 86 CJD patients who died during 1994–1996 has been completed. Neuropathology records were reviewed for 34 of these patients (ED Belay, unpublished data). Also, in collaboration with CDC, the American Association of Neuropathologists helped establish a National Prion Disease Pathology Surveillance Center at Case Western Reserve University, Cleveland, Ohio and alerted its members in 1996 about the nvCJD neuropathology and requested reports of any such cases, regardless of the clinical diagnosis or age of the patient. A similar notification and request was also sent to US members of the United States and Canadian Academy of Pathologists. These surveillance efforts have not detected evidence of the occurrence of nvCJD in the United States.

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