Prion Diseases of Human: A Review
Soundarya S, Usha V, Bhuvaneshwari S

Abstract
Prion diseases are unique group of neurodegenerative diseases including the transmissible spongiform encephalopathies associated with a unique class of infectious proteins. In humans, these diseases include Kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia and in animals, are scrapie and bovine spongiform encephalopathy (mad cow disease). Awareness about the transmission of these diseases during dental care is very low as the knowledge of such existence is indeed rare. Despite the extensive research in this field based on the proposed pathogenesis the diagnosis and management of the disease requires still further studies. Prion diseases have been clouded by mystery since the description of scrapie, human TSEs and elucidation of the prion hypothesis. The risk of transmission of prions through dental procedures draws our attention towards the need to maintain optimal standards of infection control and decontamination procedures for all infectious agents, especially prions. Hence this review is presented here to throw the light on the this rare infection.

Keywords: Prions; Prion Disease; Mink Encephalopathy Virus; Prion Proteins; PrPSc Proteins; Viral Proteins; Neurodegenerative Disease.

Introduction
Prions are abnormal protein molecules that can spread and change the structure of their normal counterparts (cellular proteins). Prions have been concerned in rapidly progressive neurodegenerative disorders. Prion diseases, are also recognized as transmissible Spongiform Encephalopathies (TSEs) that affect most species of mammals. In humans, they include Creutzfeldt - Jakob Disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and the recently described Variable Protease-Sensitive Prionopathy (VPSPr). Fatal insomnia (Fi) and Kuru are also usually reported as distinct disease entities, although recent studies have shown that their molecular features and transmission properties fall within the wide phenotypic spectrum of CJD.

The key characteristics of human spongiform encephalopathies are (1) heterogeneity of the clinical and pathologic phenotype, (2) a single pathologic process, which may present as a sporadic, genetic or infectious illness, and (3) the age dependence of genetic as well as sporadic forms. Prion diseases affect humans and animals alike and both human-to-human and animal-to-human transmission may occur. Human prion diseases include sporadic, genetic and acquired forms. Prion diseases have attracted much attention from researchers with different scientific backgrounds and coming from various areas of expertise. Many questions still remain unanswered in the study of these rare and yet unique neurodegenerative disorders.

Historical Background: Scrapie, an ancient disease of sheep and goats discovered more than 200 years ago. From then till date it has been addressed by various names in different names like "rubbers", "rickets", "goggles", "shakings" "shrewcroft" in England, "cuddie trot" in Scotland, "der Trab", "der Traberkrankheit" lub "die Zitterkrankheit" in Germany, "la maladie convulsive", "la maladie folle", "le tremblante" "la prurigo lombarde" in France and "trzêsawka" in Poland. Of the various scientific reports on scrapie published from late 1700s the first report to confirm that it was a viral disease was Besnoit in 1899 while the transmissible nature of TSEs had been proved in late thirties by seminal experiments of Cuille and Chelle. The research on scrapie was carried out by WS Gordan by conducting various studies and experiments based on Cuille and Chelle. The discovery of the first TSE in...
humans, Kuru in 1957 by Zigas and Gajdusek let to the opening of new field in medicine. This let to various findings in neurodegenerative disorders especially like Alzheimers disease. Later the first case of BSE was reported by Jeffrey et al which was a novel form of TSE. Further Will et al in 1966 reported on a new vCJD, probably transmitted to humans from bovines. Further the increasing number of vCJD cases became an alarming issue, while on the other side the BSE epidemic and appearance of vCJD in humans has accelerated TSE research and changed it from a rather small obscure field into a major scientific endeavour.

Classification: The prion diseases are associated with a range of clinical presentations and are classified by both clinico-pathological syndrome and aetiology with sub-classification according to molecular criteria. Prion diseases can be divided into three etiologic categories: sporadic, genetic, and acquired. Somatic mutation or spontaneous conversion of PrP\textsuperscript{\textalpha} into PrP\textsuperscript{\textbeta} has been suggested as the most probable mechanism of sporadic diseases. Hereditary prion diseases occur due to the germ line mutations in the PRNP gene. Ritualistic cannibalism, zoonotic infection with bovine prions results in acquired prion diseases.

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<td>Sporadic fatal insomnia</td>
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<td>Variable protease – sensitive prionopathy</td>
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<td>Fatal familial insomnia</td>
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<td>Gerstmann – Sträussler – Scheinker disease</td>
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<td>Variant Creutzfeldt – Jakob disease</td>
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<td>Iatrogenic Creutzfeldt – Jakob disease</td>
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Table 1: The etiological classification

Etiopathogenesis: The principal, if not only component of the prion is PrP\textsuperscript{\textalpha} a beta-sheet-rich conformer of Prion protein (PrP). PrP\textsuperscript{\textalpha} propagates by eliciting conversion of PrP\textsuperscript{\textbeta}, the physiological form of PrP, into a likeness of itself. The seeding hypothesis posits that PrP\textsuperscript{\textbeta} is in equilibrium with PrP\textsuperscript{\textalpha} or a PrP\textsuperscript{\textbeta} precursor, with the equilibrium largely in favor of PrP\textsuperscript{\textalpha} and that PrP\textsuperscript{\textbeta} is only stabilized when it forms an aggregate,

or seed, containing a critical number of monomers. Once a seed is present, monomer addition ensues rapidly.

Despite their rarity, human prion diseases have gained considerable importance because their unique etiology and pathogenesis challenged basic principles of biology. Furthermore prion diseases can be transmitted between humans as well as from animals to humans by an agent that is highly resistant to inactivation and which thus poses novel problems to disease control and public health.

In prion diseases, the prion agent is primarily found in the lymphoreticular and nervous systems. In both natural and experimental prion infections, the prion agent is commonly amplified by replicating in the lymphoreticular system prior to entry into nerve cells and subsequent invasion of the brain. Spread within the nervous system can occur by transport along axons and between synaptically linked neurons. Experimental studies have demonstrated that the initial pattern of prion agent spread in the spinal cord and brain follows defined autonomic, sensory, and motor pathways modest levels of prion agent replication in skeletal muscle have been reported in a few studies following intracerebral or extraneural inoculation of the prion agent. Prion infectivity in skeletal muscle was first demonstrated in mink with transmissible mink encephalopathy (TME); the amount of infectious agent in skeletal muscle was 10,000 fold less than the amount found in brain.

Crista DeJoia et al\textsuperscript{12} from the Montana university in 2006 demonstrated that PrP\textsuperscript{\textbeta} accumulates in the taste buds of fungiform papillae in the tongue following intracerebral inoculation. They concluded that epithelial cells, neuroepithelial taste cells, or olfactory sensory neurons at chemosensory mucosal surfaces, which undergo normal turnover, infected with the prion agent could be shed and play a role in the horizontal transmission of animal prion diseases. According to Christina J. Sigurdson et al\textsuperscript{13} from California in 2009 the prion protein was upregulated in intestines and mesenteric lymph nodes of mice with colitis, providing a possible mechanism for the impact of colitis onto prion pathogenesis.

The brains of patients with prion disease frequently show no recognisable...
abnormalities on gross examination at necropsy; however, microscopic examination typically reveals characteristic histopathologic changes, consisting of neuronal vacuolation and degeneration, which gives the cerebral grey matter a microvacuolated or ‘spongiform’ appearance, and a reactive proliferation of astroglial cells. Although spongiform degeneration is frequently detected, it is not an obligatory neuropathologic feature of prion disease; the presence of astro-gliosis and micro-gliosis, although not specific to the prion diseases, is more constantly seen. The lack of a lymphocytic inflammatory response is also an important characteristic.\(^6\)

The discovery that proteins could be infectious represented a new paradigm of molecular biology and medicine. Although originally deemed heretical, this protein-only model is now supported by a wealth of biochemical, genetic and animal studies. Moreover, the concept of prion diseases has important implications for other neurodegenerative disorders. Recent studies with amyloid β, tau, α-synuclein, huntingtin and superoxide dismutase one suggest that molecular and cellular mechanism that were first discovered in studies of prions are involved in the pathogenesis of other neurodegenerative disorders associated with the accumulation of misfolded proteins, including Parkinsonism, Huntington disease, amyotrophic lateral sclerosis (ALS) and Alzheimer disease.\(^2\)

**SPORADIC PRION DISEASES:**\(^{1,2,14,15}\)

**Sporadic Creutzfeldt-Jakob disease:** The presence of spongiform changes and sparse PrP\(^{Sc}\) distribution in CNS of sCJD patients are the hallmark of neuropathology of the disease. The deposits of amyloid plaques may occur. On the basis of clinic pathological findings, different variants of sCJD have been described. Amaurotic or Heindenhain variant is characterized by rapidly progressive dementia, myoclonus, visual disturbances such as hallucinations, visual agnosia and cortical blindness, and short disease duration; Brownell and Oppenheimer variant is characterized by an early and predominant cerebellar ataxia and relatively late dementia; the thalamic form characterized by dementia and movement disorders; while the panencephalic Japanese variant is characterized by high amount of cells in CSF, profound damage of the white matter and a very slow disease course.

**Sporadic fatal insomnia:** The patients show clinical and neuropathological signs similar to Familial Fatal Insomnia (FFI) but family history and mutations in PRNP were not evident and the patients were mostly 129 MM homozygotes and biochemical strain typing of these disease subtypes revealed the only difference in the intensity of the unglycosylated fragment of PrP\(^{Dis}\) type 2; the unglycosylated fragment was under-represented in FFI.

**Varially protease-sensitive prionopathy (VPSPr):** A novel form of atypical dementia. A more distinctive feature based on which the disease was named initially as “protease-sensitive prionopathy” (PSPr) was the reduced resistance of PrP\(^{Dis}\) isoforms to proteolysis by PK. The proteolysis of PrP\(^{Dis}\) isoforms by PK resulted in more than 3 PrP\(^{Dis}\) fragments.

**Hereditary Prion Diseases:**\(^{2,15,16}\) The human familial forms include three major groups: (i) Creutzfeldt-Jakob disease (CJD), a subacute dementing illness usually associated with cerebellar signs, myoclonus, and spongiform degeneration; (ii) Gertsmann- Straussler-Scheinker syndrome (GSS), a chronic condition characterized by ataxia, dementia, and the presence of amyloid plaques; and (iii) fatal familial insomnia (FFI), characterized by a loss of the ability to sleep, dysautonomia, selective atrophy of the thalamus, and usually no spongiform changes.\(^17\)

**Acquired Prion Diseases:**\(^{2,18}\) Acquired diseases are characterized by early psychiatric symptoms like depression, anxiety, social withdrawal, dysthesia later neurologic defects and cognitive decline. Iatrogenic CJD is caused by prion exposure of individuals during neurosurgical procedures such as implantation of human dura mater, corneal graft implantation, or treatment with human cadaveric pituitary extracts. Iatrogenic CJD is rare.

**Variant Creutzfeldt – Jakob disease:**\(^15\) The age of these patients was relatively younger between 16 and 39 years and they manifested a predominance of psychiatric symptoms instead of cerebellar ataxia or progressive dementia. Psychiatric and behavioural symptoms of vCJD may include agitation, aggression, depression, anxiety,
apathy, emotional lability, insomnia, poor concentration, paranoid delusion, recklessness, or withdrawal; a combination of two or more of these symptoms appears in most of the patients. Some patients may also show signs of sensory disturbance such as pain, paresthesia and dysesthesia. The neurologic symptoms occur at least 6 months after the onset of psychiatric symptoms and include cerebellar ataxia, cognitive impairment, involuntary movements which may be dystonic, choreiform or myoclonic. Incontinence of urine, progressive immobility, and akinetic mutism are the late onset signs. Death often occurs because of intercurrent infections. The mean age at onset of symptoms is 29 years, and the progression or total duration of the disease spans 18 months in average, which is similar to that is reported for kuru and iCJD linked to treatment with hGH.

**Prions in Oral Health Care:** Although the occurrence of prions in the oral cavity has been established for more than two decades, the awareness about the spread of this disease during dental care requires further emphasis. Of all the prion diseases sporadic CJD has been proved its transmission about three decades before. Infact the transmission of prions through contaminated dental instruments has been stated. Such transmission occurs through pulpal and gingival tissue. The most common manifestation of prions in oral cavity includes orofacial dysesthesia or paresthesia, as well as dyseusia or ageusia. The oral route of infection and transmission of prions has been suggested and also been established in several studies done in experimental studies.^{19,20,21}

**Diagnosis**

Susanne Krasemann et al in 2010\(^3\) investigated the result of intraperitoneal prion inoculation in rhesus monkeys. Apart from clinical signs the investigators also found an exponential increase of PrP\(^{Sc}\) in the brains of infected primates. Neuropathologic examination is the only way to achieve a definite diagnosis of prion disease. Classic electroencephalogram is usually done as a part of investigation procedures.\(^7\) Detection of surrogate markers such as such as 14-3-3 and total tau (t-tau) in the CSF. 14-3-3 proteins are a group of cytosolic polypeptides with regulatory functions, which are released in the CSF during neuronal damage. 14-3-3 CSF detection represents a significant supportive diagnostic tool only in the appropriate clinical context. Attempts are made to increase the sensitivity and specificity test by modifying the methodology of protein detection such as improved ELISA, immunoblotting and semi-quantitative western blot, paraffin embedded tissue (PET) blotting.\(^5\) Other markers for neuronal damage (neuronal specific enolase, a glycolytic enzyme, and S-100 beta protein, a glial protein) have also been tested during the past years, but currently they provide no added value to the test based on 14-3-3 and/or t-tau detection.

**Protein misfolding cyclic amplification (PMCA):**\(^1\) Apart from direct detection of the protein amplification of protein has been attempted for better expression. The theory behind the so-called prion *in vitro* conversion on which PMCA is founded, postulates that both PrP\(^{Sc}\) and PrP\(^{Sc}\) are required for PrP\(^{Sc}\) amplification to occur. In this technique, as in rPrP-PMCA, recombinant human PrP expressed by E. Coli is used as the substrate to be seeded by PrP\(^{Sc}\), although sonication is replaced by shaking at a relatively high temperature.

**Quaking-induced conversion (QuIC):**\(^1\) In this technique, as in rPrP-PMCA, recombinant human PrP expressed by E. Coli is used as the substrate to be seeded by PrP\(^{Sc}\), although sonication is replaced by shaking at a relatively high temperature. QuIC has ultimately gained more interest than PMCA as a detection technique with diagnostic applicability since it is apparently free from the potential drawbacks of the PMCA approach like the time taken, the complexity of the substrate and reliance on sonication, which is difficult to standardise.

The theoretical risk of transmission of the CJD during dental care through any contaminated instruments gives confirmation for such transmission. Prions are very much resistant to inactivation to conventional disinfection and sterilization procedures like the high temperatures of autoclaving methods. Henceforth the team of the dental practitioners should be very much aware of the precautions and principles needed for the required infection control to avoid or minimize the transmission of prions during dental care. According to the literature of the past decade there are three parameters to be integrated while considering the disinfection and sterilization to prevent the probable risk of transmission of prions. They are i) The patient’s risk of having a prion...
disease, ii). Comparative infectivity of different body tissues, and iii). The intended use of the equipment.\textsuperscript{22,23}

Sterilization precaution to be considered to prevent the risk of transmission of prions has been a great concern of controversies for decades. Risk of transmission of prions through contaminated burs has been established through animal studies. According to World Health Organization Consultation, the single use items and equipment such as disposable needles and anesthetic cartridges represented the safest method for minimizing the risk of transmission of residual infectivity. They could provide a guideline for reusable endodontic files, matrixbands and burs that might become contaminated with neurovascular tissue.\textsuperscript{24}

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<tr>
<th>Category</th>
<th>Methods</th>
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<tr>
<td>Incineration</td>
<td>• Use for all disposable instruments, materials and wastes.</td>
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<td></td>
<td>• Preferred method for all instruments exposed to high infectivity tissues.</td>
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<tr>
<td>Autoclave and chemical methods for heat-resistant instruments</td>
<td>• Immerses 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.</td>
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<td>• Immerses in NaOH or sodium hypochlorite (20 000 ppm available chlorine) for 1 h; transfer instruments to water; heat in a gravity displacement autoclave at 121°C for 1 h; clean and subject to routine sterilization.</td>
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<td>• Immerses in NaOH or sodium hypochlorite for 1 h; remove 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 h; clean and subject to routine sterilization.</td>
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<td>• Immerses in NaOH and boil for 10 min at atmospheric pressure; clean, rinse in water and subject to routine sterilization.</td>
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<td>• Immerses in sodium hypochlorite (preferred) or NaOH (alternative) at ambient temperature for 1 h; clean, rinse in water and subject to routine sterilization.</td>
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<td>• Autoclave at 134°C for 18 min (to be used for worst-case scenarios; i.e., brain tissue bake-dried on surfaces).</td>
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<td>Chemical methods for surfaces and heat-sensitive instruments</td>
<td>• Flood with 2 N NaOH or undiluted sodium hypochlorite; let stand for 1 h; nopp up and rinse with water.</td>
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<td>• For surfaces that cannot tolerate NaOH or hypochlorite, thorough cleaning will remove most infective agents by dilution, and some additional benefit may be derived from the use of one or another of the partially effective methods (chlorine dioxide glutaraldehyde, guanidinium thiocyanate [4 mol/L], iodophor, sodium dichloroisocyanurate, sodium metaperiodate, urea [6 mol/L]).</td>
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<td>Autoclave or chemical methods for dry goods</td>
<td>• Small dry goods that can withstand either NaOH or sodium hypochlorite should first be immersed in one of the other solution (as described above) and then heated in a porous load autoclave at 121°C for 1 h.</td>
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<td>• Bulky dry goods of any size that cannot withstand exposure to NaOH or sodium hypochlorite should be heated in a porous load autoclave at 134°C for 1 h.</td>
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Table 2: Infection control guidelines for TSE suggested by WHO\textsuperscript{22,24}

**Management**\textsuperscript{7,25}

Evidence is emerging that neurological symptoms in prion diseases precede neuronal loss and are due to an adverse effect of misfolded prion protein (PrP) on synaptic function. Therapeutic intervention, therefore, requires identification of the mechanisms by which abnormal PrP disrupts normal neuronal activity.

1. Antiviral medications such as amantidine, methisoprinol
2. Polyene antibiotic amphotericin B (AmB)
3. Anticonvulsants such as phenytoin, topiramate, quinacrine and chlorpromazine.
4. The non-opioid analgesic Flupirtine was used to counteract the neuronal toxicity.
5. Antioxidants such as coenzyme-Q, alpha-lipoic acid, nicotinamide adenine dinucleotide (NADH), vitamins C, E and B complex, multivitamin mineral mixture, L-glutamine, omega-3 fatty acids, magnesium, and a pureed mixture of fruits and vegetables in addition to parental glutathione and ascorbate are also used for the treatment but most of the cases there was a delayed and slow response for the treatment.
7. A conventional antipsychotic / neuroleptic – chlorpromazine
8. Tricyclic anti-depressents – Clomipramine
9. Pentosan polysulphate (PPS) is a polysulphonated polyglycoside and heparin mimetic
10. Recently tetracyclines, particularly doxycycline, as a potential treatment option.

In the field of human prion disease therapeutics, one can observe the transition from antivirals to prion conversion inhibitors. Novel approaches to treatment such as vaccines, RNA interference, and anti-inflammatory agents, among others are being examined in the laboratory setting in the hope that these therapies can be used in humans affected by prion disease.

Conclusion
Prion diseases have been clouded by mystery since the description of scrapie, human TSEs and elucidation of the prion hypothesis. Despite tremendous advances in knowledge about these uncommon diseases, major questions remain still unclear.7 The risk of transmission of prions through dental procedures draws our attention towards the need to maintain optimal standards of infection control and decontamination procedures for all infectious agents, especially prions.22 Standard procedures of precaution should be followed even in suspected cases, however additional precaution may not be required.23

Novel approaches to treatment such as vaccines, RNA interference, and anti-inflammatory agents, among others, are being examined in the laboratory setting with the hope that these therapies can be used in humans affected by prion disease. Perhaps one of the most popular approaches to treatment is to block neuronal PrP, which has been done successfully in animal models.7 Recent advances in amplification and detection of prions led to considerable optimism that early and possibly preclinical diagnosis and therapy might become a reality. Although several drugs have already been tested in small numbers of sCJD patients, there is no clear evidence of any agent's efficacy.2

Acknowledgements
We would like to thank all the staff members of the Department of Oral Pathology for their support.

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Source of Support: Nil, Conflict of Interest: None Declared.