

## Prion Diseases in Animals and Human Beings

Navya Sri Bairi<sup>1</sup>, C.V. Savalia<sup>2</sup>

College of Veterinary Science, Navsari, Gujarat

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A group of proteinaceous infectious pathogens known as 'Prions', which cause fatal neurodegenerative illnesses in man and animals, through entirely *de novo* mechanism. Transmissible Spongiform Encephalopathies (TSE) - a group rapidly progressive and rare fatal neurologic disease conditions caused by prions. It affects humans and mammals like sheep, goat, bovine, cattle and felines. The word 'Prion' was coined by Dr. Stanley B. Prusiner in 1982, which is derived from 'protein and infection'. A Prion, is proteinaceous infectious particle, neurotropic, radiation and heat resistant, sensitive to protease, devoid of nucleic acid, forms amyloid fibrils, and has high  $\beta$ -helices (normal proteins are high in  $\alpha$ -helices).

### History

The history of prion began in the 18th century, with emergence of strange disease affecting Merino sheep to pathologically scrape against fences, a defining clinical sign that led to the disease being named 'Scrapie'. In the early 20th century, pathologists, Creutzfeldt and Jakob described a neurodegenerative disease, which was later included with Scrapie into a group of diseases known as TSEs.

### Scenario In India

Over the period of span from 1968 to 1997, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, registered 69 cases of CJD from different parts of India. From 1990-1998, Department of Neurology, G.B. Pant Hospital, New Delhi admitted 10 cases of CJD from North India various studies have reported annual incidence of 0.5-1 cases of CJD per million of general population. Variant CJD was recorded in Karnataka and Kerala in 1991.

### Etiology

The nature of etiological agent was under discussion for many years. The result of the infection was described as the accumulated abnormal prion protein in the central nervous system (CNS), which is the isoform of a cellular protein ( $\text{PrP}^c$ ) with different physical and chemical properties. Prions are

devoid of nucleic acid and seem to be composed exclusively of a modified isoform of PrP designated PrP<sup>Sc</sup>. The normal, cellular PrP, denoted PrP<sup>c</sup>, is converted into PrP<sup>Sc</sup> through a process whereby a portion of its  $\alpha$ -helical and coil structure is refolded into  $\beta$ -sheet. Although the exact mechanism of prion replication remains unclear, the agent is believed to promote the conversion of the cellular prion protein into the abnormal conformer by an autocatalytic or other unidentified process.

### **Pathogenesis**

The PrP<sup>c</sup> which is the normal form, is a tissue sialo glycoprotein found at highest degree in the central nervous system (CNS) and immune systems. PrP<sup>c</sup> is involved in many functions as the formation, and maintenance of synapses, signaling, neuritogenesis and neuroprotection and copper binding. Normal PrP binds with copper and prevent oxidative damage to cell, whereas abnormal prion protein cannot bind with copper, it induces apoptosis of neurons. The protein agent (PrP<sup>Sc</sup>) induces abnormal refolding of the normal protein.

This leads to aggregation of misfolded proteins which leads to formation of dense plaques and fibers called amyloid. This amyloid deposition results in cell death and tissue damage.

The main acquisition route for animal TSEs is the oral route. During prion infection, before reaching CNS, prions are first detected in lymphoid tissues, frequently associated with follicular dendritic cells (FDCs). They then progress through the nerves of the autonomic nervous system and finally reach the CNS, although activated microglial cells and astrocytes are present. Then there is increase in density of activated microglial cells. It is associated with the upregulation of the TNF- $\alpha$  astrocyte. Astrocytes are the cells directly implicated in the direct neurotoxic effects in prion diseases and act as inflammation promoters. Microglial cells phagocytize prions and promote apoptotic cell clearance of neurons, a process mediated by the secretion of milk fat globule epidermal growth factor 8 (MFGE8) by astrocytes. Then the protective role of microglia becomes insufficient, which can induce microglia to convert from the phagocytic to pro inflammatory cells. This altered phenotype may exacerbate the secretion of cytotoxic mediators and contributes to the spreading of prions.

### **Transmission**

In animals, Scrapie showed lateral transmission (direct and indirect). The BSE transmitted through contaminated feed, bone meal and meat meal. In human beings, the transmission of Variant CJD is reported through consumption of meat of animals suffered with BSE, Kuru caused by endocannibalism, and CJD has Iatrogenic transmission.

### **Animal Prion Diseases**

In the animals, prion diseases include Scrapie, Bovine Spongiform Encephalopathy (BSE), Chronic Wasting Disease (CWD), Transmissible Mink Encephalopathy (TME) and Feline Spongiform Encephalopathy (FSE).

Scrapie is reported all over the world, except in New Zealand and Australia. BSE was mostly



reported in the European countries. In India, Scrapie was reported in Garole and Kamach breeds of sheep.

Scrapie is the natural disease of sheep and goat. The first BSE case was remarked in 1986 in which the Dairy cows had developed nervous symptoms. Chronic wasting disease (CWD) is a TSE affecting mule, deer and elk, predominantly in the USA. Transmissible mink encephalopathy (TME) is a progressive and fatal neuro-degenerative disease that affects rancher mink. FSE affects the brain and liver in felines.

### **Human Prion Diseases**

Human prion diseases, include Creutzfeldt Jakobs Disease (CJD), German- Straussler-Scheinker Syndrome (GSS), Fatal Familial Insomnia (FFI) and Kuru.

There are 4 forms of CJD: sporadic, inherited, iatrogenic and variant form/

### **Classical Clinical Signs**

Scrapie, BSE and CWD affects the brain stem, FFI - thalamus, and Kuru – cerebellum. Scrapie is the natural disease of sheep characterized by intensive pruritis; a classical disease transmitted during lambing. BSE is also known as ‘Mad cow disease’, affected cattle presents ‘dog sitting posture’.

### **Diagnosis**

From early years, the diagnosis of TSE was based upon the observation of the typical histopathologic lesions. For the development of alternative diagnostic methods, specific antibodies against the characteristic marker of TSE, the PrP<sup>sc</sup> have been developed. Scrapie is diagnosed by Biopsy of lymphoid follicle of 3<sup>rd</sup> eyelid validated in U.S.A as diagnostic test.

### **Prevention And Control**

Currently there is no treatment and vaccine available. To impose ‘Import restrictions’ on live ruminant species and their products from countries where BSE is endemic. Should follow FDA “animal feed rule. There should be a ban on mammalian proteins as food source for animals. Scrapie free flock certification programme should be implemented. Regular monitoring and surveillance for CJD/BSE. Blood/plasma should be properly screened before infusion. Disinfection of instruments is done by using 2.5N NaOH and infectious carcasses should be incinerated at 134-138°C for more than 18min and digested by using NaOH.

