MAVEN

REVIEW ARTICLE

PRIONS IN DENTISTRY- A MATTER OF CONCERN IN DENTISTRY

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Abstract

Prion diseases are a group of rare fatal neuro-degenerative disorders of humans and ani- mals that are histopathologically characterised by spongioform change of the central nerv- ous system. These diseases include Creutzefeldt-Jakob disease (CJD), Gerstmann- Straussler- Scheinker disease (GSS), Fatal Familial Insomnia (FFI), kuru and variant CJD (vCJD) in humans. Their central feature is post-translational conversion of host–encoded, cellular prion protein (PrPc), to an abnormal pathogenic isoform, designated (PrPSc). The aim of this article is to provide the dental community with a brief overview of the character- istics, risk of transmission and the infection-control implications of prions in dentistry. (2018, Vol. 02; Issue 01: Page 52 - 60)

Keywords: Prion, Creutzefeldt-Jakob disease, Gerstmann- Straussler- Scheinker disease, Fatal Familial Insomnia.

Introduction

Prion diseases are degenerative disorders of the nervous system caused by trans- missible particles that contain a patho- genic isoform of the prion protein, a nor- mal constituent of cell membranes. It is also known as transmissible spongiform encephalopathies (TSEs) (1). Stanley B. Prusiner discovered and defined prions as infectious, transmissible proteinaceous particles that lack nucleic acid and are composed exclusively of a modified iso- form of the noninfectious cellular prion protein (PrPc). He won the Nobel prize for distinguishing these infectious particles from viruses or viroids and finally desig- nated it as a prion protein (PrP) (2-4).

Prions enter a healthy individual and con- vert the existing properly folded protein into host-encoded cellular prion protein. The newly formed host – encoded cellular prion protein brings about a chain reac- tion by acting as a template to guide the

misfolding of more cell- surface protein into prion form thereby increasing their number (5).

Prion disease is incurable. It causes neu- rodegenerative conditions which can affect both animals and humans. Prions can ac- cumulate in central nervous system and can cause microscopic vacuolization of brain tissue called spongioform degenera- tion, characteristic of a group of fatal neu- rodegenerative diseases called transmissi- ble spongioform encephalopathies (TSE) which is incurable and can affect both an- imal and humans (2).

Prion disease may be sporadic, infectious or inherited in origin. The review article provides an overall knowledge regarding characteristics, risk of transmission, po- tential of infection, as well as infection- control considerations of prions in dentis- try (1).

Pathogenesis of prion infec- tion

The most typical features of the prion dis- eases are the aberrant metabolism of the PrP, which exists in at least two conforma- tional states with different physicochemi- cal properties. It exists as a soluble prote- ase sensitive cell surface protein on many cells, especially CNS (Central Nervous System) and lymphoreticular tissues (6). The PrP is expressed in most adult tissues but is found at the highest levels in the central nervous system (CNS) and im- mune systems.

PrPSc (Prion protein in Scrapie) is a dis- ease associated isoform of PrP. It is found only in infected brains as aggregated ma- terial, partially resistant to protease treat- ment and insoluble in detergents. This mutated PrPSc gives rise to TSEs, includ- ing bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goats and CJD in humans. These diseases are characterized by vacuolization of the gray matter, and these vacuoles are located in the neutrophils between the nerve cell bodies (1).

Human prion disease

Prion disease may be sporadic, infectious or inherited in origin. Human prion dis- ease can be classified into two main cate- gories:-

1. Inherited

O Gerstmann–Straussler–Scheinker syn- drome (GSS)

O Fatal familial insomnias.

O Other autosomal dominant families.

2. Acquired

O Iatrogenic Creutzfeldt- Jacob disease. O Kuru.

O Variant Creutzfeldt – Jacob disease (vCJD).

Inherited

Gerstmann–Sträussler–Scheinker- syn- drome (GSS) and Fatal Familial Insomnia (FFI) both are very rare, with an annual incidence of 1 per 10 million to 100 million people. They occur in people with an ap- parent hereditary predisposition (7, 8). The disorders are autosomal dominant in nature and this disease is characterized by lack of coordination nystagmus and ul- timately leading to death (1, 9).

Acquired forms:

1. Iatrogenic Creutzfeldt-Jacob dis- ease (iCJD):

This disease was first diagnosed in 1974, transmitted from one person to another through cadaver-derived growth hormone, pituitary Gonadotropins, dura mater ho- mograft, corneal grafts, blood or inade- quately sterilized neurosurgical instru- ments. This type of prion disease is im- portant to dentists due to the risk of cross

contamination after the use of infected dental instruments (10, 11). iCJD varies clinically from a Sporadic (Classic) Creutz- feldt-Jacob Disease (sCJD) -type disease to a disease similar to Kuru. Site of inocu- lation of the infectious agent determines the incubation period and rate of progres- sion of this disease. Intracerebral or optic inoculation gives rise to the more rapid on- set of disease than does inoculation that is more peripheral. CJD occurs spontane- ously in sporadic cases, in the 7th decade of life. In case of this disease the mortality rate is quiet high. It is about 85% within 1 year and the diagnosis is best ascertained during the final stages of the disease, at or near the time of death (4). The clinical pro- gression is typically over weeks progress- ing to akinetic mutism with median dis- ease duration of 5 months (10, 12). The disease is characterized by progressive de- mentia, ataxia, myoclonus, cortical blind- ness, akinesia and speech loss, followed by death within 4 months (7).

2. Kuru:

It is an acquired prion disease that was originally described in 1957 among the Fore linguistic group of the Eastern High- lands in Papua, New Guinea, probably ac- quired during ritual cannabilistic or sacri- ficial funeral rites. This disease is also characterized by ataxia, tremors, dysar- thria and death (10).

3. Variant Creutzfeldt-Jacob disease (vCJD):

This disease mainly affects the young adults with the mean age of onset being 29 years and it occurs in human due con- sumption of food contaminated with Bo- vine Spongiform Encephalopathy (BSE)

(7). Depression, delirium, hallucination, paresthesia and dysesthesia in hands, feet and mouth followed by dementia and akinesia are the signs and symptoms of

this disease (10).

Diagnosis

The diagnosis of CJD is based by Demon- stration of abnormal PrP immunoreactiv- ity or more specifically biochemical detec- tion of PrPSc in brain material by im- munoblotting techniques is diagnostic of prion disease, and some forms of prion disease are characterized by deposition of amyloid plaques composed of insoluble aggregates of PrP (13).

Amyloid plaques are a notable feature of kuru and GSS, but they are less fre- quently found in the brains of patients with sporadic CJD which typically show a diffuse pattern of abnormal PrP deposition (14-16).

The location of the neuropathologic find- ings is different for TSEs: for CJD, in the cerebral cortex; for vCJD, throughout the cerebrum but mostly in the brainstem, oc- cipital cortex; for Kuru and Gerstman- Straussler-Scheinker syndrome, in the cerebral cortex and cerebellum; and for fa- tal familial insomnia, in the thalamus (7).

Few diagnostics test and investigations are as follows;

1. Blood test: Extracted DNA from blood to test for mutations in person with suspected inherited prion disease.
2. EEG: For periodic sharp waves in sCJD and absence of these waves in vCJD
3. Cranial Magnetic Resonance Imag- ing: abnormal findings primarily in poste- rior thalamic area of the brain (pulvinar sign) in vCJD and occasional changes in basal ganglia in sCJD.
4. Cerebrospinal fluid test –presence of 14-3-3 protein in the cerebrospinal fluid is the only biochemical marker in- cluded in the diagnostic criteria for CJD approved by WHO
5. Tonsilar biopsy- for diagnosis of vCJD.

6. Thioflavin S shown to bind prion aggregates.

The best way to confirm the diagnosis and type of prion disease is by neuropathologic and or immunohistochemical examination of the frozen brain tissue obtained either at biopsy (not recommended for any form of CJD unless an alternative treatable condition is suspected in differential diag- nosis) or at autopsy should be performed (17).

Clinical features of human prion disease

Clinical features of prion diseases are de- scribed in table 1.

Table 1: Clinical features (2)

Types	Age of onset Year (yr)	Incubation time Year (yr)	Duration of disease (mo)	Clinical stages
CJD	60-69	Not rec- orded	3-6	Early – lapse in memory, mood swings (similar to depression), lack of interest, so- cial withdrawl and unsteadiness. Late (neurological) – Blurred vision, sud- den jerking movements and rigidity in limbs, slurred speech, difficulty swallow- ing, progressive mental deterioration, and eventually immobility and muteness.
vCJD	20-29	>4	9-35	Early (psychiatric) - mostly depression, with (less often) a schizophrenia- like psy- chosis; for half of the cases, unusual sen- sory signs, such as “stickiness” of the skin. Late (neurological)- unsteadiness, diffi- culty in walking and involuntary move- ments as the illness progresses; final stages, complete immobility and mute- ness.
Kuru	>20	Mean: 12	6-36	Early- cerebellar syndrome; communica- tion difficulties due to severe dysarthria Late- progression to total incapacitation and death in final stages

Potential risk of transmission

Blood transfusion:

Studies have failed to show evidence of transmission of sCJD by blood compo- nents or plasma products. On the con- trary, there have been four reports of prob- able transmission of vCJD via blood trans- fusion, where the donors were at preclini- cal phase of the disease at the time of blood donation (17).

Iatrogenic factor:

By cross contamination with material in or adjacent to brain like recipients of dura mater, corneal transplants, and human pituitary hormones, and those who have undergone neurological procedures (2).

Human to human contact:

There has been no evidence to show that CJD or any other amyloidosis is transmis- sible from person to person by normal contact, airborne droplets or sexual con- tact. In spite of this there is always a pos- sibility of transmission of amyloidoses such as vCJD from one individual to an- other by social contact because of the long incubation period (2).

Risk among health care workers:

There is a negligible chance of transmis- sion of TSE to health care workers, includ- ing medical doctors and dentists through clinical contact or noninvasive clinical in- vestigative procedure. Health care person- nels should be informed about the nature of the hazard of the disease and they should be properly trained to maintain safety procedures while handling patients suffering from this disease (17).

In case of an occupational exposure while performing dental procedures on TSE pa- tients, World Health Organization (WHO) has recommended "common sense" ac- tions as shown in table 2: (2)

Table 2: Common sense actions in case of an occupational exposure by WHO, 2000

Incident of occupational exposure	Common sense actions
i. Contamination of unbroken skin with internal body fluids or tissues	Wash with detergent and abundant quan- lities 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.
ii. Needle sticks or lacerations	Gently encourage bleeding. Wash with warm soup 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 pro- cedures of your hospital or health care fa- cility. Records should be kept for no less than 20 years.
iii. Splashes into eye or mouth	Irrigate with either saline (eye) or tap water (mouth). Report according to normal procedures for your hospital or health care facility.

Dental implications of prion disease

Oral manifestations of prion disease (17)

- Dysphagia (difficulty in swallow- ing)
- Dysarthria (poor articulation of speech)

• Paresthesia (tingling,pricking or numbness)

• Orofacial dysesthesia (abnormal sensation in the absence of stimulation). Risk of transmission through dentistry: Almost there are negligible chances of transmission of prion disease through dental treatment if proper standards of in- fection control and decontaminations are maintained. Up till now there has been no case reported.

There is no risk of TSE transmission in case of using commercially available bo- vine-derived xenogenic bone graft in case of human if strict protocols is maintained in sourcing and processing of raw bovine bone for human use. There is no relation- ship between tooth extraction, dental sur- gery or major dental work and human TSEs through several case- control stud- ies (3). So far, only 2 possible mechanisms for the transfer of vCJD infectivity via den- tal instruments have been risk assessed: (5, 7, 13)

i. Accidental abrasion of the lingual tonsil, known to carry infectivity in vCJD cases. Such a chance is extremely low (104 to 109 times less likely to transmit vCJD than tonsillectomy)

ii. Contact with dental pulp: As because, dental pulp originates from the richly-in- nervated tissue of neural crest, theoreti- cally, it is reasonable to presume that the dental pulp of patients subclinically in- fected with vCJD, sCJD, and familial CJD might be infectious.

All these studies give rise to the conclu- sion that inadequately decontaminated dental instruments may present a poten- tial route of infection, especially in vCJD, which has greater infectivity in peripheral tissues than CJD.

Infection control in dentistry

The protocols made by National Dental As- sociation for prevention spread of infection are sufficient for treatment of TSE patients with procedures not involving neurovas- cular tissue. However when invasive in- terventions require on patients who are at risk, much more safety and infection control measures are required to reduce the possibility of transmission of TSEs via dental instruments (3).

A combination of methods has been rec- ommended, including thorough cleaning, chemical treatment, and/ or steam sterili- zation (18-20).

The safest way for minimizing the risk of transmission of this disease is by using the one time use items and equipment such as disposable needles and anesthetic cartridges. The World Health Organization (WHO) provides a guideline as shown in table 3 (3, 21).

Table 3: Infection control guideline for TSE by WHO, 2000

Category	Methods
i. Incineration	• Use for all disposable instruments, materials and waste. • Preferred method for all instruments exposed to high in- fectivity tissues.

ii. Autoclave and chem- ical methods for heat resistant instruments	• Immerse in sodium hydroxide (NaOH) and heat in a grav- ity displacement autoclave at 121°C for 1 hour; clean and subject to routine sterilization. • Immerse in NaOH or sodium hypochlorite (20,000 ppm available chlorine) for 1 hour; transfer instruments to wa- ter; heat in a gravity displacement autoclave at 121°C for 1hour; clean and subject to routine sterilization. • Immerse in NaOH or sodium hypochlorite for 1 hour; re- move and rinse in water, then transfer to open pan and heat in a gravity displacement (121°C) or porous load (134°C) autoclave for 1 hour; clean and subject to routine sterilization. • Immerse in NaOH and boil for 10 minutes at atmospheric pressure; clean, rinse in water and subject to routine ster- ilization. • Immerse in sodium hypochlorite (preferred) or NaOH (al- ternative) at ambient temperature for 1 hour; clean, rinse in water and subject to routine sterilization. • Autoclave at 134°C for 18 minutes (to be used for worst- case scenario; i.e., brain tissue bake-dried on surfaces).
iii. Chemical methods for surfaces and heatsen- sitive instruments	• Flood with 2 N NaOH or undiluted sodium hypochlorite; let stand for 1 hour; mop up and rinse with water. • For surfaces that cannot tolerate NaOH or hypochlorite, thorough cleaning will remove most infective agents by di- lution, and some additional benefit may be derived from the use of one or another of the partially effective methods (chlorine dioxide glutaraldehyde, guanidinium thiocya- nate [4mol/L],iodophors, sodium dichloro- isocyanurate, sodium metaperiodate, urea [6 mol/L]).
iv. Autoclave or chemi- cal methods for dry goods	• Small dry goods that can withstand either NaOH or so- dium hypochlorite should first be immersed in one or the other solution and then heated in a porous load autoclave at ≥121°C for 1 hour. • Bulky dry goods or dry goods of any size that cannot with- stand exposure to NaOH or sodium hypochlorite should be heated in a porous load autoclave at 134°C for 1 hour.

The best way to prevent cross contamina- tion or control the spread of infection is quarantining instruments, linen , gowns, gloves, masks in rigid leak- proof combus- tible clinical waste container after use and transferring the container to the incinera- tor as soon as possible.

Universal precaution measures was which includes a precise case history by every dental patient and appropriate continuing education for dentists about the way of controlling cross infection in dental prac- tice, regarding prevention of TSEs (2).

Guideline for dental manage- ment of patients with prion disease

There is not much difference between the procedures for dental management of pa- tients with prion disease with that of other patients except with certain important modifications (3). According to protocols made by Centre of Disease Control and prevention (CDC) all dental instruments employed in the treatment of patients with prion disease which are difficult to clean (such as endodontic files , broaches, car- bide and diamond burs) will be discarded. Single- use instrument is highly recom- mended. Heat resistant instruments should be thoroughly cleaned and they should be autoclaved at 134ºC for 18 minutes. The dental equipments should be properly shielded using disposable, im- permeable cover sheets to prevent envi- ronmental contamination (2).

Patients who are diagnosed suffering from prion disease should be scheduled at the end of the day to permit more extensive cleaning and decontamination. An inde- pendent suction and disposable bowl must be used instead of a spittoon. The suction unit must be a stand- alone suc- tion unit to prevent cross contamination of this disease (3).

Conclusion

Previously prion diseases (except for scra- pie, which has been endemic in sheep more than 250 years) were regarded as
rare neurodegenerative disorders with no serious impact on public health issues and no immediate need for the develop- ment of diagnostic or therapeutic measures. This has radically changed with the emergence of BSE and its human counterpart, variant CJD. Recently, there has been an increase in scientific and public awareness about prion disease. The risk of transmission of prions through dental procedures draws our attention to- wards the need to maintain optimal stand- ards of infection control and decontamina- tion procedures for all infectious agents, especially prions.

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