

Prion Disease: The Implications for Dentistry

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Abstract

The aim of this article was to provide the dental community with a brief overview of the characteristics, risk of transmission, and the infection-control implications of prions in dentistry. MEDLINE, EMBASE, CINAHL, The Cochrane Library, and relevant databases were searched, and a targeted internet search was conducted up to July 2007. Transmissible spongiform encephalopathies (TSEs) are a group of fatal neurodegenerative diseases that are rapidly progressive and always fatal, with no approved cure, and their definite diagnosis can only be obtained at post mortem autopsy. The causative agent, prion protein, resists conventional sterilization methods especially when infected tissue becomes dried onto glass or metal surfaces. To date, there are no reported definite or suspected cases of disease transmission arising from dental procedures, and there seems to be no correlation between dental treatment and TSEs. Because there is a theoretical but real risk of transmission of prion disease from dental instruments (although it is extremely low, especially in North America), as a general rule, appropriate family and medical history (including the risk for prion diseases) should be obtained from all patients, before all dental procedures. TSE research regarding diagnosis, transmission, treatment, and inactivation of prions and other transmissible amyloidoses are ongoing, and, thus, dental professionals should maintain optimal and up-to-date standards of knowledge, infection control, and decontamination. (*J Endod* 2008;34:1158–1166)

Key Words

Dental, dental care, infection control, prion diseases

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Prion proteins (PrP) are infectious, transmissible proteinaceous particles that lack nucleic acid and are composed exclusively of a modified isoform of the noninfectious cellular prion protein (PrP^C) (1, 2). The noninfectious protein is a component of a common cellular receptor. The normal function of PrP^C remains unclear but is thought to be involved in copper metabolism and transport (3). It has been found at elevated levels in human odontoblasts and may be involved in dentine deposition (4). The pathogenic isoform of PrP (PrP^{Sc} or PrP^{res}) has the same amino acid content but a different three-dimensional conformation with a higher β -sheet content than PrP^C, that reduces the solubility of the protein and leads to the deposition of insoluble fibrils in amyloid plaques (3). Posttranslational changes that occur after proteins are synthesized on the ribosome are poorly understood but PrP^{res} is thought to act as a template that promotes the misfolding of newly formed PrP^C (5). When accumulated in the central nervous system of humans and animals, PrP^{res} can cause a microscopic vacuolization of the brain tissue called spongiform degeneration (Fig. 1), characteristic of a group of fatal neurodegenerative diseases called transmissible spongiform encephalopathies (TSEs) (2). It is likely that prion disease is one of a subset of transmissible amyloidoses, protein conformational diseases that are the result of pathologic depositions of fibrillar misfolded proteins (6). Other amyloidoses proteins, such as transthyretin and lysozyme have a high β -sheet content in their native form (6), but the native PrP^C has only a small β -sheet portion in the membrane-proximal carboxyterminal of the protein (7). However, the PrP^{res} isoform misfolds forming a large β -sheet section and trimers of PrP^{res} molecules stack to form stable insoluble fibrils (Figure 2) (3).

Variations in the conformation of different isolates of PrP^{res} change the stability of the misfolding process leading to isolates with differing infectivities and varying “incubation” periods (8). The “incubation” period seems to depend on the dose, the stability of the misfolded protein conformation, and the susceptibility of the host (8). There is evidence that other amyloidosis conditions may also be transmissible (9–11).

This article aimed to provide the dental community with a brief overview of the characteristics, the risk of transmission, and infection-control implications of prions in dentistry.

Methods

Search Strategy for the Identification of Studies

The literature search (from the earliest record up to July 2007) for relevant articles was performed using Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, Ovid MEDLINE (R), Ovid OLDMEDLINE (R), Cumulative Index to Nursing & Allied Health Literature (CINAHL), Evidence Based Medicine of Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, EMBASE, Health and Psychosocial Instruments, HealthSTAR/Ovid Healthstar, International Pharmaceutical Abstracts, and PubMed. Table 1 shows the Key words and combinations of the Key words used. Moreover; the targeted internet search was performed on the following web sites for any other relevant evidence: CDC and CJD Surveillance; Public Health Agency of Canada; UK Department of Health; New York State Department of Health; Centers for Disease Control and Prevention (CDC); New York City Department of Health and Mental Hygiene; National Prion Disease Pathology Surveillance Center; World Health Organization; Creutzfeldt-Jakob Disease Foundation; Inc.; The UK Creutzfeldt-Jakob Disease Surveillance Unit; The Spongiform Encephalopathy Advisory Committee (SEAC); Stanley Prusiner; MD; Structural Studies of Prion Disease; Alberta Prion Research Institute Memory and Aging Center; University of California; San Francisco; Division of Neurological Science; Tohoku University; The Australian National CJD Registry; Communica-

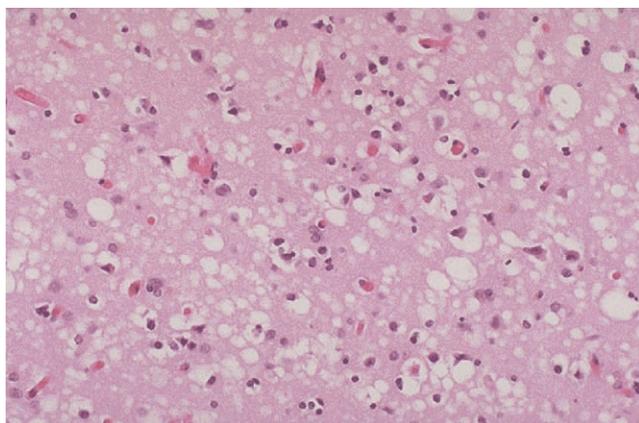


Figure 1. Spongiform lesions in the brain tissue of a classic CJD patient. Courtesy of Ermias Belay with permission from Prion Disease Office of the Center for Disease Control and Prevention (23).

ble Diseases Network of Australia; National Prion Disease Clinic; London; CJD Resource Centre of National Institute for Biological Standards and Control; and Scottish Dental Clinical Effectiveness Programme.

Methods of the Review

Limiting the searches to articles in English resulted in some 365 articles being identified. No other exclusion criteria were set at the initial stage to ensure finding all potentially relevant articles that include the search Key words. After removing duplicates; 106 articles were searched for relevancy; determined by the article title. Articles were excluded that did not address the characteristics; the risk of transmission; and infection-control implications in dentistry for prions or provide background information (review articles). Further articles were identified by reviewing the references and bibliographies of articles obtained by the search strategy.

Results

Animal TSEs

Animal TSEs include scrapie in sheep and goats; bovine spongiform encephalopathy (BSE) or mad cow disease in cattle; transmissible

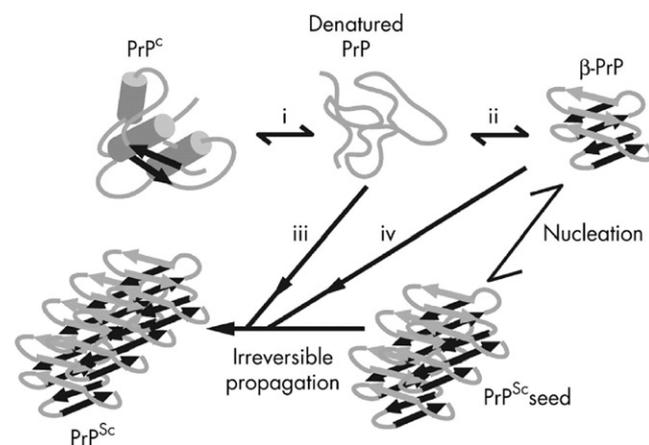


Figure 2. Possible mechanism for prion propagation. Largely α -helical PrP^C proceeds via an unfolded state (i) to refold into a largely β -sheet form, β -PrP (ii). In physiological salt concentrations, β -PrP stacks into aggregates. Unfolded PrP (iii) or β -PrP monomers (iv) are irreversibly added to the stacks because PrP is most stable when it is stacked. Reproduced with permission from Collinge J. Molecular neurology of prion disease. *J Neurol Neurosurg Psychiatry* 2005;76:906.

mink encephalopathy in farmed mink; chronic wasting disease in North American mule deer, white-tailed deer, elk, and moose; feline spongiform encephalopathy in domestic cats and captive exotic felines; spongiform encephalopathy in captive exotic ungulates; and a reported spongiform encephalopathy in a French zoologic collection (2, 12, 13).

BSE or "mad cow disease," a progressive neurologic disease, is a massive common-source epidemic in dairy cows that first appeared in UK cattle in 1986 (14). BSE appears to have originated from scrapie, an endemic and naturally occurring TSE disease of sheep and goats that has been recognized in Europe since the mid-18th century (15–17).

Prion-infected animal feed appears to have been the major cause of BSE transmission and, thus, the number of cases in the United Kingdom decreased with the implementation of a governmental order in 1988 (18), banning the use of rendered sheep or cattle offal from the dietary protein supplement of domestic animals. These prevention strategies resulted in a relatively rapid decline of BSE cases in the United Kingdom. As of May 2007, 14 cases of BSE have been identified in North America, 3 in the United States, and 11 in Canada (19). Currently, public health control measures, such as surveillance, culling sick animals, or banning specified risk materials, have been instituted in many countries in order to prevent potentially BSE-infected tissues from entering the animal feed and human food chains (19). To prevent BSE from entering North America, both the Canadian and the US governments have implemented safeguards, placing severe restrictions on the importation of beef products and live ruminants, especially from countries at risk of BSE (20, 21).

Human TSEs

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is the most commonly occurring human TSE. CJD patients experience a rapid onset of dementia as well as a range of neurologic symptoms including walking difficulties, sudden jerky movements, and, sometimes, visual deficits (22). At the moment, there is no approved cure for any type of CJD, although clinical evaluations of quinacrine and related 9-aminoacridine compounds for the treatment of human prion diseases are in progress. The disease is rapidly progressive and always fatal, usually 85% within 1 year of onset of the illness (23, 24).

TABLE 1. Search Strategy

# Search History	Results
1 (oral biology or dentist\$ or oral health or dental care or dental or oral care).mp. [mp=ti, ot, ab, nm, hw, kw, it, tx, sh, ct, de, tn, dm, mf, ac, rw]	670,147
2 (Prion or Kuru or Creutzfeldt-Jakob or Creutzfeldt Jakob or Gerstmann Straussler Scheinker or Fatal familial insomnia or Scrapie or Bovine spongiform encephalopathy or Transmissible mink encephalopathy or chronic wasting disease or Feline spongiform encephalopathy or Exotic ungulate encephalopathy or CJD or vCJD or v-CJD or sCJD or s-CJD).mp. [mp=ti, ot, ab, nm, hw, kw, it, tx, sh, ct, de, tn, dm, mf, ac, rw]	36,317
3 1 and 2	365
4 Remove duplicates from 3	282
5 Screening the titles of the relevant articles	106
6 Updating the search strategy from 2007-2008 following the steps before	9
7 Total relevant articles screened	115

CJD occurs worldwide, including the United States and Canada, at a rate of approximately one case per 1 million population per year (7, 23, 25). In recent years, the United States and Canada have reported respectively fewer than 300 and 35 cases of CJD a year (23, 26). CJD affects individuals with a mean age of 68 years (24), and its risk increases with age; in persons aged over 50 years of age, the annual rate is approximately 3.4 cases per million (23).

The great majority (80%–85%) of CJD cases are of unknown origin (sporadic [sCJD] or classic) (27–29). On the other hand, 10% to 15% of CJD cases are familial or inherited (including Gerstmann-Straussler-Scheinker Syndrome and fatal familial insomnia) and associated with mutations in the PrP gene, which possibly increase the likelihood of a conformational change in the protein (27–29). These inherited forms, which are very rare with an annual rate of one per 10 to 100 million people (30), occur in persons with an apparent hereditary predisposition (31). The clinical features of familial CJD differ from sporadic CJD; the onset happens at a younger age, the duration of the illness is longer, and the typical electroencephalogram (EEG) changes found in sCJD are often missing (32).

Less than 1% of all CJD cases are iatrogenic. Iatrogenic sCJD has been reported in over 267 patients worldwide up to 2000 (first reported in 1974) (33) as the result of human-to-human cross-contamination during invasive medical procedures in or adjacent to the central nervous system (34). These procedures include human dura mater and corneal grafts, contaminated neurosurgical devices, contaminated stereotactic EEG depth electrodes, or the administration of human pituitary growth hormones or human gonadotrophin hormone extracted from the organs of human cadavers (23, 27, 30, 34–36). It should be noted that all of the equipment-related cases occurred before the routine implementation of more rigorous decontamination procedures currently used in health care facilities, and, therefore, no such cases have been reported since 1976 (23).

Kuru

Kuru is an acquired prion disease that was originally described in 1957 among the Fore people of Papua, New Guinea, probably acquired during ritual cannibalistic or sacrificial funeral rites (37). This disease is now virtually extinct because of a ban imposed on cannibalism by the Australian authorities in the mid-1950s; however, there are still occa-

sional new cases of Kuru in patients more than 40 years of age, which suggests a long incubation time of the causative agent (38).

Variant CJD

First described in 1996 in the United Kingdom (39), variant CJD (also known as new variant CJD or vCJD) has different clinical and pathologic characteristics from classic CJD (Table 2). In summary, the median age at death for vCJD patients is lower (28 years in vCJD vs 68 years for patients with classic CJD), and almost all cases have been in persons under age 55 years; the median duration of illness for vCJD is longer (14 months in vCJD vs 5 months for classic CJD), and the clinical and neuropathology findings differ from classic CJD. These atypical clinical features include prominent psychiatric or sensory symptoms at the time of clinical presentation or early in the course of the illness, delayed onset of neurologic abnormalities, and a diffusely abnormal nondiagnostic EEG (the absence of periodic sharp waves on EEG).

Of those who suffer from CJD, 87% are homozygous for methionine at codon 129 of the PrP gene, whereas the figure for the normal population is 37% with 52% heterozygous methionine/valine (7, 40). Among other risk factors are younger age and residence in the United Kingdom (35).

Since the first report of vCJD in 1996, a total of 200 patients from 11 countries have been identified. The prevalence of vCJD as of November 2006 is as follows: 164 from the United Kingdom; 21 from France; 4 from Ireland; 3 from the United States; 2 from the Netherlands; and one each from Canada, Italy, Japan, Portugal, Saudi Arabia, and Spain. The majority of cases from outside the United Kingdom likely acquired the disease while residing in the United Kingdom (20).

There is now increasing and strong epidemiologic and laboratory evidence for a causal relationship between BSE and vCJD (41–44). This has raised issues about the consumption of food contaminated with BSE as the potential transmission route to humans (43). A recently published case-control study involving 132 vCJD cases in the United Kingdom showed an increased risk for vCJD associated with the reported frequent consumption of beef and beef products thought likely to contain meat mechanically recovered from close to the spinal column or head meat, or both, including burgers, meat pies, and sausages (45).

It should be noted that the incubation period will likely be measured as many years or decades. Consequently, consuming BSE-con-

TABLE 2. Clinical and Pathologic Characteristics Distinguishing Classic CJD from Variant CJD

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4–5 months	13–14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/behavioral symptoms; painful dysesthesias; delayed neurologic signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
“Pulvinar sign” on MRI*	Not reported	Present in >75% of cases
Presence of “florid plaques” on neuropathology	Rare or absent	Present in large numbers
Immunohistochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein	Not reported	Marked accumulation of protease-resistance prion protein

CJD, Creutzfeldt-Jakob Disease.

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*An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery sequences on brain magnetic resonance imaging (MRI); in the appropriate clinical context, this signal is highly specific for vCJD.

taminated products may cause vCJD years or even decades later (20). British estimates of the number of individuals who contracted vCJD as a result of eating beef in the United Kingdom or from blood transfusions of asymptomatic carriers vary widely; a 2004 study of appendectomy samples led to an estimate of 237 (95% confidence interval, 69-692) per million (46).

Oral Manifestations of Prion Disease

Oral symptoms occur rarely in patients with prion disease (47). Oral manifestations of human TSEs are dysphagia (difficulty swallowing) and dysarthria (speech disorder as characterized by poor articulation). In vCJD patients, orofacial dysesthesia (abnormal sensations experienced in the absence of stimulation), paresthesia (tingling, pricking, or numbness of skin) (39, 48), or loss of taste and smell (only one case) have been reported in the literature (49). Experimentally, prions have been easily transmitted to animal gingival tissues from endodontic files contaminated with suspensions of contaminated human brain tissue (50), which proves that gingival tissues in animals are susceptible and that endodontic files could be a vector. However the infectivity of dental pulp tissue in individuals suffering from clinical or subclinical vCJD (ie, the tissue an endodontic file might carry) is not known (50, 51). PrP^{res} has been found in serous and mucous glands on the posterior surface of the dorsum of the tongue (52) and in nerve fibers, taste cells, and the stratified squamous epithelium in fungiform papillae in animal forms and models of prion disease (53). PrP^{res} has also been detected in the skeletal muscles of all human forms of CJD (54).

Nonprion amyloidoses of human periapical oral tissues have been associated with rheumatoid arthritis and chronic oral infections (55). In experimental animal studies of transmission, when infection occurs via the oral route, PrP^{res} first appears in the Peyer's patches and other gut-associated lymphoid tissue (53). PrP^{res} next appears in serous and mucous glands in the oral cavity (53). Transfer to mucosally associated lymphoid tissue would be expected via the lymph system because gut-primed lymphoid and myeloid cells are known to home to oral mucosally associated lymphoid tissue (56). Transfer from the oral cavity to the olfactory bulb and brainstem seems to occur via neuronal routes (53). Routes of transmission of other infectious amyloidoses are not as well documented. Transgenic mice injected at 8 weeks with as little as 100 µg of serum amyloid A intravenously, an acute-phase reactant, formed amyloid deposits in the spleen within 3 weeks and lethal severe systemic disease within 2 months (9). Similarly, intracerebral injection of seeded amyloid-β protein from human Alzheimer's disease into transgenic mice induced conformational conversion similar to that of prion conversion and robust deposition of amyloid plaques in the hippocampus after 4 months (10). Because the amyloid protein seems to act as a template for the folding of newly synthesized protein, it might be expected that systemic acquisition of any amyloid, given enough time, could lead to a significant accumulation of amyloid deposits (11).

Diagnosis

The diagnosis of CJD is based on the clinical and pathologic characteristics as presented in Table 2. The location of the neuropathologic findings is different for the TSEs: for CJD, in the cerebral cortex; for vCJD, throughout the cerebrum but mostly in the brainstem, occipital cortex, and cerebellum; for Kuru and Gerstmann-Straussler-Scheinker syndrome, in the cerebral cortex and cerebellum; and for fatal familial insomnia, in the thalamus (57). Some diagnostic tests and investigations are as follows: (6, 22, 27, 31, 58–65)

1. Blood tests: extracted DNA from blood to test for mutations (met/met homozygosity at codon 129) in persons with suspected inherited prion diseases;

2. EEG: finding of periodic sharp waves in sCJD and absence of these waves in vCJD;
3. Cranial magnetic resonance imaging: abnormal findings primarily in the posterior thalamic area of the brain (pulvinar sign) in vCJD and occasional changes at the basal ganglia in sCJD;
4. Cerebrospinal fluid tests: tests for elevated levels of the 14–3–3 protein may be used for the diagnosis of sCJD, particularly if patients manifest with the typical clinical signs and progression. However, the protein is also found elevated in the CSF of patients with various forms of encephalitis and hypoxic brain damage.
5. Tonsillar biopsy: for diagnosis of vCJD.
6. Amyloid fibrils are birefringent when stained with Congo red and viewed with polarized light.
7. Thioflavin S shown to bind prion aggregates.

In the diagnosis of CJD, it should be noted that the clinical manifestations of some other conditions associated with rapid cell death (eg, intracerebral hemorrhages and encephalitis) could mimic those of the CJD and, thus, present a diagnostic challenge to clinicians (22). Therefore, to confirm the diagnosis and type of prion disease, neuropathologic and/or immunohistochemical examination of frozen brain tissue obtained either at biopsy (not recommended for any form of CJD unless an alternative treatable condition is suspected in the differential diagnosis) (58) or at autopsy should be performed (22, 23, 27, 31, 66).

Potential Risks to Health Care Workers

Social Contact

There is no evidence to show that CJD or any other amyloidosis is transmissible from person to person by normal social contact, airborne droplets, or sexual contact (23, 33). However, because of the long incubation period of amyloidoses such as vCJD, it is too early to conclude unequivocally that they are not transmitted from one individual to another by social contact. Neither clustering of cases among families or social groups living together nor the transmission to sexual partners has yet been reported (33).

Blood Transfusion

Studies performed over 25 years have failed to show evidence of transmission of sCJD by blood components or plasma products (7). On the other hand, to date, there have been four instances of probable transmission of vCJD infection via blood transfusion. In these cases, the donors were at a preclinical phase of the disease at the time of donation (36, 67–69). It should be noted that the long incubation period of prion diseases results in a long asymptomatic phase in infected individuals (70). Estimates of the number of people incubating vCJD in Britain range from a few hundred to hundreds of thousands (7, 71). These subclinical carriers could pose a risk for contamination of blood products, surgical instruments, and tissue transplants (36, 46, 54, 72). However, it should also be noted that the extremely low incidence of vCJD in North America (four cases until now) suggests that the risk of acquiring vCJD or the risk of blood transmission of vCJD in North America is extremely low (20). As a precaution, the governments of the United States of America and Canada have set some deferral policies since 1996. For example, the Canadian Blood Services excludes potential blood or plasma donors who have spent a cumulative total of 3 months or more in the United Kingdom or France between 1980 and 1996 or if they have spent a cumulative total of 5 years or more in Western Europe outside the United Kingdom or France since 1980. In addition, people are not eligible to donate blood or plasma if they have had a blood transfusion or have received medical treatment with a product made from blood in the United Kingdom, France, or Western Europe since 1980 (73). Canada has banned the use of plasma products

TABLE 3. Commonsense Actions in Case of an Occupational Exposure

Incident Of Occupational Exposure	Commonsense Actions
Contamination of unbroken skin with internal body fluids or tissues	Wash with detergent and abundant quantities of warm water (avoid scrubbing), rinse, and dry. Brief exposure (1 minute, to 0.1N NaOH or a 1: 10 dilution of bleach) can be considered for maximum safety.
Needle sticks or lacerations	Gently encourage bleeding; wash (avoid scrubbing) with warm soapy water, rinse, dry and cover with a waterproof dressing. Further treatment (e.g., sutures) should be appropriate to the type of injury. Report the injury according to normal procedures for your hospital or healthcare facility/laboratory. Records should be kept for no less than 20 years.
Splashes into the eye or mouth	Irrigate with either saline (eye) or tap water (mouth); report according to normal procedures for your hospital or healthcare facility/laboratory.

imported from the United Kingdom but uses products imported from the United States, which still uses UK plasma products (74).

Prion and Dentistry

Occupational Exposure and Patient Care

There is no risk of transmission of TSE to health care workers (including medical doctors, nurses, dentists and dental auxiliaries, laboratory workers, and ambulance personnel), relatives, or the community through normal social and clinical contact or noninvasive clinical investigations (75). As of 2005, a total of 24 cases of sCJD were reported in health care workers (33). Theoretically, it is possible that health care workers may acquire TSE from patients through accidents such as needlestick injuries (75). However, so far, there has been no such case reported, and there is no epidemiological evidence that proves an association between the acquiring of sCJD and any occupational exposure (75, 76). Moreover, a reanalysis of pooled data from three case-control studies (77–79) did not show any significant association of CJD with employment as a health professional (80). Therefore, although there is no reason to defer, deny, or in any way discourage the admission of a TSE patient into any health care setting, health care personnel should be appropriately informed about the nature of the hazard and relevant safety procedures (75). In case of a needlestick injury while performing dental procedures on a TSE patient, the World Health Organization (WHO) common-sense actions as presented in Table 3 are recommended.

Dental Procedure Clusters

In analyzing the geographic distribution of the 402 cases who died from definite or probable sCJD cases in France between 1992 and 1998, a statistically significant cluster detection was found only among three cases living in a small rural area in South-West France; two of them had lived in the same area throughout life (28). Among other potential risk markers, these two individuals had both undergone dental treatment by the same dentist who practiced in the area they lived. However, the precise mechanism underlying this cluster of cases was unclear.

In another investigation on three pairs of geographically associated cases of vCJD in northeast England, no common source of exposure, including dental procedure, was found between the cases (81). In contrast, small clusters of CJD cases possibly connected by dental procedures were suggested but never proven (82, 83).

It should be noted that to date, there are no reported definite or suspected cases of vCJD transmission arising from dental procedures (50, 51), and there seems to be no correlation between dental treatment and sCJD (77–79,84–87) or vCJD (45, 88).

Risk

So far, only two possible mechanisms for the transfer of vCJD infectivity via dental instruments have been risk assessed (51):

1. Accidental abrasion of the lingual tonsil, known to carry infectivity in vCJD cases. Such a chance is extremely low (10^4 to 10^9 times less likely to transmit vCJD than tonsillectomy).
2. Contact with dental pulp: dental pulp originates from the richly innervated tissue of the neural crest. Therefore, theoretically, it is reasonable to assume that the dental pulp of individuals subclinically infected with vCJD (perhaps also inherited CJD [iCJD], sCJD, and familial CJD [fCJD]) may be infectious (89, 90).

More recently, Bourvis et al (91) used a modeling approach to theoretically assess the risk of iatrogenic transmission of sCJD during endodontic treatment. They estimated the risk of being infected during endodontic treatment, if no effective prion-deactivation procedures were used, ranged from 3.4 to 13 per million procedures. However, the probability that more than one case was infected secondary to endodontic treatment of an infected sCJD patient ranged from 47% to 77% depending on the assumed quantity of infective material necessary for disease transmission. These results show that the risk of sCJD transmission because of the reuse of instruments during endodontic treatment may not be ignored in the absence of effective prion-decontamination procedures.

To date, there has been no evidence in humans of the presence of PrP^{res} in dental tissues, including dental pulp in vCJD cases (89, 92), although increased sensitivity of assays is being achieved (54). Also, there are no data from infectivity studies on human oral tissues (50). However, there is evidence that infected laboratory animal models develop some level of infectivity in the oral cavity (including gingival and dental pulp tissues, trigeminal ganglion, salivary glands, and tongue muscle) (75, 77, 93–100).

Achieving reliable decontamination of endodontic files intended for reuse is difficult (101–109). Therefore, there is a possibility that these inadequately decontaminated dental instruments that have been in contact with dental pulp may transfer prion proteins from patients with subclinical, suspected, or confirmed cases of vCJD.

It should also be noted that even in the United Kingdom, which has the highest numbers of CJD and vCJD cases worldwide, the relative risk to public health from potential transmission via dental procedures as compared with hospital surgery was considered to be relatively low (90). Comparing the UK incidence to that of North America (four cases so far), the chance of vCJD transmission via dental procedures in North America would be extremely low.

General Recommendation for Dentists Treating Patients at High Risk For CJD

It is critical that dental staff receive adequate training about CJD precautions and its occupational risks and hazards. As a general rule, appropriate medical history (including a risk assessment for CJD) should be obtained from all patients before all dental procedures

TABLE 4. Ineffective or Suboptimal Disinfectants

Chemical Disinfectants	Gaseous Disinfectants	Physical Processes
Ineffective –Alcohol –Ammonia – β -propiolactone –Formalin –Hydrochloric acid –Hydrogen peroxide –Peracetic acid –Phenolics –Sodium dodecyl sulfate (SDS) (5%)	–Ethylene oxide –Formaldehyde	–Boiling –Dry heat (<300°C) –Ionizing, ultraviolet, or microwave radiation
Variably or partially effective –Chlorine dioxide –Glutaraldehyde 15 minutes –Guanidinium thiocyanate (4 M) –Iodophors –Sodium dichloro-isocyanurate –Sodium metaperiodate		–Autoclaving at 121°C for –Boiling in 3% sodium dodecyl –Sulfate (SDS) –Urea (6 mol/L)

(110). For example, in the United Kingdom, if the history taking for a candidate for surgery shows a positive answer to family dementia before the age of 65; dura mater grafts; corneal transplant; pituitary hormone injection pre-1986; insulin injection pre-1989; problems concentrating, reasoning, remembering; and unsteadiness walking, jerky movements, or lacking previous coordination, the patient should be referred to a neurologist for more evaluation. However, these specific questions are not considered necessary by the CDC in the US context because of the low prevalence there of the disease (111).

For practical considerations, it is essential to distinguish between symptomatic patients (definite, probable, possible, or suspected CJD or vCJD cases) and asymptomatic patients (those with no clinical symptoms but potentially at risk because of having a medical or family history) (12). In performing dental procedures not involving neurovascular tissues on a high-risk patient, the general infection control practices recommended by national dental associations are sufficient (75). However, when a dental procedure involves exposure of neurovascular tissues on a high-risk patient, more stringent infection control (see later) should be followed. Therefore, it is recommended that such a procedure be performed in appropriate referral centers by personnel familiar with CJD precautions (110, 112).

In treating suspected or confirmed CJD patients, it is recommended that the appointment be scheduled in specialist clinics or the hospital (112) at the end of the day to permit more extensive cleaning and decontamination; to use disposable coversheets whenever possible to avoid environmental contamination (75); and to use a separate waterline (eg, syringe) for cooling dental handpieces, a standalone suction unit, and a disposable bowl instead of the spittoon of the dental unit (33, 38).

Proper Infection Control in Treating High-risk Patients

Prion agents, unlike infectious microorganisms, resist conventional sterilization methods such as steam autoclaving, even at increased temperatures, or by ethylene oxide gas (75, 113, 114). It has been reported that human sCJD prions were more than 100,000 times more resistant to inactivation than hamster prions, which have been historically used as the standard for prion inactivation procedures (115). Table 4 lists a number of commonly used chemicals and processes that have been shown to be either ineffective or only partially effective in inactivation of the prion protein and cannot be depended on for decontamination (75).

In dentistry, presterilization cleaning is an essential stage of instrument reprocessing. Any instruments contaminated with residual protein could pose some level of risk. Thus, any decontamination that removes

protein residue reduces the risk. Recent studies of instrument sets from UK National Health Service Trust sterile-service departments deemed clean after treatment with washer-disinfector machines, and steam sterilization showed evidence of residual proteinaceous material on all instruments tested (64). Some dental instruments are difficult to clean after contamination with blood or neurovascular tissue, and, even after routine decontamination and sterilization, they may carry significant residues of material (51, 104). This is especially important for endodontic files (because they have intimate contact with terminal branches of the trigeminal nerve and are difficult to clean by virtue of their design) (101–109), matrix bands, retainers (because they frequently become contaminated with blood and other proteins) (101, 116, 117), and used dental burs (because they too are difficult to decontaminate) (101, 118). It should be noted that thus far, there has been only one study (119) that reported a successfully tested clinical cleaning protocol for rotary nickel-titanium endodontic files before sterilization, comprising 10 vigorous strokes in a scouring sponge soaked in 0.2% chlorhexidine solution, a 30-minute presoak in an enzymatic cleaning solution, 15 minutes of ultrasonication in the same solution, and a 20-second rinse in running tap water. However, the stain used by this study (Van Gieson) unlike that used by Lipscomb (64) is not specific for amyloid and would not detect prions.

The most recent position statement of the SEAC on vCJD and endodontics concludes: “It is unclear whether or not vCJD infectivity can be transmitted via endodontic files and reamers. However, given the plausibility of such a scenario and the large number of procedures carried out annually, it would be prudent to consider restricting these instruments to single use as a precautionary measure. Since sufficiently rigorous decontamination of these instruments is difficult, single use of these instruments would eliminate this risk, should it exist” (90). Therefore, a precautionary approach is justified.

The single-use of endodontic instruments is controversial. The CDC, WHO, and British and German national organizations consider that the risk justifies the single use of endodontic instruments; other national dental organizations have no policy (United States and Canada), whereas Australian authorities consider no risk in the reuse of these instruments. Based on the WHO and CDC recommendations for suspected or confirmed CJD patients, the safest and most unambiguous method for minimizing the risk of residual infectivity is the use of single-use items and equipment (eg, needles and anesthetic cartridges) whenever possible and incinerating reusable instruments difficult to clean (eg, endodontic files, broaches, carbide and diamond burs, and dental matrix bands) (75, 120). The single use of endodontic reamers and

files is now the new guideline for all dentists in England as issued by the Chief Dental Officers and approved by the SEAC (50, 121). In Germany, since 2006, endodontic instruments have been categorized in the class of highest concern as “critical instruments class B” because of close contact to tissue and blood (108). In contrast, in Australia, for all high- and low-risk patients, endodontic files can be routinely reprocessed (122). The American Association of Endodontists has not stated a position to date.

However, destruction of heat-resistant surgical instruments that come in contact with high infectivity tissues (brain, spinal cord, and eye) may not be practical or cost-effective for many devices and materials that were not designed for single use (23, 75). In this case, the nondisposable instruments should be mechanically cleaned and passed through stringent decontamination protocols before cleaning, terminal sterilization, and reuse, as recommended by the WHO and the CDC. Recommendations for exact procedures are available from the WHO (75). The most stringent one for heat-resistant instruments is “Immerse [the instruments] in sodium hydroxide (1 N NaOH) and heat in a gravity displacement autoclave at 121°C for 30 min; clean; rinse in water and subject to routine sterilization” (75). It should be noted that hazardous substances such as NaOH can condense in the autoclave and cause corrosion. Some sterilizer manufacturers have stated that this will void their warranty (114). Recently, some noncorrosive systems (containment pan-and-lid combinations [114] or acidic sodium dodecyl sulphate [115]) have been proposed. The CDC is considering (without recommendation) the least stringent of sterilization methods offered by the WHO: “Clean instruments thoroughly and steam-autoclave at 134°C for 18 minutes” (120). For surfaces and heat-sensitive re-usable instruments, the WHO recommends to “Flood with 2N NaOH or undiluted sodium hypochlorite; let stand for 1 hr.; mop up and rinse with water” (75).

In some clinics like the University of California at San Francisco Memory and Aging Centre, if the possibility of prion disease cannot be ruled out, the dental instruments are either quarantined pending diagnosis, incinerated, or cycled 10 to 20 times (111).

It is important to note that the prion agent resists inactivation by autoclaving even more when infected tissue becomes dried onto glass or metal surfaces (123). Therefore, the nondisposable instruments and other materials subject to reuse should be kept moist and not allowed to air dry throughout the surgical procedure by immersing them in water or disinfectant solution between the time of exposure to infectious materials and subsequent decontamination and cleaning (23, 75).

Discussion and Conclusion

This article aimed to provide dentists with an overview of the characteristics, the risk of transmission, and infection-control implications of prions and other transmissible amyloidoses in dentistry. TSEs are a group of fatal neurodegenerative diseases that are rapidly progressive and always fatal, with no approved cure, and their definite diagnosis can only be obtained at post mortem autopsy. The causative agent, prion protein, resists conventional sterilization methods especially when infected tissue becomes dried onto glass or metal surfaces. There is now increasing and strong epidemiologic and laboratory evidence for a causal relationship between BSE and vCJD; however, whether vCJD will result in a major public health problem in the future is unknown.

In terms of transmission, there is no good evidence to show that sCJD can be transmitted by blood components or plasma products. However, there is now good evidence that blood, during the preclinical stage of vCJD, is infectious. There has never been a transmission of sCJD by normal social contact, through environmental contamination, by airborne droplets, by blood, or sexual contact. However, because of the

long incubation period of vCJD, it is too early to conclude the same for the vCJD or for other transmissible amyloidoses.

To date (June 2008), there are no reported definite or suspected cases of vCJD transmission arising from dental procedures, and there seems to be no correlation between dental treatment and TSEs. Because there is a theoretical but real risk of transmission of prion disease from dental instruments (although it is extremely low, especially in North America), as a general rule, appropriate family and medical history (including the risk for prion diseases) should be obtained from all patients before all dental procedures. TSE investigations regarding diagnosis, transmission, treatment, and inactivation of prions and other transmissible amyloidoses are ongoing, and, thus, dental professionals should maintain optimal and up-to-date standards of knowledge, infection control, and decontamination.

A recent and comprehensive guideline on the cleaning of dental instruments is available from the Scottish Dental Clinical Effectiveness Programme (101). There is a need for cost-benefit and cost-effectiveness analyses of the improvement of infection control guidelines in dental practices. The British General Dental Council requires continuing dental education including education on instrument decontamination and decontamination quality-assurance programs in order to stay on the register (maintain licensure), but it is not clear how such quality-assurance programs would insure that reusable instruments were free of proteinaceous materials. It would seem prudent that other jurisdictions should add educational and continuing educational programs and materials on prion infection and instrument decontamination.)

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