Role of prions in endodontics -"A Review"

Atul Jain[1], Anukreti Agrawal[2,*], Rachana Bahuguna[3], Deepa Davis[4], Shantwana Singh[5]

[1,3]Professor & HOD, [2,4,5]PG Student, Dept. of Conservative Dentistry & Endodontics, [3]Dept. of Pedodontics & Preventive Dentistry, RKDF Dental College & Research Centre, Bhopal, Madhya Pradesh, India

***Corresponding Author:**
Email: anuagrawal56@gmail.com

Abstract

Endodontic treatment could result in cross infections, from prions. This could result by transmission as a result of inadequate sterilisation of the previously used endodontic instruments in an infected individual. A review search was carried out online and 47 articles were found. Based on the preselected inclusion and exclusion criteria 22 articles were selected.

The normal prion protein is found throughout the body and is non-infectious. As a result of conversion in the protein structure is transformed to an infectious form. The latter results in various diseases can be carried out. Identification of the prion diseases can be carried out with the help of specific biomarkers, found in tissue or body fluid.

Prion diseases cannot be cured but there progress might be slowed down. The most effective form of treatment for these diseases is prevention of transmission, which could be carried out by proper sterilisation and infection control.

These diseases run a rapid course with majority of patients dying within a year. During endodontic treatment, files used for biomechanical preparation are highly susceptible towards adherence of this entity, owing to their unique configuration. The normal sterilisation process is not adequate to eliminate the infectious form of the prions. Another major source of cross infection is the air retention system in dental and suction unit.

Prion diseases are a group of fatal neurodegenerative disorders with no known cure. Adequate precautions in spread of the infection form of prions during endodontic treatment, is the most effective way of preventing these diseases.

Keywords: Scrapie disease, Creutzfeldt–Jakob disease, Transmissible spongiform encephalopathies, Misfolded PrP.

Introduction

Endodontic treatment is fraught with the possibility of cross-infections. Conventionally, bacteria, fungi and viruses, have been implicated in the cross-infections but of late, another entity has been added to this list viz. 'PRIONS'.

Prions were discovered by Stanley B. Prusiner. He implicated these infectious transmissible protinaceous particles in animal. A Transmissible spongiform encephalopathies (TSE) derived from scrapie in sheep.[1] Subsequently other diseases like Bovine spongiform encephalopathy (BSE), Creutzfeldt–Jakob desease (CJD) and its variant (vCJD), Gerstmann– Straussler–Scheinker disease, Kuru and Fatal familial insomnia were found to be caused by prions.[1] In the dental perspective, prions have a high possibility of transmission during endodontic treatment.[2] This transmission usually takes place as a result of inadequate sterilisation of the previously used endodontic instruments, in an infected individual. Although relatively uncommon, these agents have been implicated in Creutzfeldt–Jakob disease (CJD) and its variant (vCJD).[2]

Transmission of these diseases, does not take place through contact nor are they transmissible through inhalation.[3] A few cases have been reported, resulting from blood transfusion. In dentistry, there are two known route of transmission for these agents, accidental abrasion of lingual tonsil by infected instrument and by direct contact with the dental pulp tissue.[4] When endodontic instruments are reused, there is a high risk of cross infections, if sterilisation is not adequate.[5]

This review article is an attempt to analyse the structure, physiology, mode of transmission, resultant diseases and prevention of cross infection of prions.

Methodology

For data collection search was carried out online on various sites: Pubmed, Medline, Research Gate and EBSCO. For search-words and phrases:- 'Prions', 'Diseases due to prions', 'Prevention of diseases due to prions' and 'Prions in dentistry' were used in various combinations. 47 articles were found, out of which 22 were selected. The selected articles comprised of research and review articles.

Inclusion Criteria: Review and research articles on prions comprising of studies on their structure, physiology, resultant diseases and their treatment in humans.

Exclusion Criteria: Studies conducted on animals were excluded.

History of prions

In 18th century, Spanish shepherds observed a disease that compelled their Merino sheep to scrapie. In the late 19th century, Robert Koch published his postulates for defining causative agents of disease.

Later in 1982, Stanley B. Prusiner of the University of California, San Francisco and his team found an infectious agent that consisted of a specific protein, which was coined as prion. The specific protein, that

the prion is composed of, is also known as the Prion Protein (PrP). This protein occurs both in infectious and non-infectious forms.[6]

Structure of prions

The normal prion protien (PrP) is found throughout the body, even in healthy people and animals. The normal form of the protein is called PrP^{C}, while the infectious form is called PrP^{SC} (where the C refers to 'cellular' PrP, while the Sc refers to 'scrapie').[7]

PrP^{C}

Prion protein in its original form, referred to as PrP^{c}, is a cell-surface protein, which is present in numerous cells, especially in neuronal cells. The normal protein is not sedimentable. It has 209 amino acids (in humans), one disulfide bond, a molecular mass of 35–36 kDa and predominantly alpha-helical structure. Several topological forms exist; one cell surface form anchored via glycolipid and two transmembrane forms.[8]

PrP^{sc}

The infectious form of prions is called PrP^{sc}, which is formed as a result of conversion of the normal PrP^{c} proteins through alteration of its conformation, or shape; which in turn, alters the way, the proteins interconnect, causing prion diseases. It has a higher proportion of β-sheet structure, in place of the normal α-helix structure and is resistant to proteases. The exact structure of PrP^{SC} is not known, collection of these abnormal isoforms constitutes the structured amyloid fibers, which accumulate to form plaque. The end of each fiber, acts as a template onto which free protein molecules may attach, allowing the fiber to grow. Under most circumstances, only PrP molecules with an identical amino acid sequence to the infectious PrP^{sc} are incorporated into the growing fiber.[7]

Phsiology

PrP^{c} protein has predominant positioning in central nervous system, although it is present though out the body tissues. It is involved in numerous physiologic functions, the most prominent being:

1. Neural reactions.[9]
2. Immune response comprising of memory and reactivity in inflammation.[9]
3. Programmed cell death.[9]
4. It is an integral part of several transduction pathways like mitogen activated proteinkinase cyclic AMP/Proteinkinase A, mitogen-activated protein kinase, phosphatidylinositol 3-kinase/Akt pathways, as well as soluble non-receptor tyrosine kinases.[9]
5. It is an integral part of plasma membrane domains, as well as endocytic pathways.[9]

Diseases caused by prions

Following diseases have been confirmed to be caused by Prions in humans:

In humans

1. Creutzfeldt-Jakob Disease (CJD)
2. Variant Creutzfeldt-Jakob Disease (vCJD)
3. Gerstmann-Straussler-Scheinker Syndrome
4. Fatal Familial Insomnia
5. Kuru

Identification and diagnosis

Identification of prions disease, can be carried out by specific biomarkers, in easily accessible tissues or body fluids. Misfolded PrP accumulates in the CNS and other tissues of infected hosts. PrPsc can be detected by western blot or immunohistochemistry methods after removing the cellular isoform.[10]

Potential Assays for the Detection of Misfolded PrP in Blood are: Immunocapillary Electrophoresis (ICE), Surface Fluorescence Intensity Distribution Analysis (Surface-FIDA), Ligand-Based Immunoassay, Solid-State Binding Matrix, EP-vCJD Blood Screening Assay, Conformation-Dependent Immunoassay (CDI), Misfolded Protein Diagnostic Assay (MPD), Multimer Detection System (MDS).[10]

Clinical diagnosis: Clinical features of TSEs include fatigue, insomnia, depression, weight loss, headaches, general malaise, and ill-defined pain sensations. In addition, neurological presentations, like-extrapyramidal signs, cerebellar ataxia, pyramidal signs, cortical blindness and psychiatric features are present.[11] Definite diagnosis of prion diseases can only be given after histopathological examination of biopsied or autopsied brain material. Clinical tests like detection of proteins in cerebrospinal fluid(CSF), the patterns of electroencephalogram (EEG) and technologies such as computer tomography(CTScan) and magnetic resonance imaging (MRI)can be used.[10]

Histological diagnosis: Prion related diseases can be diagnosed by their signature histological features of spongiform changes, astrocytic gliosis and amyloid plaques. Neuropathological examination of brain tissue from an animal or humans is the hallmark for TSE diagnosis.[12] This analysis includes detection of vacuolation within specific brain regions by light microscopy and can be applied to the analysis of different prion strains.[10]

Treatment and prevention

Prion diseases cannot be cured, but the progress might be slowed.

Prevention of the disease from transferring from one patient to other, is most effective and important. It can be done by taking precautions like maintaining proper sterilization and infection control, since prions are heat resistant and bind tightly to surgical steel

instruments[13]. Recommended methods for sterilisation are:

In confirmed patients: Disposable instruments should be used and later subjected to incineration.

In high risk patients: Heat resistant instruments should be immersed in NaOH for 1 h; instruments are transferred to water; heated in a gravity displacement autoclave at 121°C for 1 hr; cleaned and subjected to routine sterilization.[14]

Heat sensitive instruments should be flooded with 2 N NaOH; allowed to stand for 1 hr; mopped up and rinsed with water.[14]

Dry instruments should be heated in a porous load autoclave at 134°C for 1 hr.

Discussion

Stanley B. Prusiner identified prions in Scrapie disease.[15] He found prions to have predominant populance in the nervous tissue. According to Chesebro[16] and Race[16] prions are not a harmful entity. Once the structure of prions is altered, they are capable of causing a wide range of neurodegenerative diseases, most of which do not have a cure.[1] In 1920, neurologists Hans Gerhard Creutzfeldt and Alfons Maria Jakob discovered CDJ and its variants[16]. Safar et al. 1993, 1998; Bessen and Marsh 1994; Telling et al. 1996 conducted separate studies on structure of infectious prions, idendified the differences between the normal and infectious forms. They found the latter, to posses higher proportion of β sheets, which was attributed to the alteration of amino acid sequence in the former.[17-19]

Prions were unknown as an infectious agent to dentistry till Prusiner SB (1982) pointed out their role as an infectious agent. [16] Although they do not spread by inhalation, but they are transferable through blood and contaminated endodontic instruments.[20]

Prions do not have a widespread role in communicable disease as related to endodontics but WHO identified the route of transmission being highly significant for the prions during endodontic treatment via contaminated instruments. Endodontic files used for bio-mechanical preparations are highly susceptible towards adherence of this entity, owing to their unique configuration.[20] Endodontic files poses multiple lands and edges, which render them prone towards harbouring these entities.[20] The normal sterilisation employed for these endodontic instruments, is not adequate to get rid of the infectious prions. WHO in year 1999 came out with detailed protocol for sterilization of endodontic instruments infected by prions.[21]

The possibility of these diseases resulting from prions through endodontic treatment is limited. All the same, these diseases are quite fatal. They run a rapid course with majority of patients dying within a year.[22] Hence, WHO emphasised the fact that due precautions should be taken for prevention of spread of prions during endodontic treatment. It would be best, if disposable instruments were to be used, for each patient. Since disposable instruments are used in limited number of clinics, the emphasis has to be upon following the exact protocol for sterilisation of these instruments. Studies also show that the spittoons used for the patients suffering from these diseases, should be incinerated after use.[23] Another major source of infection is the air retention system in the dental and suction units.[24] Thus, it becomes important to properly clean and disinfect the whole tubing of the dental chair and the suction unit.[25] It has been suggested by the WHO that only specialised and highly skilled staff should handle the histologic sample of the high risk patient.[21]

Conclusion

Prions diseases are a group of fatal neurodegenerative disorders, with no known cure. They resist conventional sterilization methods. Although there appears to be very low risk of CJD transmission during dental procedures, account must be taken of this possibility. Appropriate medical and family history should be taken from all the patients before dental procedures, which would indicate taking adequate precautions and measures.

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