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and the Committee on Infectious Diseases

## Technical Report: Transmissible Spongiform Encephalopathies: A Review for Pediatricians

**ABSTRACT.** Transmissible spongiform encephalopathies (TSEs) are a family of rare, slowly progressive, and universally fatal neurodegenerative syndromes affecting animals and humans. Until recently, TSEs were of little interest to pediatricians. However, since the outbreak in adolescents and the association of TSEs with new-variant Creutzfeldt-Jakob disease (nvCJD), interest among pediatricians and the general public has increased. Even before bovine spongiform encephalopathy and nvCJD were linked, the recognition that iatrogenic Creutzfeldt-Jakob disease (CJD) had been acquired from administration of cadaveric human growth and gonadotropic hormones and from corneal and dura mater transplants prompted medical vigilance. Furthermore, recent concern about the potential for transmission of CJD by blood and blood products has raised awareness among public health and regulatory agencies, pediatricians, and the public, although no epidemiologic data support this concern. Because of worldwide concern (although no cases have been reported in North America), this review focuses on the potential impact of TSEs, particularly CJD and nvCJD, on the pediatric population.

**ABBREVIATIONS.** TSEs, transmissible spongiform encephalopathies; PrP, prion protein; TME, transmissible mink encephalopathy; BSE, bovine spongiform encephalopathy; nvCJD, new-variant Creutzfeldt-Jakob disease; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; FDA, US Food and Drug Administration; CDC, Centers for Disease Control and Prevention.

**T**ransmissible spongiform encephalopathies (TSEs [or prion diseases]) are a group of clinical syndromes in animals and humans that are characterized by slowly progressive neurodegenerative disease.<sup>1,2</sup> Tables 1 and 2 identify the diverse entities that are considered TSEs and their typical features. All have incubation periods of months to years before onset of neurologic illnesses, which gradually increase in clinical severity until death. There is no host immune response, and all TSEs share a noninflammatory pathologic process that is limited to the central nervous system. All appear to have a common mechanism of pathogenesis, and they may have a common origin. The pathogenesis of these diseases is mediated by the progressive accumulation in the central nervous system of an abnor-

**TABLE 1.** TSEs

Animals (excluding experimentally transmitted disease)
Scrapie in goats and sheep
TME in mink
Chronic wasting disease in deer and elk
BSE in cattle
Feline spongiform encephalopathy in cats and zoo felines, probably from BSE
TSE of zoo ruminants, probably from BSE
TSE in zoo monkeys, probably from BSE
Humans
Kuru
CJD
Iatrogenic
Sporadic
Familial
nvCJD, probably from BSE
Gerstmann-Straussler-Scheinker syndrome
Fatal familial insomnia
Sporadic fatal insomnia

mal form of a normal glycoprotein found in host membranes known as the prion protein (PrP).<sup>3,7</sup>

The first recognized TSE, scrapie, was reported by sheepherders more than 200 years ago. During the 20th century, transmission of scrapie from an affected sheep to healthy sheep and goats was reported, and subsequently, experimental transmission to mice and hamsters (animal models of prion disease) was accomplished. More recently, naturally occurring TSEs have been documented in the United States among ranch mink (transmissible mink encephalopathy [TME; last reported in 1985]) and among deer and elk (chronic wasting disease) mainly in Colorado and Wyoming. A link between scrapie, TME, or chronic wasting disease and human disease has not been established.

In 1986, the first case of a TSE in cattle was reported in the United Kingdom, bovine spongiform encephalopathy (BSE). BSE has attracted more public attention than the other animal TSEs, first because of the magnitude of the BSE epidemic in the United Kingdom, then because of its spread to other European countries, and finally because of its disturbing association with the human disease new-variant Creutzfeldt-Jakob disease (nvCJD). More than 170 000 cases of BSE have been diagnosed in the United Kingdom alone since it was first discovered. Several other European countries have identified much smaller numbers of cases in native-born cattle.<sup>4</sup>

Unlike scrapie, which spreads to sheep and goats by contact, evidence does not suggest lateral transmission of BSE from cow to cow, although the pos-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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**TABLE 2.** TSEs and Typical Features

Syndrome in Animals	Year First Described	Typical Clinical and Other Features
Scrapie (sheep and goats)	circa 1750	Ataxia, pruritus
TME (mink)	1965	Ataxia, somnolence, seizures
Chronic wasting disease (deer, elk)	1980	Altered behavior, excessive salivation, wasting; florid amyloid plaques
BSE (cattle, zoo ruminants)	1987	Ataxia, wasting
Feline spongiform encephalopathy	1990	Altered behavior, ataxia
Syndrome in Humans	Year First Described	Typical Clinical and Other Features
CJD	1920	Dementia, myoclonus, variable ataxia; spongiform changes, variable amyloid plaques (about 15% of cases)
Familial CJD	1924	Same as CJD with autosomal-dominant pattern of expression, longer survival; amyloid plaques more common
Gerstmann-Straussler-Scheinkes syndrome	1936	Familial, autosomal-dominant pattern; ataxia, dementia; amyloid plaques universal
Kuru	1957	Ataxia, tremor, cranial nerve abnormalities; amyloid plaques common
Fatal-familial insomnia	1986	Autosomal-dominant inheritance, mutation at PRNP codon 178 linked to 129 Met; insomnia, dysautonomia, ataxia, myoclonus, late mild dementia; minimal vacuolation, no plaques, PrP <sup>Sc</sup> difficult to detect
nvCJD	1996	Young age at onset; psychiatric presentation, dysesthesias, ataxia; PRNP codon 129 Met homozygous; no periodic electroencephalographic complexes; bilateral increased thalamic densities on magnetic resonance imaging; florid amyloid plaques
Sporadic familial insomnia	1999	Same as fatal familial insomnia but negative family history; no mutation identified in either PRNP gene

sibility of maternal transmission to calves has not been ruled out. It is thought that most infected calves were exposed to the BSE agent early in life from feed supplements containing meat and bone meal, a protein rendered from animal offal. As with other TSEs, BSE can be transmitted experimentally to a variety of animals from infectious brain tissue by parenteral and oral routes of exposure. In 1988, a ban on the feeding of nonmilk ruminant proteins to ruminants was implemented in the United Kingdom. A decrease in recognized cases of BSE was observed 4 years later, an interval consistent with the predicted incubation period of BSE. Subsequently, sales of bovine offal, meat products from cattle more than 30 months old, and meat on the bone for human consumption were banned in the United Kingdom in an attempt to reduce opportunities for human exposure. After evidence of cross-species transmission of BSE to house cats and felines in zoos (causing feline spongiform encephalopathy) was found, incorporation of bovine offal into any animal feed, including pet food, and into fertilizer was also prohibited.

More than 40 years ago, kuru (epidemic among the fore people in remote mountain areas of Papua, New Guinea) was the first human TSE to be identified. Kuru was transmitted by exposure to infected tissues during ritualistic cannibalism and has never been recognized in people born after that practice stopped. This progressive neurologic disorder provided an important model, leading to the recognition that Creutzfeldt-Jakob disease (CJD) and nvCJD were also infections. When inoculated into the brains

of chimpanzees, brain specimens obtained from patients with kuru transmitted a similar disease after incubation periods of 14 months or longer (brain tissue specimens from patients with CJD transmitted disease to chimpanzees after only 11 months). Chimpanzees and other primates have also been infected with kuru and CJD agent by peripheral routes and by intracerebral injection.

CJD has been recognized in humans as sporadic cases and as a familial disease with an autosomal-dominant pattern of occurrence. Familial CJD accounts for about 10% of cases. Twelve-point mutations and several insertions associated with familial CJD have already been identified in the gene encoding PrP (designated the PRNP gene in humans). The 2 best-known foci of familial CJD are in rural Slovakia and among Libyan Jews living in Israel. Susceptibility to sporadic and iatrogenic CJD is increased by homozygosity, especially for methionine, at the normal polymorphic codon 129 of the PRNP gene.<sup>3,5</sup> Thus far, all patients with nvCJD have been homozygous for methionine at this locus. Various medical and surgical interventions have been linked with iatrogenic CJD, including treatment with human pituitary growth and gonadotropic hormones derived from cadavers, manipulation of the brain with contaminated instruments and brain electrodes, and transplantation of infected corneas and dura mater allografts. Incubation periods of iatrogenic CJD have ranged from 15 months to more than 20 years.

In 1996, the initial report of nvCJD (a TSE with a unique constellation of clinical and histopathologic

findings that affected people of an age at which CJD had only rarely been diagnosed) immediately suggested that animal-to-human transmission of BSE had occurred. This event led to an increase in worldwide restrictions on the importation of beef from the United Kingdom and renewed the urgency of efforts to eliminate British cattle herds affected with BSE. It also prompted this review. The remainder of this report focuses on issues relating to individuals at increased risk of TSEs, consideration of the potential contamination of blood and blood products (an unlikely but worrisome prospect) and the need to provide supportive counseling of people thought to be at increased risk of TSEs.<sup>6</sup>

Barriers to the transmission of TSEs between species are known to exist, but the robustness of those barriers varies from one species to another and among strains of agents. TSE agents were known to have crossed species barriers before the bovine-human barrier was accidentally breached by the BSE agent to cause nvCJD.<sup>8</sup> The sheep scrapie agent had passed into goats and probably into cattle (causing BSE), agents of BSE had passed into nonbovine ruminants and cats, and a scrapie-like agent was postulated to have passed from ruminants into mink to cause TME.

For all TSEs, in whatever species, infectivity is greatest in central nervous system tissues and least in peripheral tissues. Cerebrospinal fluid (CSF) of some patients with CJD has also been found to be infectious. The infectivity of human blood has never been convincingly demonstrated. However, the fact that blood from rodents experimentally infected with several TSE agents has been consistently infectious even before the onset of overt illness—albeit infectious only at very low levels—has been taken to imply that blood of human subjects with TSEs or incubating TSEs should be considered potentially infectious. Infection with some TSE agents—those of kuru, BSE, TME, and probably nvCJD—has clearly been foodborne. Other TSEs have been transmitted iatrogenically. It remains unclear whether familial CJD results from increased susceptibility to an exogenous infection or from endogenous infectivity of mutant PrP. The sources of infection in sporadic CJD are completely unknown, though spontaneous changes in conformation of PrP have been postulated as a corollary to the prion theory.<sup>1</sup>

#### THE AGENT AND ITS PATHOGENESIS

The agents that cause TSEs remain infectious after treatments that inactivate most viruses and nucleic acid (eg, treatments such as heat, ionizing radiation, alcohol, formalin, some proteases, and nucleases). On the basis of this characteristic and the partial sensitivity of the agent to harsh treatment with some proteases, Prusiner postulated that the agents were composed of a self-replicating protein that he termed “prion” for proteinaceous infectious agent. In the laboratory, infectivity has been consistently associated with a relatively protease-resistant form of PrP (termed “PrP-res” or “PrP<sup>Sc</sup>” [for scrapie-associated prion protein]).<sup>3</sup> In the conversion to PrP-res, the protease-sensitive form of PrP (PrP-sen) undergoes a

posttranslational change from a predominantly  $\alpha$ -helical structure to one with a high  $\beta$ -sheet content. As the abnormal protein accumulates in neurons, neuronal dysfunction, vacuolization, reactive astrocytosis, and cell death occur.

The pathogenesis of TSEs has been best studied with the scrapie agent. The intestinal tract and abdominal lymph nodes are infected first; infection appears in the brain a year or more later. Gastrointestinal tract involvement implies that, in nature, the scrapie agent probably infects sheep by the oral route. In experimental mouse and goat models of scrapie, after subcutaneous inoculation, the pathogenic agent also first appears in the lymphatic tissues and spleen before it can be detected in the nervous system. The route of entry of the pathogen, the infectivity of blood and of other tissues at different stages of infection, and the distribution of the agent in infected animal species all pose central questions for estimating the risk to humans from potential exposures to various TSE agents.

#### EPIDEMIOLOGY AND DISEASE MANIFESTATIONS OF CJD AND nvCJD

CJD occurs worldwide at an estimated annual incidence rate of 0.5 to 1.5 cases per million population with no seasonal or geographic predisposition except for areas of high familial occurrence. It is important to note that there is no evidence of person-to-person transmission among family members. There has been no increase in the incidence of CJD detected in the United States since the disease was recognized to be a TSE in 1968. The incidence is no higher among individuals with the greatest exposure to human blood and blood products, namely those with hemophilia, sickle cell anemia, and thalassemia. In mortality surveys in the United States, none of more than 4000 people who died of CJD had any of those diagnoses recorded as comorbid conditions. Classic sporadic CJD most often occurs between the ages of 50 and 70 and is characterized by dementia, myoclonus, or, less often, other abnormal movements (chorea, dystonia), pyramidal and extrapyramidal-tract signs and cerebellar ataxia. Neurologic deterioration progresses relentlessly. Late in the course of CJD, patients become mute and akinetic. Most patients survive for less than 1 year after onset of neurologic findings.

Most laboratory tests are of little value in the diagnosis of CJD. Examination of the CSF may reveal a mild elevation in the protein, but otherwise, the CSF is normal. Rapid immunoassay tests have detected the presence of several normal brain proteins in the CSF not usually found there (a finding that has been of value in premortem diagnosis of CJD). Of those proteins (that do not include PrP), the 14–3–3 protein has been most useful. However, the 14–3–3 protein has also been found in the CSF of patients with other neurologic diseases (eg, acute viral meningoencephalitis) and in patients after cerebrovascular accidents. The electroencephalogram (EEG) shows generalized slowing early in the course of classic CJD and then typically progresses to show periodic bursts of biphasic or triphasic sharp-wave complexes. As myoc-

lonus abates, the EEG again becomes less specific. At later stages of CJD, computed tomography typically reveals generalized atrophy, whereas magnetic resonance imaging often shows hyperintense signals in the basal ganglia. These later findings are present in the majority of patients.

Microscopic examination of brain specimens from people with all types of CJD reveals a spongiform change accompanied by neuronal loss and gliosis. The diagnosis of CJD is facilitated by the immunohistochemical demonstration of PrP-res in the brain parenchyma. In addition, amyloid plaques composed of PrP-res may be found in specimens, depending on the TSE. In nvCJD, "florid" plaques (flower-like amyloid plaques surrounded by halos of vacuoles) have been consistently present. Biopsy specimens of the pharyngeal tonsil that show a marked accumulation of PrP-res have also been valuable in the diagnosis of nvCJD.<sup>9</sup>

Iatrogenic CJD has been transmitted by corneal transplants and allografts of dura mater and by contaminated electrocorticographic electrodes and neurosurgical equipment. For iatrogenic forms of CJD, the clinical presentation and laboratory findings are similar to those in sporadic CJD, but the incubation period can be much shorter (less than 2 years).<sup>10,11</sup> Additional cases of iatrogenic CJD that resulted from the administration of growth and gonadotropic hormones derived from cadavers have longer, but variable, incubation periods of up to 30 years. Epidemiologic studies have not incriminated exposure to blood or blood products as a cause of iatrogenic CJD. However, as previously noted, the disease has been transmitted when the blood of mice and hamsters experimentally infected with TSE agents was injected into healthy animals of the same species; a substantial fraction of the infectivity was associated with cellular elements.<sup>12</sup>

As a precautionary measure, the US Food and Drug Administration (FDA) has recommended the withdrawal of whole blood and blood components (including donor plasma before its pooling for further processing into derivatives) prepared from individuals who later developed CJD or nvCJD and the deferral of blood and plasma donors who are at risk of getting CJD. Pools of plasma to which donors who subsequently developed CJD contributed and derivatives manufactured from those pools are no longer recommended for withdrawal for several reasons:

1. The risk of transmitting CJD through injected plasma derivatives is, as has been previously noted, entirely theoretical.
2. Most people who are likely to get CJD cannot be identified during the prolonged incubation period. Some such people must unknowingly serve as donors of plasma incorporated into the very large pools of plasma used to prepare derivative products; the risk of that occurrence is unavoidable and substantial, yet no adverse consequences have been detected.
3. Currently, no available test can detect the very small numbers of TSE agents that might be

present in donor blood within a reasonable time period.

4. In experimental studies, some of the processing steps used to prepare plasma derivatives removed very substantial numbers of the TSE agents. However, until the potential infectivity of blood from persons incubating nvCJD is determined, plasma derivatives prepared from pools to which they contributed should be considered unacceptable. Current precautionary policies of the FDA regarding risk of CJD and human blood or blood products are available.<sup>13</sup> New developments in FDA and US Public Health Service policies are expected as the understanding of TSEs and the risk of their transmission via blood improves.

Familial CJD accounts for as many as 10% to 15% of cases in some series. Familial disease tends to occur at a slightly younger age than sporadic CJD and typically has a more protracted course than sporadic or iatrogenic CJD. The disease occurs with an autosomal-dominant pattern of inheritance. Penetrance of familial CJD associated with some PRNP mutations has not been complete, at least within the expected lifespan of most people. With other mutations, penetrance has been close to 100% by age 80. Genetic counselors must consider these differences.

The nvCJD has attracted more attention worldwide than the other forms of CJD, because it is a potential emerging infection and represents the first recognized instance in which a TSE of animals crossed a species barrier to infect humans. This disease differs markedly from classic sporadic CJD in several ways. nvCJD is uniformly associated with cerebellar ataxia and a type of sensory involvement (dysesthesia) not typical of sporadic CJD. It results in periodic complexes on EEG. Florid amyloid plaques have rarely, if ever, been seen on histopathologic examination of brain specimens in other forms of CJD. Most striking has been the difference in age distribution. nvCJD occurs in much younger patients (mean age at onset is 29 years, vs 60 years for sporadic CJD patients in the United Kingdom). nvCJD has already been reported in several adolescents since its first description in 1996, whereas sporadic CJD has been extraordinarily rare in adolescents.

## TRANSMISSION

The inoculation of brain and spinal cord homogenates; eye, lung, liver, kidney, spleen, and lymph node tissues; and CSF from patients with CJD can infect primates. Secretions and excretions have not been demonstrated to transmit infection. Only standard universal precautions are indicated in the management of patients with CJD in that the risk of transmission to family members and care providers is low. Strict isolation is not necessary. However, caution should be used in obtaining CSF and handling tissues obtained at autopsy. Recommended decontamination of instruments is by soaking them in  $\geq 1N$  sodium hydroxide solution for at least 1 hour and then autoclaving them at 134°C for at least 1 hour. Use of disposable instruments and incineration

of materials contaminated with tissues are preferred when possible.

In North America, no cases of nvCJD have been diagnosed, and BSE has not been recognized. The US Department of Agriculture has prohibited the importation of cattle, sheep, and other ruminants and ruminant-meat products from countries where BSE is prevalent. The Department of Agriculture also has programs in place to monitor for TSEs in cattle, sheep, and goats in the United States. Even with increasingly active surveillance of death certificates and diligent efforts at case finding by the Centers for Disease Control and Prevention (CDC), there has been no discernible increase in incidence of classic forms of CJD observed in the United States during the past 2 decades.

#### AWARENESS OF EPIDEMIOLOGY AND NATURAL HISTORY

Because of worldwide concern about TSEs, pediatricians and other health care providers for children and adolescents must be aware of the epidemiology and natural history of TSEs in humans to allay undue anxiety about theoretical risks of TSEs while also remaining vigilant about exposures known to constitute a risk. Consumption of beef or beef products in the United Kingdom, even before policies for cattle raising and slaughter were altered, should not cause undue concern. The incidence of nvCJD in the United Kingdom has been low and is not increasing rapidly. The CDC estimates that, even during the peak years of the BSE outbreak, the risk of exposure to the BSE agent by US travelers to the United Kingdom was exceedingly low. Since 1996, that risk has been even more remote.

Reliable data have not incriminated the receipt of blood or blood products from a potentially infectious source in the transmission of CJD to humans. Individuals who received blood or blood products from a person later recognized to have a TSE may benefit from counseling and reassurance. Unfortunately, validated effective postexposure interventions are not available to abort infection (though some have been proposed recently), and no clinical test is able to detect infection before the onset of symptoms. The FDA has recommended that consignees of products withdrawn because of TSE in a donor be notified, but that disclosure of the hypothetical risk to the recipient be left to the judgment of the consignee. Recipients of blood products should be made aware of the remote chance of exposure to infectious agents, a risk that should, if the product is used for adequate indications, be far outweighed by the potential benefit of treatment. Some products previously available only as human plasma derivatives are now available as recombinant products; their increased use and the further development of other recombinant biologicals to replace products derived from human blood products are to be encouraged.

Genetic screening and qualified genetic counseling should be made available to families with familial CJD if requested for family planning or other reasons. The diagnostic evaluation of persons with symptoms suggestive of a TSE should be undertaken

by a qualified neurologist. A suspected or confirmed diagnosis of CJD in any person younger than 55 should be reported to the CDC. In the United States, genetically engineered growth hormones, follicle-stimulating hormone and luteinizing hormone, are now available. Pituitary hormones derived from cadavers are no longer approved or acceptable in the United States. Patients who received cadaveric hormones or dura mater allografts should be identified in case unusual neurologic symptoms appear. Fortunately, the empirical risk to individual recipients of those materials has been small, especially during the past 20 years.

Extraordinary precautions are not indicated for family members of an individual with CJD, because epidemiologic and laboratory studies have not shown that contact with most ordinary body fluids and excretions (feces, saliva, urine, and others) poses any identifiable risk of transmitting infection. CSF and tissues of patients with TSEs must be considered potentially infectious.

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