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A CLINICAL NOTEWORTHY BRIEF REVIEW ON PRION DISEASE

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ABSTRACT

Prion disease is a rare inherited autosomal neurodegenerative disorders whose exact reported prevalence is still unknown. Prions are proteinaceous infectious agents without any nucleic acid. These agents are also termed 'Transmissible Spongiform Encephalopathies (TSEs)' which also caused 'Mad cow disease' in other animals as termed 'Brain eater agents'. But various clinical studies are suggested that this disease affects about one person per million worldwide each year. This disease is deteriorated the neuronal conditions with the time that impair brain function, loss in memory, personality disorder and behavior fluctuation, a decline in intellectual function (dementia) and abnormal gait movements and ataxia. The signs and symptoms of prion disease is typically begun in adulthood and progressively worsen with time, leading to brain death within a few months to several years. In, this disease, one copy of the altered PrP gene in each cell is sufficient to cause this neural disorder. In most of the cases, an affected person inherits the altered gene from one affected parent. So, genetic counseling and effective genetic analysis are played very important role to diagnose Prion disease at right time with their existing lethal symptoms during onset of this disease. This disease must be diagnosed, treated and managed well at right time in recorded cases of Prion diseased patients with effective neuroprotective and suggestive clinical measures along with palliative care. Then, it can be medically managed to control its clinical and genetic burden in affected population of any country worldwide.

KEYWORDS: Prion disease; neurodegenerative disorder; ataxia; PrP gene; Prion diseased patients.

1. INTRODUCTION: PRION DISEASE

Prions are proteinaceous infectious agents without any nucleic acid. These agents are also termed 'Transmissible Spongiform Encephalopathies (TSEs)' that caused Prion disease in human and some animals where it is called 'Mad cow disease'. Due to not having nucleic acid, its chemical encoded chemical informatios are very difficult to map and still it is known. This disease is inevitably manifestated by several fatal neurodegenerative conditions that affect humans and a wide variety of animals.[1] Prions diseases may present as genetic, infectious, or sporadic disorders, all of which involved in alteration or modification of prion protein (PrP).[2] The word prion, coined in 1982 by Stanley B. Prusiner, is derived from the words protein and infection, in reference to a prion's ability to self-propagate and transmit its conformation to other prions.[3] Prions (proteinaceous infectious particles) are responsible to cause spongiform encephalopathies (SSE) in man and animals.[4] Prusiner was also received nobel prize in medicine in 1997 for his research on prion. Its 30 pathogenic mutations have now been described and all causing autosomal dominantly inherited diseases in which different mutations exhibit wide phenotypic variability, even within affected families carrying the same mutation.[5] Prion diseases may present with certain morphological and pathophysiological features that parallel other progressive encephalopathies, such as Alzheimer's and Parkinson's disease.[6] The only unique feature among other reported neurodegenerative disorders is that it is a transmissible. There is no cure for prion diseases and most don't have any type of effective available treatments that making its clinical implications more difficult to managed its relative socio-economic burden in the prevailing populations of the affected individuals worldwide.

2. EPIDEMIOLOGY: PRION DISEASE

Prion disease is reported to be occurred worldwide with an incidence of 1 per 106 population per year.[7] CJD (Creutzfeldt–Jakob disease) is the most common type of 'Human Transmissible Spongiform Encephalopathies (TSEs)' and also called Prion disease. Spielmeyer is introduced term CJD to describe a human neurological disease as Prion disease that was characterized by rapidly progressive myoclonus, ataxia and dementia.[5] Previous findings are also reported that CJD can be classified as sporadic Prion disease (sCJD), familial Prion disease (fCJD), iatrogenic Prion disease (iCJD) and variant Prion disease (vCJD). Iatrogenic Prion disease caused by cadaveric HGH (a growth hormone treatment) has been reported in seven countries with the highest number in

France (74 cases), the United Kingdom (35 cases), USA (22 cases) and New Zealand (5 cases) in 2000.[8] Sporadic prion disease generally presents in the seventh decade or later and has a typically short course (average 4 to 6 months). In contrast, inherited forms usually start at a younger age with its onset symptoms and have a more protracted course. About 15% of cases of prion disease are autosomal dominantl inherited, although this estimate may be spuriously low because of the variability in clinical phenotype and often its late onset in some patients. Iatrogenic Prion disease (iCJD) has resulted from neurosurgery (including the use of EEG depth electrodes), corneal grafting, human dura mater implants or exposure and administration of human cadaveric growth hormone (hGH) and human pituitary gonadotrophin (hGNH).[8,9,10] The incidence of sporadic Prion disease is found to be between 0.5 and 1 per million inhabitants per year, varying from around 0.5 per million inhabitants in Japan; around 0.75 cases per million in England, France and Germany.[9,10,11] However, due to the age-distribution of cases with sporadic Prion disease, the incidence is above 3 per million per year in the 65–74 year-old group and lower than 0.2 per million in those below 40 years of age.[12] The mutation in codon 200 with a glutamate to lysine substitution in PrP is a frequent mutation in familial Prion disease described in more than 60 families. The largest cluster of this mutation is found in Jews of Libyan origin.[13] In coming years, it can be expected that the number of familial Prion disease cases and mutations identified will increase with more patients suspected of having Prion disease genotype.[12]

3. PATHOPHYSIOLOGY: PRION DISEASE

All the reported types of Prion diseases are characterized by the accumulation of misfolded prion protein (PrP) and associated with their widespread neurological damages. Rising levels of misfolded PrP is lead to sustained dysfunction of an endogenous cellular pathway, the unfolded protein response (UPR), which regulates protein synthesis at the translational level. It was resulted into the sustained reduction of protein synthesis rates in neurons that lead to synaptic failure followed by permanent neuronal death causing dementia and cognitive failure. Therefore, UPR alteration is somewhat found to be reported that it can be restored at protein synthesis levels in neurons that might be used potentially an important new therapeutic strategy for other neurodegenerative disease. There are three PrP species, the normal noninfectious cellular isoform PrPC, the full-length infectious form PrPTSE and PrP27–30 which is formed after partial proteolysis of PrPTSE. The nascent PrP molecule is approximately 250 amino acids in length. It has an amino-terminal signal peptide and a hydrophobic carboxy-terminal domain for membrane attachment via a glycosylphosphatidylinositol (GPI) anchor.[14] Although PrP is predominantly found in brain tissue, high levels are also present in the heart, skeletal muscle and kidney, in liver with notable concentration.[15]

In 1986, a other type of Prion disease, a Transmissible spongiform encephalopathy (TSEs) was also found in cow, called ‘bovine spongiform encephalopathy (BSE)’ or 'mad cow disease'.[16] Most likely it has been transmitted to cows via using infected feeding materials which presumably transmitted in to humans causing new variant CJD (nvCJD).[17] Most clinical studies are postulated that “protein-only” model according to which the transmissible pathogen is a misfolded form of the normal cellular prion protein (PrPC) and The rouge conformer, PrPSc. Those are believed to propagate by binding to PrPC and acting as a template to alter its refolding into the abnormal PrPSc isoform.[18] The N-terminal of contains 5 repeats of an 8 amino acid sequence and mutations in this region, resulting in addition of integral numbers of additional repeats, lead to forms of inherited prion disease.[19]

A couple of hypothesis, it was postulated that the normal functions of PrPC and PrPC are expressed constitutively on the neuronal cell surface by a glycosyl phosphatidylinositol (GPI) anchored proteins, suggesting that PrPC may function as a receptor or adhesion molecules.[20] The route of entry of prions was found to be followed the oral exposure that may follow invasion of Peyer’s patches (aggregated lymphoid modules) and other gut lymphoid tissues. The relative protease resistance of prions are also presumably allowed a significant proportion of infectivity to its survival in the digestive tract.[19]

4. NEUROPATHOGENESIS: PRION DISEASE

Neuropathogenesis of prion diseases is found to be evolved in complex ways whereas intracellular accumulation of PrP forms might significantly impair cell function and lead to cytopathology, mere extracellular deposition of PrPTSE as a direct cytotoxic factor.[21] Tissue damage may also result from several parallel, interacting or subsequent pathways that involve cellular systems associated with synapses, protein processing, oxidative stress, autophagy and apoptosis.[22] Several neurotransmitter systems are damaged such as including acetylcholine; GABA (Gamma-aminobutyric acid; dopamine and lead to lethal synaptic alteration in Prion diseased patients.[23] Dendritic atrophy is also reported a prominent feature of prion diseases.[24] The key features of Prion disease mechanism are the pathogenic process which is initiated by amyloid structures different from PrPSc that accompanied by a long clinically silent stage. Other form is characterized by the accumulation of atypical transmissible PrP forms that have limited neurotoxicity before PrPSc emerges in diseased population.[25]

5. DIAGNOSIS

Initial diagnosis of prion diseases is required histopathological examination of brain tissue followed by autopsy, biochemical analysis, immunohistochemistry, molecular diagnostic methods e.g. Western blot and available genetic analysis e.g. PrP

gene sequencing and mapping to confirm the type of prion disease. Certain chosen diagnostic approaches such as electroencephalography (EEG) and MRI are also helped to know the elevated level of tau protein in cerebral spinal fluid (CSF) which is mainly responsible for rapidly progressive dementia in diseased patients and animals.[26] MRI of the brain is observed a remarkably good diagnostic test considering abnormal signal change on fluid-attenuated inversion recovery, or diffusion-weighted imaging in the caudate, putamen, thalamus and cortex in brain during its established clinical phase.[27] Sandwich CDI (conformation-dependent immunoassay) for PrPSc and histological based autopsies of brain have been done by Hematoxylin and Eosin staining (H&E staining) to know the pathogenesis of Prion disease in affected individuals.[28]

6. TREATMENT

Current therapeutic efforts are centered on the assumption that disease is occurred due to the transformation of PrPc to PrPres and subsequent accumulation of this protease-resistant isomer in neurons.[29,30,31] It can also be presumed that it can be managed well by direct inhibition of this conversion, its degradation and its interference with important accessory molecules (Fab, glycosaminoglycans) or altering PrPc expression and cell surface localisation which must be considered the important target strategies.[31,32,33] Quinacrine (an antimalarial drug) and chlorpromazine (a widely used antipsychotic drug) were found to be effective inhibitors of PrPsc formation in vitro.[34,35] Other reported therapeutic measures have been used for the treatment of Prion disease includeing (1) Preventing the actions of PrPSc using compounds that reduce PrPSc accumulation in prion-infected cell culture models such as quinacrine; (2) Preventing the conversion process by locating the associated ligands that can bind to and stabilize PrPC such as the use of antibodies that bind or sequester PrPC, or methods which downregulate PrP transcription or translation; (3) Elimination of PrPC by RNAi gene suppression; (4) Repair of neuronal damage by using stem cell therapy or neuronal precursor cell therapy; and (5) Enhanced administration of natural prion clearance agents called antioxidants such as Vitamin A, Vitamin C and Vitamin E.[36] Uss of lentiviral mediated RNA interference (RNAi) was also reported quite effective against native prion protein (PrP).[37,38] Other therapeutic clinical trials were also reported for the treatment of Prion diseases e.g. pentosan polysulfate; thioflavine; amphotericin B; Tricyclic; Desipramine; Lithium chloride; immunotherapies administrated by active and passive immunization might stimulating antibody induced phagocytosis; antibody disruption of peptide aggregates; mobilisation of toxic soluble peptides; stimulation of cell mediated immunity mechanisms.[39,40]

7. CONCLUSION

From this review, it was found that the existence of different PrPSc forms might be a common denominator of Prion diseases in humans and animals. The exact mechanism of neurodegeneration caused by this disease is not yet known because of proteinaceous nature of its infectious agents, altered PrPs. But still, it is believed that alterations of PrP and subsequent deposition of prion protiens in the CNS triggers certain abnormal neural mechanisms leading to apoptosis, autophagy and oxidative stress that damage the neurons with the time. Many methods including RNAi silencing and other immune-therapeutics have been used to combat these diseases but still no exact cure have been found. Hence, most important clinical criteria must be opted to managed this disease by adopting cost-effective medical diagnostic measures, timely genetic counseling, pedigree analysis, effective treatments, supportive socio-economic to the diseased individuals and their family to plan its better suggestive and genetic measure for the risks passing into next generations via genetic inheritance.

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