Prion diseases - animal health and zoonotic concern: a review

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Abstract
As the level of exposure to the prion diseases increases, risk of getting infection is also increases. Prion diseases are incurable, infectious and neurodegenerative disorders of mammals including humans which are caused by prion particles. Prions are the proteinaceous infectious particles and are self-reproducing structures that are totally different from bacteria, fungi, parasites and viruses. Prion diseases are generally known as transmissible spongiform encephalopathies (TSEs). Transmission of these diseases occurs through mis-folding of protein while the mechanism of action is still poorly known. Prion particles lack nucleic acid thus bestows a challenge for its timely diagnosis and specific treatment of these diseases. TSEs have longer incubation period and major clinical features are anxious behavior, dementia, hyperesthesia, ataxia and debility. Till date no vaccine, antidote and effective treatment is available for prion diseases. Research in last few decades add more to our understanding regarding causative agent, mode of transmission, diagnosis of TSEs, but still there is much more required to be known for appropriate diagnosis and specific treatment measures of prion diseases. Prion diseases, the most terrifying diseases are present challenge to medical and veterinary fraternity.

Keywords: Prion diseases, animal health, zoonoses, treatment.

Introduction
In 1982, Stanley B. Prusiner coined the word prion, this is a portmanteau derived from two words viz. protein and infection. Prion diseases are poorly understood neurodegenerative disorders of animals and humans that are chronically fatal (Prusiner, 1998). Occurrence of most common human prion disease i.e. Creutzfeldt-Jakob disease (CJD) is worldwide and 1-2 cases in million per year are reported. During last few decades the shocking impact on human, animal health and economics was felt in the UK due to the prion disease - bovine spongiform encephalopathy (BSE). Recently, genetic aspects that result in prion disease or modification of its risk or phenotype is thoroughly reviewed (Brown and Mastroianni, 2010).

In year 1986, the first confirmed case of mad cow disease was reported in UK. Two year later in 1988 the UK banned meat and bone meal products for inclusion into cattle feed. The peak outbreak of BSE in the UK occurred in year 1993 when more than 1000 cases reported per week. Approximately 5.8 million cattle over 2-3 years of age were slaughtered (till 2003) as continued efforts to stop the spread of this devastating disease in the UK. Same suit was followed by the US. Most of the countries banned import of meat and bone meal as well as livestock from the countries which were reported to have prion disease outbreaks (OIE, 2010). Still threat exists as 11 cases in 2010; 7 cases in 2011; 3 cases in 2012 are reported in the UK and 6 cases in 2012 reported in Spain. Recent data as of April 2013, one case is reported from Poland (OIE, 2013). Also one atypical BSE case in 2012 was reported in USA (OIE, 2013).

The UK government in year 2000 estimated the losses due to outbreak to the tune of more than £ 3.7 billion. However, compensation alone in year 1996/97 was approximately £ 850 million. Earlier, UK government had spent £ 288 million on research, surveillance, compensation, and other related items. Thus, prion diseases seem to be costly diseases that have repercussions far beyond the lost meat production. In 2003, US beef export valued at $3.95 billion and accounted for 9.6% of US beef production was lost due to mad cow disease.
to outbreak. In 2005, Kansas State University reported the economic impact since first case of BSE was reported in the U.S. Further, most of the countries banned the import of cattle and beef products from US. Thus, it is evident that prion diseases are challenge not only to animal health but also a threat to economy of the affected countries. Apart from this human population is at the greatest risk. For this reason, concerted efforts should be directed in terms of research and extension to deal with this deadly disease.

**Different forms of this diseases and zoonoses**

The human transmissible spongiform encephalopathies or human prion diseases are one of the most intensively investigated groups of rare human neurodegenerative conditions (Head and Ironside, 2012). In human the prion diseases are Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker disease (GSS), and variant CJD (vCJD) and Kuru. While in animals prion diseases are bovine spongiform encephalopathy (BSE), chronic wasting disease in deer and elk, feline spongiform encephalopathy, scrapie in sheep and transmissible mink encephalopathy (TME). The human prion diseases such as Creutzfeldt-Jakob disease (CJD) and Kuru shows four features viz. neuronal loss, spongiform change, amyloid plaque formation and astrocytosis. One of these features (spongiform change) is responsible to refer this disease as spongiform encephalopathy. The same features are reported in prion diseases of animals thus, making transmission of human prion disease such as CJD, Kuru etc. to non-human primates. The brain cells consists of amyloid-β peptides and non infectious prion particles to which infectious prion proteins may interact resulting in Alzheimer’s disease (Lauren et al., 2009). Hence, future line of research should be aimed at to block this interaction in brain by using preparations made up of mouse brains that may halted some neurological defects caused due to the accumulation of amyloid-β peptide. In the past, it was thought that infectious form of prion particles have role in degeneration of brain rather than non infectious prions. Confirmation by trial and error basis is yet to be done in human studies but it suggests an alternative to treat Alzheimer’s disease by targeting infectious prion. Hence, proper understanding and function of prion particles and their conversion to pathological form provides new insight into mechanism of prion diseases including Alzheimer disease, amyotrophic lateral sclerosis and Parkinson’s disease (Ferencik et al., 1998).

On contrary to all neurodegenerative diseases prion diseases are transmissible hence these are known as Transmissible Spongiform Encephalopathies (TSE) (Bodemer and Kaup, 2002). Transmission of diseases from animal to human and vice versa is known as zoonoses. As animal prion diseases are able to transmit or infect to human they all are zoonotically important. Some diseases are discussed in brief as hereunder.

**Creutzfeldt-Jakob disease (CJD)**

Creutzfeld a disease named after him described CJD in 1920. Though the cases of CJD were observed, they remained unnoticed or unreported for couple of years in 1980’s until it was recognized in the UK and was strongly associated with consumption of cattle products which were contaminated with bovine spongiform encephalopathy. CJD is an incurable disease caused by prion particles affecting mainly brain (degenerative disease of brain) of adult human beings. In CJD major symptoms are difficulty in walking, multifocal dementia, usually with myoclonus i.e. involuntary muscle twitching without unconsciousness (Collinge, 2001) symptoms followed by death within two years. Prominent clinical features include fatigue, insomnia, depression, weight loss, headaches, general malaise and ill defined pain sensations. In addition, neurological features include extrapyramidal signs, cerebellar ataxia, pyramidal signs, cortical blindness and psychiatric features (Zerr and Poser, 2002). CJD is difficult to diagnose and confirmative diagnosis is possible only after brain biopsy. Some general clinical criteria for the differential diagnosis of sporadic and variant CJD have been established (Will et al., 2000).

CJD is the most important spongiform encephalopathy of human. Now days it is feared that people may contract this disease from beef eating. CJD has been in existence long before BSE was discovered. Typically, the sporadic cases of CJD began in the 1960s in human with amnesia or along with behavioral changes and higher cortical function disturbances such as dysphasia or dyslexia. Patients with progressive form of disease showed rapidly developed dementia as dysphasia or dyslexia. Patients with progressive neurological signs include extrapyramidal signs, cerebellar ataxia, pyramidal signs, cortical blindness and psychiatric features (Vegad and Katiyar, 2001). CJD is incurable disease caused by prion particles affecting mainly brain (degenerative disease of brain) of adult human beings. In CJD major symptoms are difficulty in walking, multifocal dementia, usually with myoclonus i.e. involuntary muscle twitching without unconsciousness (Collinge, 2001) symptoms followed by death within two years. Prominent clinical features include fatigue, insomnia, depression, weight loss, headaches, general malaise and ill defined pain sensations. In addition, neurological features include extrapyramidal signs, cerebellar ataxia, pyramidal signs, cortical blindness and psychiatric features (Zerr and Poser, 2002). CJD is difficult to diagnose and confirmative diagnosis is possible only after brain biopsy. Some general clinical criteria for the differential diagnosis of sporadic and variant CJD have been established (Will et al., 2000).

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results in degeneration. Prion particles may come in contact with infectious form by means of injecting human growth hormone, grafting of various organs, transplant, may be inherited through genes and/or may be due to eating a brain of dead human by their relative as ritual practice in New Guinea Island.

**Kuru**

Kuru is a neurodegenerative disease of humans caused by infectious form of prion particle and occurs in human population where they took part in a ritual practice of eating human cadaver's brain by close relatives in New Guinea Island. Major symptoms of this disease are tremors, jerks in various muscles, truncal ataxia, imbalance posture, swallowing difficulty, relentless and inevitable progression to memory loss and ultimately death.

Initially it was assumed that cause may be environmental or genetics. Finally it was found that this disease was transmissible and spongiform features revealed as by histo-pathology. Dr. Carleton Gajdusek received the Nobel Prize for medicine in 1970 for the crucial finding that Kuru had an infectious etiology (Gajdusek et al., 1966).

**Bovine spongiform encephalopathy (BSE)**

A bovine spongiform encephalopathy (BSE) disease is also known as mad cow disease which showed symptoms after long preclinical phase. This is fatal and neuro-degenerative disease affecting a number of mammalian species including humans (Ahmad and Thangaraj, 1998). The epidemic of BSE was first described in UK in 1986 (Wilesmith et al., 1992). Reports showed that the animals infected were Friesian and crossbred cattle but, infection was likely to be function of management and practices rather than genetics (Novakofski et al., 2005). Transmission of BSE from UK to Oman, Canada, Germany, Denmark, Belgium, Italy and the Falkland, Channel Islands and other countries occurred through the exported cattle trade (OIE, 2010). Epidemiological studies reported that calves were infected the most by BSE (Wilesmith et al., 1988). But due to long incubation period, the clinical signs appear between 4-5 years. The young stock (2 years old) and old (15 years old) were reported to be infected by BSE (Wilesmith et al., 1992). BSE has major impact on meat and milk industry in terms of monetary returns and to human population in terms of fear of contamination and further grave consequences.

Though BSE is a disease of cattle but there are reports of secondary outbreaks in bison, eland, gemsbok, goats, sheep, and in cats, lab rodents, mink, pigs, humans and non human primates. Chronic wasting disease in deer and elk and even in mink as transmissible mink encephalopathy is reported (Novakofski et al., 2005).

**Causative agents**

The prion diseases are caused mainly by conversion of endogenous host encoded prion protein (PrP) which is normally present in brain to an abnormal conformation designated as PrPSc (Prusiner, 1982, 1994). Research on this causative agent has revealed that prion is a heavily glycosylated specific polypeptide protein of 30 kiloDalton (kD) and is called as prion protein (PrP) (Prusiner, 1994). Prion proteins have set of amino acids, glutamine and asparagine which form the core structure of prion particle. Generally, prion domains lacked definite structure and ready to take any shape. Thus, number of molecules of a particular protein form the order of amyloid fiber. The end site of the amyloid fiber acts as a template on which free protein molecules bind; which results in growing of amyloid fibre. Generally, normal protein is soluble but prion protein particles are insoluble in water due to the sequence and configuration of amino acids. In addition, the prion particle variant which is a causative agent for mad cow disease (BSE) have significant ability to cross species barrier resulting in transmission of BSE to other species of animals and human also. As the viruses do prions also replicates but properties, structure and modes of replication of prion particles are fundamentally different. Prions particles lack nucleic acid (RNA or DNA). Further, they do not produce any inflammatory or immune reaction in the host species they infect therefore making prion particles - the most exceptional disease causing agents. Due to lack of nucleic acids, prions are surprisingly resistant to most of the chemotherapeutic agents which generally inactivate viruses, making condition more hostile for any treatment and cure of this disease. Prof. Stanley Prusiner, a Biochemist of the University of California, San Francisco, USA was conferred the Nobel Prize in Physiology and Medicine in 1997, for discovery of prions.

The normal prion particles abbreviated as “PrPc” are the trans-membrane glycoprotein’s normally found at the surface of neural cells in brain, it also have secondary structure dominated by α-conformation. These are easily soluble and digested by proteases. The abnormal prion particle abbreviated as “PrPSc” (for scrapie) has the same amino acid sequence as the normal protein “PrPc” suggesting their primary structures are identical but secondary structure is predominated by β-conformation. These are insoluble but soluble in strongest solvents and are highly resistant to digestion by proteases. Now, when “PrPc” comes in contact with “PrPSc”, it converts “PrPc” to “PrPSc”. Fig 1 shows both prion particles and their conversion. These molecules bind to each other forming aggregates. But it is not understood as how this aggregation causes degenerative changes.
Transmission

Research suggests that the primary way of infection in animals and humans is by ingestion. Further, most important concern regarding transmission of prion diseases is that they might be deposited in the environment, the remains of dead animals and via urine, saliva and other body fluids. Prions may remain in the soil by binding to clay and other minerals (Johnson et al., 2007). Therefore, it is thought that prion particles may take infectious form whenever opportunity persists which pave the way to the big outbreak.

Through feed: In general, practice of feeding of concentrate feedstuffs fortified with meat meal and/or bone meal to livestock is followed throughout the globe. These meals are prepared by feed industry from materials discarded in slaughter houses, from the culled and dead livestock. Usually, processing involves use of organic solvents and hydrocarbon fat solvent which may remove infectious agents of prion diseases and other zoonotic diseases, but as there is no check in processing methods in most of the countries for these industries, these industries stopped the use of organic solvents and hydrocarbon fat solvent which resulted in earlier outbreak of prion diseases in European and western countries. Afterwards, due to increased awareness and imposition of ban on such feeds, now there is a steep fall in incidence of prion diseases. This substantiates the importance of meat and bone as the major route of infection (Radostits et al., 2005). Therefore, proper care should be taken while formulating rations for the livestock and use of blood, bone, meat meal should be discouraged.

Non-feed transmission: This is of minor way of transmission. To date, there is no evidence of animal to animal transmission. Semen, chemicals, biologics, pharmaceuticals have already been ruled out as the source of infection (Novakofski et al., 2005). Vertical transmission is not considered significant for the continuation of this disease. There is little evidence for vertical transmission from mother to fetus; however, calves born in close contact with BSE infected cows may be infected within days after calving (Hoinville et al., 1995). Animals may develop prion disease by means of ingestion of PrPSc or by peripheral exposure to PrPSc, such as an iatrogenic route e.g. surgery, cadaveric growth hormone injection, corneal transplantation etc. or by hereditary transmission as an autosomal, dominant trait or by sporadically by unknown origin (Novakofski et al., 2005), yet for the majority of cases transmission of disease is not clear.

Clinical Symptoms

Clinical course progresses over several weeks of duration from 1 to 6 months. The clinical sign includes alterations in behavior, temperament, posture, sensorium and movement, but these signs vary from day to day as disease progress over the time. The predominant neurological symptoms are anxious behavior, hyperesthesia, ataxia and debility and cows have a diminishing milk yield during the clinical course of the disease.

Gradual behavioral changes such as reluctance to movement, disorientation, staring at imaginary objects for long periods etc. may develop. There are signs of hyperesthesia to any sound or touch like alertness by twitching of the ears, shaking of head or more general muscle fasciculation and tremors. Some other signs are to avoid other animals in loose housing and in confinement antagonistic behavior to herd mates and humans, kicking during milking and resistance to handling. Early in the course of the disease there is hind limb ataxia with a shortened stride, swaying gait and difficulty in turning. Other symptoms such as knuckling, stumbling and falling, difficulty in rising are the common in later stages of this disease. Cows showing progressive weakness with ataxia and weight loss should be sent to cull because of locomotor disabilities or changes in temperament prior to the common recognition of the disease (Radostits et al., 2005).

Diagnosis

Prevention is always better than cure. Even though the disease occurs precise diagnosis is important to carryout appropriate treatment of the disease on time. Important features of any diagnostic protocol are analytical sensitivity and specificity that determines the effectiveness at field level. Analytical sensitivity refers to minute level of antigen detected in
samples by diagnostic test. Concentration of prion particles in samples is very less thus, makes it difficult to diagnose by simple assay techniques. New diagnostic techniques aimed at increasing sensitivity to detect and specificity to bind specific antigen of PrPSc in body fluids and at identifying novel surrogate markers are under development. Further, diagnosis from clinical signs is difficult as in most of the time it may be confusing due to fact that most of the symptoms are commonly seen in other CNS disorders. So, prion diseases should be differentiated from hypomagnesaemia, nervous acetonemia, rabies, lead (Pb) poisoning, listeriosis, encephalomalacia, tremorgenic toxin (Radostits et al., 2005).

Immunological tests include western blotting (Ahamad and Thangaraj, 1998; Oesch et al., 2000), 14-3-3-protein immunoassay in CSF (Lee and Harrington, 1997; Zerr and Poser, 2002), assay based on polyclonal antibodies produced in PrP gene knockouts and assay based on monoclonal antibodies produced against engineered prion protein isotopes (Safar et al., 2002). Prion bioassay by means of mice or hamster as animal model is also useful (Chandler, 1961; Raebel et al., 1998). A novel in vitro approach for the detection of PrPSc was reported by Saborio et al. (2001). They developed a method to convert PrPSc molecules into protease-resistant PrPSc-like molecules that depend on the presence of exogenously added PrPSc in the sample. They claimed that otherwise undetectable levels of PrPSc are amplified to detectable levels (Soto et al., 2002) and therefore, able to detect PrPSc molecules in blood samples from infected animals. Other techniques developed are very technical in nature and not yet applicable for easy handling or high through put screening. Among these are spectroscopy-based methods such as fluorescence correlation spectroscopy (FCS) (Bieschke et al., 2000), multispectral ultraviolet fluorescence spectroscopy (MUFPS) (Rubenstein et al., 1998) and Fourier transform infrared spectroscopy (Schmitt et al., 2002). Brain biopsy is the last resort consists of immune- histochemistry and immune detection of PrPSc, immune-gold electron microscopy, histopathology after Congo red staining which imparts a pink or red color to amyloids. At present, no confirmatory diagnostic test exists for the detection of prion diseases in live animals or humans. There is no treatment for prion diseases (Radostits et al., 2005). Thus, major setbacks for cure of prion diseases in human and animals are inability to accurately diagnose and relevant treatment.

Several methods have recently been developed to facilitate sensitive and precise detection of PrPSc viz. protein misfolding cyclic amplification, conformation-dependent immunoassay, dissociation-enhanced lanthanide fluorescent immunoassay, capillary gel electrophoresis, fluorescence correlation spectroscopy, flow microbead immunoassay etc. Additionally, functionally relevant prion-susceptible cell culture models that recognize the complexity of the mechanisms of prion infection have also been pursued, not only in relation to diagnosis, but also in relation to prion biology. Prion protein (PrP) gene-deficient neuronal cell lines that can clearly elucidate PrPSc functions would contribute to understanding of the prion infection mechanism (Sakudo et al., 2007).

**Indian scenario**

In India, the disease is still under reported. Over the period spanning from 1968 to 1997, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India recorded 69 cases of CJD from different parts of India (Mehndiratta et al., 2001). New cases are emerging and many may have been unreported as no autopsies were carried out. From 1990 to 1998, Department of Neurology, G.B. Pant Hospital, New Delhi, India admitted 10 cases of CJD from North India. Mehndiratta et al. (2001) concluded that, if it is taken into account that India has a population of more then one billion and assuming an annual incident of 0.5 per million population probably there would be at least around 500 new cases of CJD annually in India. This sounds correct theoretically but practically doubtful as blood, bone meal are rarely added in animal rations and greater populace is aware regarding various disease outbreak and eating of brain of diseased human is rare practice in India. Greater awareness and high degree of suspicion only can give the true scenario of this dreaded disease, for which no treatment is available till date.

**Preventive measures**

As rightly said, prevention is not only better but also cheaper than cure; control measures are needed to be taken to prevent occurrence of prion diseases rather than treatment. General control measures include strategic and controlled management of livestock farm. Prions are relatively resistant to proteases, heat, radiation and formalin treatments (Qin et al., 2006) even though their infectivity can be reduced by such treatments. Successful prion decontamination relies upon protein hydrolysis and/or reduction and/or destruction of tertiary structure of protein. Following control measure should be followed to control these diseases:

a. Import of livestock, feed, beef, meat, frozen semen and embryos from the countries having recent outbreaks should compulsorily be avoided or should be banned.

b. Affected animals should be sacrificed and cremated or should be buried deep with lime.
c. The contaminated or suspected feed should be destroyed by charring followed by deep burring.
d. Animal entrails should be avoided as supplement in livestock and poultry rations.
e. Growth hormone preparations and pituitary extracts should not be given to the animals unless they are confirmed to be prion free. The hormone preparations should specifically avoided from dead or diseased animals.
f. Sheep brain medium should not be used for virus propagation in vaccine production unless the sheep are tested against the prion specific monoclonal antibodies to detect prion titre in cerebrospinal fluid (CSF).
g. Prion contaminated surgical, needles, gloves and EEG electrodes should be destroyed to completely to rule out the possibility of iatrogenic infections (Ahamad et al., 1997).
h. Discourage the people which take part in ritual practice of cannibalism

**Treatment**

Some drugs are in process with the target: PrP$^C$, for treatment which played central role in causing disease. Amphotericin-B, quinacrine and chlorpromazine were tried for inhibition of PrP$^C$ conversion in prion infected cultured cells or in animal models as they cross the blood-brain barrier. However, clinical trials in humans revealed no significant improvements in the course of chronic disease (Collinge et al., 2009).

Complex polyamines have been shown to disaggregate PrP$^C$ but suffer poor bioavailability (Supattapone et al., 2009). Therefore, it would be desirable to identify new classes of compounds with drug-like properties including high bioavailability and low toxicity that directly influence amyloid propagation. Although no effective treatment has been revealed but these experimental studies provided important considerations for future line of experiments to develop treatment to this disease (Appleby et al., 2011).

Luminescent conjugated polythiophenes (LCPs) significantly reduced prion infectivity while increasing the protease resistance of PrP$^C$. They are versatile probes with affinity to a variety of amyloids (Nilsson et al., 2010). After binding with amyloids, LCPs adopt distinct conformations with characteristic spectral properties (Sigurdson et al., 2007) specific to distinct amyloid types. LCPs efficiently cross the blood-brain barrier, enabling visualization of protein aggregates in vivo and potentially in clinical trials. LCPs significantly reduced prion infectivity while increasing the protease resistance of PrP$^C$. The interaction of the LCPs with PrP$^C$ causes a structural transformation in a surfactant-like manner mostly independent of the molecular character of the LCPs. The treatment renders PrP$^C$ more resistant to PK digestion without affecting proteolysis of PrP$^C$ and profoundly reduces prion infectivity. Therefore, LCPs may represent a promising new class of antiprion compounds (Ilan Margalith et al., 2012).

**Conclusion**

Prion diseases are very intricate in nature and already caused a setback to the livestock industry in the European and western countries. Recently, newer challenges have been identified for the feed processing industries related to biopharmaceutical production. Knowledge regarding prion particles has increased dramatically in the past decade, but still there is no way to tackle this disease efficiently. However, the great concern engendered by the strong association of all prion diseases. Further, these complexities demonstrate the pivotal importance of extensive and specific research in this direction where humans and animal species are at the highest risk of diseases. Hence, extension activities, surveillance and monitoring, rapid diagnostic tools are the need of hour throughout the globe for general understanding of prion diseases to larger mass of populace.

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