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PRION DISEASES IN HUMAN: UNDERSTANDING AND FIGHTING BACK

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ABSTRACT

Prions are smallest infectious particles. They are protein in nature and possess ability to reproduce by their own. Prions cause various types of diseases in animals including human beings. Accumulation of misfolded proteins in brain causes different types of neurodegenerative diseases. Prions are considered one among those disease causing misfolded proteins. Besides, prions can multiply. In 1982 the term "prion" was coined by Dr. Stanley Prusiner and he won the Nobel Prize in Medicine and Physiology in 1997. Prions are responsible for causing diseases like Classic CJD or Creutzfeldt-Jakob disease, Kuru, Fatal Familial Insomnia, Gerstmann–Straussler–Scheinker disease, in humans. Prions are only proteins, they are not alive .It is not possible to kill already not living entities like prion. Search for ways or drugs to destroy dangerous prions are in search around the globe. We need a better understanding of prions, their nature, molecular mechanism of prion infection and transmission and pathophysiology of prion diseases in order to strengthen and win against the deadly prions.

KEYWORDS: Prion, Creutzfeldt-Jakob disease, Kuru, Fatal Familial Insomnia, Gerstmann–Straussler–Scheinker disease, pathophysiology.

INTRODUCTION

The name prion is derived from "Proteinaceous Infectious particle.[1] They can occur in two forms called PrP-sen and PrP-res. Prion diseases are incurable and degenerative in nature.

Prions not only infect humans but also infect cattle also and cause diseases like scrapie disease in sheep, bovine spongiform encephalopathy (BSE) in cow, chronic wasting disease in deer[2] etc. In human prions are found to infect primarily the nervous system. As initially the causative agent of the diseases caused by prion were not recognised and well understood, it was difficult to target and destroy the pathogen. Later it was discovered that prion diseases are infectious and they were doubted to be similar to viruses as prions could pass through pores like viruses. Then, incubation period of prion diseases came to light and was found to be longer than those of viral diseases.[3]

Prions cause several types of diseases in human beings. Those are fatal and irreversible. Variably protease sensitive prionopathy (VPSPr) is a newly recognised disease caused by prions in humans. Though prion diseases are rare. But the most scarybthing about prion diseases is that they are practically incurable i.e., there is no cure for prion diseases yet. They are progressive and mostly neurodegenerative.[4] They develop slowly. A glycoprotein of 33-35kD, produced by the PrP gene has been recognized as the responsible protein of prion. Its highly resistant to proteases, insoluble and is found only in infected organisms. The protein accumulates in brain of person suffering from prion disease and causes the symptoms of the disease. Scientists have found that PrP gene if knocked out in mice, makes them immune to prion diseases.[5]

Types of Prion Diseases in Humans

Human prion diseases are primarily of three different types depending on the mode of occurrence i.e.,

- Genetic
- Sporadic and
- Acquired

Another relatively newly described human prion diseases is Variably protease sensitive prionopathy (VPSPr). The etiology of this disease is not yet recognised.[6]

How Prion diseases are transmitted?

Genetic prion diseases are inherited genetically and are rare. Genetic prion diseases is actually related to a mutated gene i.e., the rion protein gene gets mutated in individual and produce abnormal prion protein. The gene is autosomal dominant. Therefore if any of the parents have the mutated gene there remains a 50% chance of inheritance of the mutated gene

to his progeny. Genetic CJD, Fatal Familal Insomnia (FFI), and Gerstmann Sträussler-Scheinker Syndrome (GSS) are the three genetic prion diseases recognised in humans. The diseases are different from each other with respect to their symptoms and neuropathology.

Aquired Prion diseases are transmitted from one individual to another like viral diseases do. Aquired prion diseases may be transmitted from an animal to a human being or from another human being.[6] Acquired prion diseases are primarily of three types i.e., Kuru, Variant CJD and Iatrogenic CJD. Iatrogenic CJD gets transmitted during the medical or surgical procedures.[6] Studies reveal that Iatrogenic CJD may get transmitted by transplant of dura and cornea, by using the same surgical tools which has already being used on some CJD patient, use of contaminated EEG depth probe or may at times through blood transfusion from infected person.[5] Variant CJD also occurs from contamination of human food by from BSE (Bovine Spongiform Encephalopathy). The prion fund in BSE is very similar to that found in Variant CJD in human.[6] Transmission of prion from cattle to human is termed as primary transmission while that from human to human is called secondary transmission.[7]

Sporadic CJD is the most vastly occurring CJD and occurs all around the world; The cause of such prion diseases is not yet known but they are equally transmissible as other prion diseases.[6] The duration of illness, age of onset and the symptoms of variant and sporadic CJD are a lot different. Also, the abnormal modified protein 'prion' is different in variant and sporadic CJD.[6,7]

Pathophysiology of Prion infections

The protein responsible for prion diseases is PrP which is an abnormal protein. Studies show that on Western blot, PrP produces three distinct bands.[3] It is further interesting to note that Prion diseases are species specific. Prion protein is expressed in most tissues in adult people. Though the highest amount is found in the central nervous system as well as in the immune system.[8] Prions are chemically sialoglycoprotein, with high concentration of alpha helical structure and are found on cell surfaces. Prion proteins have high affinity for copper and this finding suggests that the protein may be probably involved with transport of copper and copper metabolism.[9,10] There is a complex relationship between infectivity and toxicity of misfolded proteins like prions.[11] Prion proteins do not significant amount of nucleic acid.[12] Prions accumulate in the nervous system and cause pathogenic symptoms which vary in different types of prion diseases. The symptoms of Kuru includes myoclonus, unsteadiness of gait, slurring of speech, dysarthria, tremor, uncoordination extremities initially. Later stages

include, inappropriate laughter and extreme depression, impairment of cognitive function, urinary and fecal incontinence, dysphagia (difficulty swallowing), lapse into coma, and lose control of breathing. Prions have been revealed to destroy the proteostatic mechanisms in an individual and thus induce misfolding of proteins and cause prion diseases.[3,11]

Therapeutics of Prion Diseases & Anti-Prion Agents

Complete understanding of the structure of prion proteins, their mode of trandmission and mechanism of infection is necessary for investigating a full proof cure against prion diseases and for finding a therapeutic agent against prion diseases. There are several compounds reported which have potent activity against the onset of prion diseases. But most of these compounds have been found to prevent the onset of prion diseases. Unfortunately, none them have been found to cure prion diseases. Though the fact that those therapeutic agents interact with prion proteins and thus slow down the progression of prion diseases, ignites the hope of that at least it is possible to delay the progression of prion diseases. Some such compounds recognised are dextran sulphate, pentosan polysulfate.[13] congo red, β- sheet breaker peptides, anthracycline.[14] Those are the compounds reported as anti-prion agents and are known to interact with prions and delay the progression of prion diseases.[3] Again the bad news is that those anti-prion compounds are either toxic in nature and their bioavailability is considerably poor.[13,14]

CONCLUSION

Though prion diseases are not yet that common in the Indian sub continent compared to the that of the European and American countries, yet as the disease is highly transmissible it can any time begin as a outbreak in India also like in other parts of the world. Studies have revealed that the underlying pathophysiology of prion infection and neurodegenerative diseases is related to prion induced disruption of the proteostatic mechanism of the organism. A detailed and better understanding of the progression of various prion diseases is inevitable for finding new weapons against prion diseases. We have in hand therapeutic agents who can delay the progression of prion diseases and can prevent prion infection to some extent. But they are not full proof and we need to find out therapeutic agents who can cure prion diseases and eliminate prions from an organism's body forever.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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