

Prion Diseases in Humans: Oral and Dental Implications

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Abstract

Prion diseases are a group of neurodegenerative disorders characterized by accumulation of abnormal prion proteins in the central nervous system. The prions resist conventional sterilization procedures especially when infected tissue becomes dried onto metal or glass surfaces. This article, a review of literature collected using Pubmed as search engine, describes the oral manifestations of prion diseases in addition to studying the possibility of cross contamination in the dental office. The article emphasizes the importance for dentists to be aware of these diseases, to identify the high-risk patients by obtaining adequate medical history and to know the appropriate deactivation procedures to be followed.

Keywords: Contamination, Deactivation, Oral, Prions

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Introduction

Prion diseases also known as transmissible spongiform encephalopathies (TSEs), are a group of fatal neurodegenerative diseases occurring in both humans and animals. Stanley B. Prusiner was the first person to purify the infectious agent of prion disease and won the 1997 Nobel Prize in Physiology/Medicine. Prusiner defined prions as infectious, transmissible proteinaceous particles that lack nucleic acid. The normal cellular prion protein (PrP^c) is encoded by PrP^c gene, which is located on the short arm of chromosome 20. PrP^c has predominantly alpha helical structure, is soluble and proteinase sensitive. The normal function of PrP^c is not well-known, but the suggested functions are signal transduction, cell adhesion, regulation and distribution of acetylcholine receptors.^[1]

PrP^c is transformed into abnormal isoform of the protein (PrP^{Sc}) due to post translational modification or

mutation in the PrP^c gene. PrP^{Sc} has predominantly beta structure, is insoluble and partially proteinase resistant. This mutated PrP^{Sc} gives rise to TSEs, including bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goats and Creutzfeldt-Jakob disease (CJD) in humans. These diseases are characterized by vacuolization of the gray matter and these vacuoles are located in the neuropils between the nerve cell bodies.^[2,3]

Although the risk of transmission of CJD through dental procedures is still unclear, the theoretical possibility of transmission through contaminated dental instruments should be kept in mind. This article aims to give a brief overview of the clinical characteristics, risk of transmission and infection control methods of prion diseases for dentists using data obtained from literature search in Pubmed search engine.

Etiopathogenesis

The infectious agents for prion disease are composed of a 35-kD brain sialoglycoprotein called PrP^{Sc} that is essential for the transmission and pathogenesis of several neurodegenerative diseases. PrP^{Sc} is able to propagate itself in the host by stimulating the conversion PrP^c to PrP^{Sc}, leading to its accumulation.^[4]

Accumulation of PrP^{Sc} can result either from exposure to infectious prions iatrogenically or through ingestion,

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or because of mutations in the PrP gene. Sporadic CJD has an unknown cause; that is, thus far no apparent infections or mutations of the PrP gene have been found in association with such cases, although the brain in these patients also accumulates PrP^{Sc}.^[2]

Human Transmissible Spongiform Encephalopathies

Based on the etiopathogenesis, different types of human TSEs have been recognized. Table 1 describes the transmission routes and clinical features of TSEs in humans.

Sporadic Creutzfeldt-Jakob disease

This is the most common type of CJD accounting for 85% of all CJD cases, occurring in middle or older age group. The disease is characterized by progressive dementia, ataxia, myoclonus, cortical blindness, akinesia and speech loss, followed by death within 4 months.^[5]

Iatrogenic Creutzfeldt-Jakob disease

The disease occurs following neurosurgery, duramater transplantation, corneal grafting, and injection of pituitary hormones obtained from human cadavers. This type of prion disease is important to dentists due to the risk of cross contamination after the use of infected dental instruments. The incubation period is variable ranging from 2 to 35 years. The clinical features are similar to sporadic form, but cerebellar motor symptoms are predominant in this type.^[5]

Variant Creutzfeldt-Jakob disease

vCJD is associated with the intake of BSE-contaminated beef and beef products. The disease is characterized by depression, delirium, hallucinations, paresthesia and dysesthesia in hands, feet and mouth followed by dementia and akinesia. Deposition of amyloid plaques in the lymphatic tissues throughout the body is a prominent feature.^[5]

Kuru

Kuru is endemic in Papua New Guinea and is transmitted by intake of infected nervous tissue in cannibalistic practices. The disease is characterized by ataxia, tremors, dysarthria and death. Though cannibalism is banned in 1950, the incubation period is more than 40 years and the chance of appearance of new cases is still possible.^[4]

Fatal familial insomnia

The disease presents with progressive insomnia, dysautonomy in the form of hyperthermia, myosis and loss of sphincter control, followed by dysarthria, tremors, motor dysfunction and cognitive deterioration. Death occurs within 7-18 months.^[6]

Gerstmann-Straussler-Scheinker syndrome

Gerstmann-Straussler-Scheinker syndrome gives rise to lack of coordination leading to ataxia, dysarthria and nystagmus. Death occurs after 1-10 years.^[6]

Oral Manifestations

Oral manifestations are rarely seen in prion diseases. Dysphagia (difficulty in swallowing) and dysarthria (poor articulation of speech) are noticed in all forms of human TSEs. Dysphagia and dysarthria could be early symptoms of the disease and occur as a consequence of pseudobulbar paralysis.^[7] In vCJD, parasthesia (tingling, pricking or numbness), orofacial dysesthesia (abnormal sensations in the absence of stimulation) and one case of loss of taste and smell have been reported in the literature.^[8,9]

Infectivity of human oral tissues

Studies on human oral tissues for the presence of PrP^{Sc} showed positivity in limited number of oral tissues. Various human tissues like tonsil, tongue, submandibular and parotid salivary glands, trigeminal ganglia, inferior alveolar nerve, dental pulp and gingiva taken from different post mortem cases of vCJD were analyzed for the presence of PrP^{Sc}. Majority of the cases showed positive PrP^{Sc} in tonsils and trigeminal ganglia, while the other human tissues were negative for PrP^{Sc}. Western blot, paraffin-embedded tissue blot, and immunohistochemical techniques were used for the study and the sensitivity of these assay indicated that PrP^{Sc} must have been at the level of less than 1% of that found in the brain tissue.^[10]

Presence of PrP^{Sc} in trigeminal ganglia may raise concerns about the extent of deposition of PrP^{Sc} along the cranial nerves and possible extension into oral and nasal cavities which are innervated by the ganglia. Guiryo *et al.*,^[11] have noted positive PrP immunostaining of axons in the nerve root and around the degenerating ganglion cells of trigeminal ganglion, suggesting centripetal or centrifugal extension of the infectious agent along the axons.

Blanquet-Grossard *et al.*,^[12] have investigated the presence of protease-resistant PrP^{Sc} in pulp tissues from eight patients with sCJD using specific monoclonal antibody by Western blotting. Though the authors were unable to detect protease-resistant PrP^{Sc} in pulpal tissues, they suggested that the negative results could be due to low sensitivity of the technique used and the potential for transmission of CJD via dental procedures could not be dismissed. The authors have calculated that 1 g of sCJD infected pulp would be expected to contain 40 log₁₀ LD₅₀/g of infectivity, compared to 10_{8,9} LD₅₀/g of infectivity in brain tissue.

Prions and Dentistry

There is no evidence to show that TSE is transmissible from one person to other by normal social contact, sexual contact or airborne droplets. Studies have failed to show evidence of transmission of sCJD by blood components or plasma products. On the contrary, there have been four reports of probable transmission of vCJD via blood transfusion, where the donors were at preclinical phase of the disease at the time of blood donation [Table 1].^[13]

Occupational exposure

There is no risk of transmission of TSE to health care workers including medical doctors and dentists through clinical contact or noninvasive clinical investigative procedure. A total of 24 cases of sCJD have been reported in health care workers as of 2005.^[14] Theoretically, it is possible that the health care workers may acquire prion diseases from affected patients through needle stick injuries. However, there is no epidemiological evidence to prove an association between occupational exposure and sCJD. The health care personnel should be informed about the nature of the hazard as well as the relevant safety procedures. The World Health Organization (WHO) has recommended “common-sense” actions in case of an occupational exposure while performing dental procedures on TSE patients [Table 2].^[15]

Dental procedures

To date, there are no reported definite or suspected cases of human TSEs arising from dental procedures. Bourvis *et al.*,^[16] had theoretically assessed the risk of iatrogenic transmission of sCJD during endodontic treatment. They estimated that the risk of being infected during endodontic treatment ranged from 3.4 to 13 per million procedures, if no effective prior deactivation procedures were used. However, the probability that more than one case was infected secondary to endodontic treatment ranged from 47% to 77% depending on the quantity of

the infective material. The results of this study showed that the risk of sCJD transmission is higher because of the reuse of endodontic instruments in the absence of effective prion decontamination procedures.

Achieving appropriate decontamination of endodontic instruments intended for reuse is extremely difficult. Therefore, there is a possibility that these decontaminated instruments that were in contact with dental pulpal tissue may transfer the prion proteins from the infected patients to other patients.^[17]

There are two possible mechanisms assessed for the transfer of CJD via dental instruments:

- Accidental abrasion of lingual tonsil during dental procedures. Such a chance is extremely low (10^4 - 10^9 times less likely than tonsillectomy).
- Contact of dental instruments with pulp tissue. As dental pulp originates from richly innervated neural crest cells, it is theoretically possible that the dental pulp of individuals infected with CJD may be infectious.^[12]

General recommendations for dentists

The role of the dentist is to identify the patients with different forms of CJD and to take appropriate measures to reduce the possible risk of cross contamination. This can be achieved by obtaining: (a) complete medical history of the patient, (b) family history of prion diseases, (c) travel history to know about the possible exposure during visits to endemic areas like United Kingdom. Based on this information, patients can be classified as being at high risk or low risk for developing the disease.^[2]

High-risk patients

Patients with diagnosis or suspicion of CJD; asymptomatic patients with a gene mutation; all members of the family with a case of hereditary CJD; all members of a family with a case of vCJD.

Table 1: Transmissible spongiform encephalopathies in humans

Disease	Age of onset	Transmission route	Clinical features
Sporadic CJD	Middle age-older adults	Unknown	Multifocal dementia, ataxia, myoclonus, EEG changes
Iatrogenic CJD	Any age group	Neurosurgery, corneal graft, duramater transplant, pituitary hormone treatment	Cerebellar motor symptoms, cognitive deterioration
vCJD	Adolescents and young adults	Intake of BSE contaminated food	Neuropsychiatric symptoms and sensory disorders
FFI	5 th decade	Autosomal dominant	Insomnia, dysautonomy, motor and cognitive dysfunction, circadian rhythm disorder
GSS	3 rd decade	Autosomal dominant	Lack of coordination, ataxia, nystagmus, dysarthria
Kuru	Any age group	Cannibalism	Ataxia, dysarthria, tremor

BSE: Bovine spongiform encephalopathy, CJD: Creutzfeldt-Jakob disease, EEG: Electroencephalogram, FFI: Fatal familial insomnia, GSS: Gerstmann-Strausler-Scheinker, vCJD: Variant Creutzfeldt-Jakob disease

Low-risk patients

Patients with undiagnosed progressive neurological disease with or without dementia; members of a family with history of undiagnosed dementia or neurological disease; recipients of human pituitary hormone or duramater; patients undergoing transdural surgery between 1972 and 1989 as infectious agent could be transmitted during those procedures.

Prion inactivation methods

The routine physical and chemical sterilizing procedures are ineffective against prion agents, as they are heat

resistant and bind tightly to surgical steel instruments. The prions also become more resistant to inactivation when dried and have shown to transmit disease experimentally and clinically, even after disinfection.^[18]

It is advisable to use disposable instruments whenever possible and incinerate reusable instruments that are difficult to clean (endodontic files, broaches, carbide and diamond burs and dental matrix bands). Endodontic files used in the treatment of pulp cavity contain blood and peripheral nerves known to carry the prion proteins and their intricate surface topography enable to trap the proteins. Therefore, a recent communication in 2007 titled "Advise for dentists on re use of endodontic instruments and variant Creutzfeldt-Jakob Disease" issued by UK Department of Health, has advised dentists to ensure single use of endodontic reamers and files as a precaution to reduce any potential risk of transmission of vCJD. The nondisposable instruments should be mechanically cleaned and passed thorough stringent decontamination protocols before reuse, as recommended by WHO in 2000 [Table 3].^[15]

The handling of instruments depends on the risk of the patient being treated. When treating high-risk patients, all materials must be incinerated. The source of refrigeration and aspiration system should be external to the equipment due to the possibility that some residues might pass via internal systems and compromise sterilization. The patient should never use the normal spittoon but a disposable receptacle that is later incinerated. The histological samples of high-risk patients must be handled by specialized staffs that are aware of the risk. As routine formalin fixation does not inactivate prion proteins, the samples must be immediately immersed in 98% formic acid for 1 h prior to paraffin embedding and labelled as biohazardous.^[5]

In patients with suspicion of CJD, all the instruments must be stored separately in a rigid container labelled

Table 2: Common sense actions in case of an occupational exposure (World health organization, 2000)^[15]

Incident of occupational exposure	Common sense actions
Contamination of unbroken skin with internal body fluids or tissues	Wash with detergent and abundant quantities of warm water, rinse and dry Exposure to 0.1N NaOH or 1:10 dilution of bleach for 1 minute can be considered for maximum safety
Needle sticks or lacerations	Gently encourage bleeding Wash with warm soap water, rinse, dry and cover with a water proof dressing. Further treatment like suturing should be appropriate to the type of injury. Report the injury according to normal procedures of your hospital or health care facility 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 health care facility

Table 3: Recommendations from world health organization for disinfection/sterilization approaches for preventing iatrogenic transmission of creutzfeldt Jakob disease (World Health Organization 2000)^[15]

Type of material	Disinfection/sterilization methodology
Disposable materials/organic remains/instruments in contact with highly infectious tissue of suspected or confirmed TSE	Incineration
Heat resistant instruments in contact with high or low infectious tissue of suspected or confirmed TSE	Immerse in a pan containing 1 N sodium hydroxide (NaOH) and heat in a gravity displacement autoclave at 134oC for 30 min, clean, rinse in water and subject to routine sterilization (OR) Immerse in 1 N NaOH or sodium hypochlorite (20,000 ppm available chlorine) for 1 h; transfer instruments to water; heat in a gravity displacement autoclave at 134°C for 1 h, clean and subject to routine sterilization
Heat sensitive instruments used on persons with suspected or confirmed TSE	Soak or flood with 2 N NaOH or undiluted sodium hypochlorite for 1 hour and rinse with water

TSE: Transmissible spongiform encephalopathy

with data of the patient, type of treatment provided and details of the attending clinician until a definitive diagnosis is arrived. The instruments are incinerated if the diagnosis is confirmed or sterilized by conventional methods like autoclaving if diagnosis is ruled out.^[5]

Conclusion

TSEs are a group of fatal neurodegenerative disorders with no approved cure. The prion proteins resist conventional sterilization methods used in dental clinics and laboratories. Although there appears to be very low risk of CJD transmission during dental procedures, account must be taken of this possibility. As a general rule, appropriate medical and family history should be taken from all the patients before dental procedures. The dental professionals should have up to date knowledge about transmission, diagnosis, infection control and decontamination procedures regarding prion diseases.

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