Prions: Potential Threat to Mankind and Dental Implications

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ABSTRACT
Prion diseases are fatal, infectious, neurodegenerative disorders with special implications for infection control in the health care system. The causative agent is highly resistant to routine disinfection and sterilization processes and has been transmitted during health care interactions. Thus, it is important to use evidence gained through research and case reports to minimize risk of infection. There is no data suggesting that prions are transmitted easily during dental sittings but there remains a rare risk of such transmission if appropriate infection measures are not adhered to.

Keywords: Prions, Fatal disease, Sterilization resistant.

INTRODUCTION
Dr Stanley B Pruisner initially discovered and coined the term prions, which credited him Noble Prize in Medicine in 1997.1 Prion diseases are caused by a unique class of pathogens able to initiate infections without the traditional inflammatory response. They occur naturally, are transmissible both naturally and experimentally, have long incubation periods and do not give rise to any host response.

Prions give rise to spongiform change within the gray matter of the brain and the accumulation of abnormal, partially protease-resistant isoform of a host-encoded glycoprotein known as prion protein within the central nervous system. The silent incubation period ranges from months to as long as 40 years.2 These infectious agents are smaller than viruses and unlike any other pathogens, contain no DNA or RNA. Their only known component is an abnormally conformed protein. The popular term prions (pronounced pree-ons) is used when referring to these proteinaceous and infectious agents.2

Prions affect both animal and human species. Prions are responsible for atleast six diseases in animals, where scrapie is by far the most commonly studied disease of this category affecting sheep and goats.2 Other of interest being the mad cow disease representing the bovine spongiform encephalopathy (BSE). Based on strong evidence, it is now accepted that eating beef contaminated with BSE has led to new strain of human prion disease known as (vCJD), variant of Creutzfeldt-Jakob disease3 (Table 1).

Of all the prion diseases studied, CJD has received a critical review because of its fatality and limited known diagnostic features. Though the disease is rare, affecting approximately one case per one million per year of which 5 to 15% are inherited less than 5% are transmitted and more than 80% are sporadic in nature because there is no family history and no source of transmission verified.1

ACQUIRED PRION DISEASES4-6

Kuru: It is an acquired spongiform encephalopathy, which affected the people of New Guinea around 1950 due to their cannibalistic rituals.

Sporadic (classic) Creutzfeldt-Jakob disease: sCJD accounts for the majority of human Transmissible Spongiform Encephalopathy (TSEs) worldwide, and it typically arises in middle to late life.

Iatrogenic Creutzfeldt-Jakob disease: The prion is acquired via cadaver derived growth hormone, pituitary gonadotropins, dura mater homografting, corneal grafts or inadequately sterilized intracerebral surgical equipment.

Variant Creutzfeldt-Jakob disease: vCJD is localized geographically to Europe, particularly the United Kingdom affecting primarily teenagers or young adults.

The above four prion diseases are summarized along with their clinical features, incubation period, and the age of onset in following table (Table 2).

Table 1: Classification of prion diseases. The human prion diseases are classified into two categories

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerstmann-Straussler-Scheinker syndrome (GSS)</td>
<td>Kuru</td>
</tr>
<tr>
<td>Fatal familial insomnia (FFI)</td>
<td>Sporadic Creutzfeldt-Jakob disease (sCJD)</td>
</tr>
<tr>
<td>Other autosomal dominant families</td>
<td>Variant Creutzfeldt-Jakob disease (vCJD)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic Creutzfeldt-Jakob disease</td>
</tr>
</tbody>
</table>

**PATHOGENESIS OF PRION INFECTION**

In humans, prion protein is located on chromosome 20. Normal prion protein, or PrPc, is a cell membrane glycoprotein. It exists as soluble protease sensitive cell surface protein on many cells, especially CNS and lymphoreticular tissues but its function is unknown, though it has been suggested that it may be important in copper metabolism (for example, transportation). In acquired prion disorders, PrPSc causes disease at a posttranslational level of PrPc production, causing the conversion of PrPc to PrPSc. PrPc is rich in alpha–helical structures but the disease associated isoform PrPSc is composed of beta-pleated sheet and postulated to act as conformational template that promotes conversion of PrPc to PrPSc. This unit continues to grow by accretion and divide by breaking in smaller infectious unit, eventually leading to accumulation of further insoluble PrPSc in neural cells, disrupting the functions and leading to vacuolization and cell death. This pathogenic process is self-propagating, and therefore levels of the abnormal protein rise causing the generation of plaques of amyloid material and neural death. But the exact mechanism is still not known.

**MODE OF TRANSMISSION OF PRIONS**

The mode of transmission of sporadic CJD is not known. Approximately 5 to 15% of human prion disease is familial (i.e. inherited) and <1% is acquired through iatrogenic transmission or consumption of BSE-infected animal tissues. Rare cases of human prion disease have been acquired through medical procedures from contaminated human-derived pituitary hormones, dura mater grafts, corneal grafts or neurosurgical equipment.

In all species affected by transmissible spongiform encephalopathy, (TSE), infectivity is highest in brain tissue and is also present in some peripheral tissues. Transmission of sCJD as a result of dental treatment was proposed 20 years ago but never proved. Case-control studies have not established any association between dental health care and the development of sCJD or vCJD. There are no data to suggest any clustering of vCJD in dental practice. It is not always been successful. The incubation period depends on the dose of prions and the route of exposure.

**CLINICAL FEATURES AND ORAL MANIFESTATIONS**

In sCJD, there is rapid progression of symptoms over a period of weeks to an akinetic mutism. Besides from the predominant mental deterioration and myoclonus, there can be extrapyramidal and pyramidal signs, cerebellar ataxia and cortical blindness. Few of patients may have prodromal symptoms that include insomnia, fatigue, depression, weight loss, headache, general malaise and ill-defined pain. Orofacial manifestations of human TSEs comprise dysphagia and dysarthria (due to pseudobulbar palsy) and, in vCJD patients, there may be orofacial dysesthesia or paraesthesia or abnormal taste sensation. Currently, no treatment can prevent the cognitive and motor decline associated with widespread neurodegeneration in prion disease.

**INFECTIVITY OF ORAL TISSUES IN PRION DISEASES**

Prions of sCJD and scrapie can be present in oral tissues. The prions possible route of transmission from the brain to the oral tissue and vice versa was suggested on the basis of observation of neuronal degeneration with probable prion protein accumulation in the trigeminal ganglia of patients with sCJD. There is no relevant information concerning vCJD, but a prion of BSE has been detected in the trigeminal ganglion of affected animals. Prion proteins were not detected in the pulpal homogenates of eight US patients with sCJD. The prion protein of vCJD is present in tonsillar lymphoid tissue, and thus it is likely to be present in lingual tonsils. The tendency for a prion of vCJD to occur at a site outside the central nervous system would suggest that it would be present in the trigeminal ganglion. The precise infectivity of prion infected oral tissues remains unclear, but the study of scrapie-infected hamsters established that the infectivity of pulpal tissue was substantially lower than that of gingival tissue.

**GUIDELINES FOR DENTAL MANAGEMENT OF PATIENTS WITH PRION DISEASES**

Existing guidelines for clinical management of the patients with prion disease do not address dental health care in any detail. At present oral tissues are considered to be of low infectivity so no additional infection measures are recommended than those employed in universal cross infection control. The Department of Health in the United Kingdom has published the results of a detailed analysis of the risks of prion transmission in dentistry. The report concluded that the risk of transmitting vCJD in a single dental procedure on an infected patient would be about 1 billion times less likely than transmitting vCJD during a tonsillectomy.

No special decontamination procedures need to be adopted for

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**Table 2: Clinical features of human prion diseases. Summary of clinical features of acquired human transmissible spongiform encephalopathies**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age of onset (Years)</th>
<th>Incubation time</th>
<th>Clinical picture</th>
</tr>
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<tbody>
<tr>
<td>Kuru</td>
<td>&gt;20</td>
<td>&gt;12 years</td>
<td>Motor anomalies predominate. Dementia is not common or predominant</td>
</tr>
<tr>
<td>S CJD</td>
<td>60-69</td>
<td>Not recorded</td>
<td>Dementia is predominant. There is rapid progression to akinetic mutism. Few have prodromal symptoms such as insomnia, fatigue, depression and weight loss.</td>
</tr>
<tr>
<td>i CJD</td>
<td>&gt;20</td>
<td>Not recorded</td>
<td>Dementia predominates. Speed of development may depend on site of inoculation of infective material.</td>
</tr>
<tr>
<td>V CJD</td>
<td>20-29</td>
<td>&gt;4 years</td>
<td>Psychiatric disease and dementia predominate. Initial psychiatric condition can last for several months followed by motor disease and eventual akinetic mutism.</td>
</tr>
</tbody>
</table>
providing dental treatment for patients with TSEs, and these patients can be treated in general practice as long as good generic decontamination procedures are applied.

METHODS OF DECONTAMINATION AND STERILIZATION TO PREVENT CROSS INFECTION OF PRIONS

Standard Gravity Seam

Standard gravity (i.e. unwrapped cycle) steam sterilization at 121°C for 15 minutes is only partially effective against prions. At 126°C standard gravity steam was only partially effective against one strain of scrapie. Thus, standard gravity steam is not recommended for deactivation of prions because of the unreliability of these lower temperatures. But the effectiveness of standard gravity steam sterilization increases with prolonged exposures at higher temperatures. This demonstrates the uncertainty health care professionals face when attempting to deactivate prions in complex surgical equipment (e.g. power drills, saws).1

For devices that come into contact with sterile tissue and mucous membranes, the Association for Professionals in Infection Control and Epidemiology (APIC) recommends standard gravity steam sterilization for 30 minutes at a temperature of at least 132°C and the American Neurological Association recommends 60 minutes of exposure time at that temperature.1,4

Prevacuum Sterilization

Researchers have studied the effectiveness of prevacuum (i.e. wrapped cycle) sterilization at 136°C using different amounts of dried, macerated brain tissue in cycles varying in length of time. Four minutes of exposure time with an additional 14-minute heating and four-minute cooling phase was effective against two strains of scrapie; both APIC and the Advisory Committee on Dangerous Pathogens (ACDP) in the United Kingdom recommend prevacuum steam sterilization for 18 minutes at a temperature of at least 132°C as a method of deactivating prions. Wiping off excess bioburden before exposure to steam also has been recommended.1,4

Chemicals used for Deactivation of Prions

Researchers found sodium hypochlorite (NaOCl) and sodium hydroxide (NaOH) to be the most effective chemicals for reducing the infectivity of prions. Dilute concentrations (i.e. 0.5 to 1.3%) of sodium hypochlorite reduce the infective agent by 40 to 60%. Higher concentrations provide a greater level of effectiveness, but increasing exposure time provides little benefit. Researchers found that a concentration of 6.25% eradicates more than 99% of the infectivity of one isolate of CJD agent in 45 minutes, and 12.5% concentration eradicates all infectivity in 30 minutes. Two strains of BSE were deactivated completely in 30 minutes in 8.25% concentration. Sodium hypochlorite is not recommended as a sterilant, but concentration with 20,000 parts per million available chlorine and repeated wetting for one hour contact time is recommended by the ACDP for contaminated environmental surfaces. The APIC recommends concentrations of 0.52 to 5.2% for 15 minutes or less.1,4

Formalin is ineffective against prions, and because pathologists use tissue for a definitive diagnosis, researchers investigated alternative methods for deactivating infectivity in highly infectious tissue. The inclusion of a formic acid step in the usual formalin fixation process eliminates almost all infectivity and retains the histologic characteristics of the tissue required for diagnosis. Use of this procedure for tissue specimens is recommended by the American Neurological Association, ACDP, and APIC.

RECOMMENDED METHODS OF INACTIVATION OF HUMAN AND TSE AGENTS

- 20,000 ppm available chlorine of sodium hypochlorite for one hour
- 2 M sodium hydroxide for one hour
- Nonporous load steam sterilizer 134°C to 137°C for single cycle of 18 minutes, or six successive cycles of 3 minutes each (but this is not known to be completely effective).4

The current UK guideline is that all instruments employed in treatment of patients with known prion disease should be discarded. Single use instruments are preferred.

CONCLUSION

A little more than a decade ago, prion diseases (except for scrapie, which has been endemic in sheep for more than 250 years) were regarded as rare neurodegenerative disorders with no serious impact on public health issues and no immediate need for the development of diagnostic or therapeutic measures. This has radically changed with the emergence of BSE and its human counterpart, variant CJD. Because of the long incubation times and other unknown factors, such as genetic predisposition and exposure criteria, it is difficult to predict whether the incidence of variant CJD will increase, and to what extent. Also epidemiological evidence does not suggest that prion transmission as consequence of dental health care but there is need for research to establish the susceptibility of oral tissues to infection by prions and to determine the exact infectivity of prion containing oral tissues.

REFERENCES