



## Review On Molecular Mechanisms Of Prion Pathogenesis

Ayalew Negash<sup>1</sup>, Eyachew Ayana<sup>2</sup>, Dembel Jida<sup>3</sup>, Mebrie Zemene<sup>4</sup>, Gashaw Enbiyale<sup>5</sup>, Anteneh Wondimu<sup>6</sup>

<sup>1</sup> Lecturer at University of Gondar, College of Veterinary Medicine and science, Unit of Biomedical Science Unit, University of Gondar, P.O. Box. 196, Gondar, Ethiopia;

<sup>2</sup> Candidate of Veterinary medicine, College of Veterinary Medicine and science, University of Gondar, P.O. Box. 196, Gondar, Ethiopia;

<sup>3</sup> Candidate of Veterinary medicine, College of Veterinary Medicine, Haramaya University, Haramaya, Ethiopia;

<sup>4</sup> Lecturer at University of Gondar, College of Veterinary Medicine and science, Department of Veterinary Pharmacy, University of Gondar, P.O. Box. 196, Gondar, Ethiopia; Assistant Professor of Veterinary Medicine at University of Gondar, College of Veterinary Medicine and science, University of Gondar, P.O. Box. 196, Gondar, Ethiopia;

<sup>5</sup> Field Practitioner at University of Gondar Veterinary Clinic, College of Veterinary Medicine and science, University of Gondar, P.O. Box. 196, Gondar, Ethiopia

<sup>6</sup> Assistant Professor at Haramaya University, College of Veterinary Medicine, Haramaya University, Haramaya, Ethiopia

[drayalewdvm@gmail.com](mailto:drayalewdvm@gmail.com); Telephone: (+251) 966751899

**Abstract:** Prions are infectious proteins that cause disease in variable species of animals, including human being. The normal, cellular protein PrP (PrPC) is converted into PrP<sup>Sc</sup> through a post translational process during which it acquires a high  $\beta$ -sheet content which made the protein resistant to degradation by proteinase K due to its PrP 27-30 domain that increase its half-life to >48 hours as compared to that of the normal 3-6 hours, its stay leads to self-propagation and toxicity. The disease pathology is associated with many disturbances mainly in central nervous system which resulted from increased oxidative stress and mitochondrial dysfunction, disturbance of iron metabolism, alteration of calcium metabolism, increases of inflammatory cytokines, chemokine's and nuclear factor-kappa  $\beta$  activity. The entire process creates a spongy hole inside the nervous system which leads to condition called encephalopathy. The agent cause scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle (known as mad cow disease), transmissible mink encephalopathy (TME) in mink, chronic wasting disease (CWD) in white tailed deer, elk, mule deer and moose, feline spongiform encephalopathy in cats, exotic ungulate encephalopathy (EUE) in Nyala and Oryx. In humans it causes Creutzfeldt-Jakob disease (CJD) and its varieties, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (sFI) and Kuru. Prion diseases have zoonotic and interspecies transmission. Banning Meat bone meal and culling infected animals are recommended.

[Ayalew N, Eyachew A, Dembel J, Mebrie Z, Gashaw E, Anteneh W. **Review On Molecular Mechanisms Of Prion Pathogenesis.** *N Y Sci J* 2021;14(2):1-8]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 1. doi: [10.7537/marsnys140221.01](https://doi.org/10.7537/marsnys140221.01).

**Key words:**-Prions, Nervous system, Spongiform Encephalopathy

### 1. Introduction

The name Prion is derived from its definition as a proteinaceous infectious particle that lacks nucleic acid (Emmanuel *et al.*, 2015). The normal protein PrP is a GPI anchored cell surface protein occurs naturally in the brains of animals and humans with, its function is not clearly understood, but in experimental models it appears to play a role in signal transducing properties, cell adhesion, copper transport or metabolism (antioxidant Properties), protecting cells and helping them respond to oxygen deficiency and prevents Alzheimer's plaques formation (regulates  $\beta$ -secretase cleavage of the Alzheimer amyloid

precursor protein), but still its exact function is unknown (Jackson *et al.*, 2001).

The normal, cellular PrP (PrPC) is converted into PrP<sup>Sc</sup> through a post translational process during which it acquires a high  $\beta$ -sheet content which made the protein resistant to degradation by proteinase K due to its PrP 27-30 domain that increase its half-life to >48 hours as compared to that of the normal 3-6 hours, its stay leads to self-propagation and toxicity. The key molecular event in the pathogenesis of the prion diseases is the conformational conversion of PrPC into PrP<sup>Sc</sup>. In a process that is not fully understood, PrP<sup>Sc</sup> binds to PrPC and promotes its

transformation into PrP<sup>Sc</sup>. Eventually, the abnormal protein isoform leads to neurodegeneration and cell death, and as a consequence many microscopic, sponge-like holes (vacuoles) can be seen in the brain, a symptom of prion disease (Claudia *et al.*, 2014). Therefore this paper highlights the molecular mechanisms of prion pathogenesis.

## 2. Literature Review On Prion Pathogenesis

### 2.1 Prion Protein Structure

The full-length PrP<sup>C</sup> has a 22-amino acid signal peptide in the N-terminal. The signal peptide determines the PrP should be exported to the cell surface, and will be cleaved after reaching the membrane. It also has a C-terminal glycosylphosphatidylinositol (GPI) anchor sequence locating after amino acid residue 230 or 231. It is well known that PrP<sup>C</sup> is located at the outside membrane through its GPI anchoring, which can be digested by phosphatidylinositol-specific phospholipase C. PrP<sup>C</sup> has a long NH<sub>2</sub>-proximal flexible random-coil sequence, followed by a globular non-random COOH-proximal domain (Aguzzi and Calella, 2009).

The flexible disordered structure of a less-defined NH<sub>2</sub> proximal region consists of the sequence from residues 23 to 124 and contains a stretch of several octapeptide repeats, which is important for PrP binding with metal ions. The N-terminal half of the molecule does not have regular structure at all, whereas the C-terminal half has many normal secondary structure including three  $\alpha$ -helices at the residues 144–154, 173–194, and 200–228, and also interspersed with two antiparallel  $\beta$ -sheets formed at residues 128–131 and 161–164. Only a single disulfide bond is found between cysteine residues 179 and 214. Many important amino acids affect prion protein fibril formation, such as mouse prion protein polymorphism Phe-108/Val-189, human prion protein polymorphic residue 129, and the methionine oxidation (Younan *et al.*, 2012).

Once present PrP<sup>Sc</sup> is capable of inducing other normal PrP<sup>C</sup> molecules to undergo conformational change to the PrP<sup>Sc</sup> form, resulting in the generation of extremely large number, of abnormal molecules. PrP<sup>C</sup> is rich in  $\alpha$  helical content and has little  $\beta$  sheet structure; whereas PrP<sup>Sc</sup> has less  $\alpha$  helical content and is rich in  $\beta$  sheet structure (Mukund *et al.*, 2012).

### 2.2 Prion Disease Pathogenesis

#### 2.2.1. Disease transmission

The diseases can be transmitted within and between species by several mechanisms, including ingestion, iatrogenic transmission and blood transfusion. The possibility for spreading through environmental exposure cannot be discounted, because the infectious agent persists in the environment for many years. The case of fore tribe of New Guinea

cannibalism contributes to the transmission between peoples of the tribe (Jianhui *et al.*, 2015).

Practice of feeding of concentrate feedstuffs fortified with meat meal and/or bone meal to livestock is followed throughout the globe. 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). Zoonosis also occurred from cattle's to human's i.e. mad cow disease to CJD (Patrick and Erik, 2000).

#### 2.2.2. Disease Epidemiology

Since the first recorded case of vCJD in 1996, 177 cases of definite or probable vCJD have been reported in the UK (as of April 2014). The annual number of deaths reached a peak in 2000 with 28 deaths but since 2006, deaths from vCJD have leveled off at 2–5 per year with none reported in 2012 and only one in 2013 (NCJDSRU, 2014). Originally restricted to the UK, 51 cases have now been reported in 11 other countries with a worldwide total of 228. Outside of the UK, most cases have occurred in France (27 cases to date) and are thought to be related to the peak in volume of beef imports originating from the UK during 1985–1995. This potential relationship is shown in the peak in number of deaths from vCJD in France in 2005, 5 year after a similar peak in the UK. Further evidence of the link between UK and French vCJD has arisen from comparative studies comparing epidemiologic, clinical, pathological, and biochemical analyses of vCJD cases from both countries indicating that the same strain of agent could be responsible (Brandel *et al.*, 2009).

Scrapie can be found worldwide. This disease has been reported in Europe (including the United Kingdom), the Middle East, and Japan, Canada, the United States, Kenya, South Africa, Colombia and parts of Asia. The scrapie status of many countries is not known because they have no surveillance for this disease. Australia and New Zealand have remained free of scrapie; although outbreaks occurred in these two countries, the disease was eradicated by slaughtering the imported sheep and their flock mates soon after they were released from quarantine (CFSPH, 2007). In 1957 Kuru was the first human disease identified as a prion disease Kuru was reported among the fore tribe people in Papua New Guinea (Prusiner, 1997). There are no reported prion disease cases in Ethiopia.

#### 2.2.4. Control and Treatments of the Disease

Prion diseases are currently incurable and there are no available effective drugs for individuals who are already infected (Mallucci and Collinge, 2005). If prion propagation depends on the conversion of PrP<sup>C</sup> to PrP<sup>Sc</sup>, then the prevention of this conversion

should prevent disease progression and early neuronal changes should be reversed. Prion therapeutics should therefore aim for the design of compounds that prevent disease onset and/or alter progression, or for the use of neuronal precursor cells. To date, therapeutic approaches include the use of compounds such as Congo red, polyanionic compounds, amphotericin B, porphyrins and quinacrine, each of which has been shown to reduce accumulation of PrPSc in prion-infected cell models. However, such models are not stringent screens and these compounds have produced only modest effects in vivo (Aguzzi *et al.*, 2001).

Targeting endogenous PrPC in mice with early prion infection reverses spongiform change and prevents clinical symptoms, neuronal loss, cognitive and behavioral deficits. Strategies to prevent the conversion process may also include the use of antibodies to bind and stabilize PrPC, but the use of large quantities of anti-PrP antibodies in the CNS is not feasible as yet as they have been reported to lead to marked neurodegeneration in mice (Solforosi *et al.*, 2004).

The use of RNA interference (RNAi) has been demonstrated to inhibit PrPC expression in neuroblastoma cells and to prevent PrPSc accumulation in scrapie infected cells. In a recent study using a single administration of lentivirus-expressing shRNA targeting PrP into each hippocampus of mice with established prion disease resulted in significantly prolonged survival times compared to control mice (White *et al.*, 2008).

It was reported early that anti-PrP antiserum reduces the titer of infectious hamster brain homogenates some hundred-fold. Anti-PrP antibodies were found to inhibit formation of protease-resistant PrP in a cell-free system. Also, antibodies and antigen binding fragments directed against PrP can suppress prion replication in cultured cells. These data suggest the feasibility of antiprion immunoprophylaxis, which could be implemented as passive immunization (transfer of antibodies) or active immunization (administration of antigens as vaccines). Active immunization is generally more effective, but it proved exceedingly difficult to elicit humoral immune responses because the mammalian immune system is largely tolerant to PrP of the same species, due to this effect vaccination bears immunosuppression rather than immunostimulation (Perrier *et al.*, 2004).

### 2.3 Molecular Mechanisms of Prion Pathogenesis

A prion disease occurs when the normal protein PrPC exists in an abnormal form PrPSc (scrapie variant). PrPSc represents a conformationally modified form (rich in beta-sheet) of PrPC (mainly an alpha-helical structure). The high beta-sheet content correlates with PrPSc resistance to enzymatic

digestion and infectivity. The change from PrPC to PrPSc can occur by a spontaneous mutation in the PRNP gene or inheritance of the abnormal gene or when pre-formed PrPSc is introduced into normal healthy tissue which surprisingly results in further conversion of normal PrPC into abnormal PrPSc by a self-perpetuating vicious cycle. This is followed by abnormal processing of neuronal proteins, diminished clearance and intra-cellular accumulation followed by neuronal death (Arun and Ranjit, 2002).

Recent research shows that PrPSc is heterogeneous with the existence of several distinct isolates or strains which are associated with differing PRNP genotypes and also have a major influence on the disease phenotype in both sporadic and familial human prion diseases. A unifying feature of all the prionoses is their neuropathology. These illnesses tend to affect the gray matter of the central nervous system (CNS), producing neuronal loss, gliosis, and characteristic spongiform change. In addition, plaques with the typical staining properties of amyloid (e.g. apple-green birefringence after Congo red staining when viewed under polarized light) are observed in many of these conditions. vCJD is characterized by florid plaques (Daisy plaques) throughout the cerebrum and cerebellum (Baron, 2002).

#### 2.3.1 Mechanism of Cell Death in Prion Diseases

A large number of studies has been undertaken to analyse the role of PrP in neurodegeneration. Of particular interest are the function of PrPC in neuroprotection, and the mechanism of cell death induced by, or during, the conformational conversion from PrPC into PrPSc. Despite much progress in the elucidation of the molecular pathways involved in the activation of cell death cascades, the mechanism of prion-induced cell death still remains obscure. Apoptotic cell death has been described in various cell culture systems and in vivo, and several hypotheses have been put forward to explain the neurotoxicity that leads to apoptosis, among them oxidative stress, microglia-mediated damage, and even the involvement of copper leading to increased levels of caspase, Fas activation, and up-regulation of the transcription factor c-jun (Fraser, 2002).

The role of PrPC as a protein with anti-apoptotic function has been highlighted. It could be speculated that alteration of PrP function also affects a homo or heterodimerization of Bcl-2, or their expression, resulting in neuronal apoptosis. It has also been argued that binding and sequestration of ubiquitous members of the Bcl-2 family should also trigger cell death in non-neuronal cells. Since these show little or no alteration, further brain-specific factors, other than the Bcl-2 family members, may be more relevant. However, while loss of neurons can hardly be compensated, replacement of non-neuronal cells may

happen unnoticed, particularly in the lymphoreticular compartment. Overall loss of neurons may not be the most relevant event in prion disease. Patients may even be symptomatic through loss of neuronal connectivity and neurite degeneration, causing cell death only at a later stage (Sebastian, 2003).

#### 2.4. Pathology of Prion Disease

The unique feature of prion diseases is that they are self-propagating and transmissible. Once PrP<sup>Sc</sup> is generated endogenously or introduced into the body from the environment, it converts normal prions into abnormal ones. This conversion begins with the initial production of a small polymer of mis-folded prions, (aseed), perhaps no more than 28 molecules. This seed converts normal adjacent prions into abnormal ones by an unknown mechanism. As more PrP<sup>Sc</sup> polymers are produced they in turn act as seeds propagating the conversion of normal to abnormal prions (Cohen *et al.*, 2013).

##### 2.4.1 Increased Oxidative Stress and Mitochondrial Dysfunction

Mitochondrial damage and increased oxidative stress may play key roles in the pathogenesis of prion diseases. To further verify whether mitochondrial dysfunction can be associated with the pathogenesis of prion diseases, it was analysed antioxidant systems and calcium levels in the mitochondria of control and scrapie-infected mice. In the mitochondria of scrapie-infected mice, level of oxidized form of glutathione (GSSG) and calcium content were markedly increased, whereas mitochondrial membrane potential and energy metabolites (ATP/ADP ratio) were decreased (Martin *et al.*, 2007; Yuan *et al.*, 2013).

There is growing evidence that oxidative stress induced by ROS or free radicals play key roles in the pathogenesis of neurodegenerative disorders including prion diseases. A number of oxidants are produced as by products in the normal aerobic metabolism and particularly at a high rate in neurodegenerative disorders. CNS is especially vulnerable to oxidative stress that has relatively insufficient antioxidants, consumption of high level of oxygen, and large amount of lipid and metals that can produce free radicals (Yun *et al.*, 2006; Cohen *et al.*, 2013). It was reported that the levels of Malondialdehyde (MDA) and heme oxygenase-1 (HO-1), which are oxidative stress markers, and the generating rate of free radicals, especially superoxide anion ( $O_2^{\cdot-}$ ), were significantly increased in the brains of scrapie-infected mice (Cohen *et al.*, 2013).

Alterations of mitochondrial permeability transition and of energy metabolites due to disturbed mitochondrial respiratory system may result in abnormal calcium accumulation in the mitochondria of scrapie-infected rodents, indicating that mitochondrial dysfunction caused by oxidative damage, abnormal

calcium accumulation and altered energy metabolism may contribute to neurodegeneration in prion diseases. It has been known that phospholipase D (PLD) can be induced by ROS including hydrogen peroxide ( $H_2O_2$ ) and that breakdown of phospholipids by PLD can be recognized as an important signalling in CNS (Asuni *et al.*, 2015).

##### 2.4.2. Disturbance of Iron Metabolism

Brain iron-dyshomeostasis is an important cause of neurotoxicity in prion disorders, a group of neurodegenerative conditions associated with the conversion of prion protein (PrP (C)) from its normal conformation to an aggregated, PrP-scrapie (PrP (Sc)) isoform. Alteration of iron homeostasis is believed to result from impaired function of PrP (C) in neuronal iron uptake via its ferrireductase activity since reabsorption by glomerular filtrate by kidney proximal tubule cells (PT), requiring ferrireductase activity (Singh, 2014)

Reports suggest that imbalance of brain iron homeostasis as a significant associated cause of neurotoxicity in prion-infected cell and mouse models. However, systematic studies on the generality of this phenomenon and the underlying mechanism (s) leading to iron dyshomeostasis in diseased brains are lacking. Prion disease-affected human, hamster, and mouse brains show increased total and redox-active Fe (II) iron and a paradoxical increase in major iron uptake proteins transferrin (Tf) and transferrin receptor (TfR) at the end stage of disease. Furthermore, examination of scrapie-inoculated hamster brains at different time points following infection shows increased levels of Tf with time, suggesting increasing iron deficiency with disease progression (Haldar *et al.*, 2015; Singh, 2014).

##### 2.4.3. Alteration of Calcium Metabolism

Disruption of calcium homeostasis in the cell is probably the most adverse and immediate effect caused by ER stress. In neurons, the effect of calcium is particularly deleterious, because  $Ca^{2+}$  waves are important for neuronal activity.  $Ca^{2+}$  is a second messenger in cellular signaling pathways; thus, maintaining a specific concentration of  $Ca^{2+}$  in the cytoplasm is critical for normal cellular biology. The ER is the main site for intracellular storage of  $Ca^{2+}$ . The presence of mis-folded proteins can result in an increase in cytoplasmic  $Ca^{2+}$  owing to ER stress. The release of calcium from the ER to the cytoplasm occurs when cells are exposed to mis-folded prion protein. Indeed,  $Ca^{2+}$  release appears to be one of the first changes after prion infection in cells. Increased  $Ca^{2+}$  in the cytoplasm deregulates downstream targets including calcineurin (CaN), a type 2B phosphatase (Claudio and Nikunj, 2011).

CaN activation is implicated in neuronal death induced both by PrP<sup>Sc</sup> and PrP synthetic peptides.

Moreover, CaN activity increases in the brain at the beginning of the symptomatic phase of prion disease. Strikingly, blocking CaN activity in sick prion infected mice increases animal survival decreases the progression of deterioration and reduces neurodegeneration. PrPSc produces synaptic damage and neuronal death in TSEs through ER stress, changes in calcium homeostasis and the induction of CaN activity (Mallick *et al.*, 2015).

2.4.4. Increases of Inflammatory Cytokines, Chemokines and Nuclear Factor-Kappa B (NF- $\kappa$ B) activity

PrP (C) is highly expressed in diverse organs that by multiple means are particularly protected from inflammation, such as the brain, eye, placenta, pregnant uterus, and testes, while at the same time it is expressed in most cells of the lymphoreticular system. In this paradigm, PrP (C) serves two principal roles: to modulate the inflammatory potential of immune cells and to protect vulnerable parenchymal cells against noxious insults generated through inflammation (Bakkebø *et al.*, 2015). General low level of repression of gene expression in lymphoid tissue, including many inflammatory genes, contrasts with the pro-inflammatory and pro-apoptotic events that occur within the CNS at equivalent stages of disease progression as assessed by PrP (Sc) accumulation (Gossner and Hopkins, 2015).

2.4.5 Modes of Neurodegeneration: Apoptosis or Necrosis

Apoptosis is a programmed form of cell death that plays a central role during development and homeostasis of multicellular organisms and is also implicated in pathological conditions. Apoptosis induced by aggregated PrP peptide fragments or mutant PrP variants (such as truncated or cytosolic PrP) proceeds via the mitochondrial pathway. Indeed, important roles for the well-known regulators of the mitochondrial apoptosis pathway Bcl2 (B-cell lymphoma protein 2) and Bax (Bcl-2-associated x protein) have been reported. However, two studies showed that neither Bax deletion nor Bcl-2 overexpression decrease neuronal death induced by prion infection or alter the progression of prion disease in animals. These findings suggest that apoptosis in prion disease might be induced by mechanisms other than the mitochondrial pathway. Disruption of calcium homeostasis in the cell is probably the most adverse and immediate effect caused by ER stress (Pierluigi *et al.*, 2011).

## 2.5. Animal Diseases Caused by Prions

Prion diseases occur worldwide and affect both genders equally. Scrapie was the first prion disease to be identified in the 1730s. Later other prion diseases were described: GSS (1920s); CJD (1920s); kuru (1952–1953, among the Fore people of Papua New

Guinea, transmitted via ritualistic cannibalism); CWD (1967); and the most recent major animal disease: BSE (1987). Prion diseases are classified based on the mode of transmission and infection as sporadic (arise spontaneously for no known reason, with an incidence 1 per 106 population per year), inherited (with an incidence of 1 per 107–108 population per year) and acquired (by medical procedures or contaminated food) (Claudia *et al.*, 2014).

### 2.5.1. Scrapie

Scrapie is a fatal contagious disease of sheep and goats that causes degeneration of the central nervous system. Scrapie is contracted early in life and is believed to be transmitted from dams to offspring primarily through contact with afterbirth, but other means of transmission cannot be ruled out. Although it may require years for clinical signs to appear, the disease is always fatal. (Moore *et al.*, 2016).

Scrapie can be found worldwide. This disease has been reported in Europe (including the United Kingdom), the Middle East, and Japan, Canada, the United States, Kenya, South Africa, Colombia and parts of Asia. The scrapie status of many countries is not known because they have no surveillance for this disease. Australia and New Zealand have remained free of scrapie; although outbreaks occurred in these two countries, the disease was eradicated by slaughtering the imported sheep and their flock mates soon after they were released from quarantine. The Nor98 form of scrapie was first reported from Norway in 1998. Since 2002, Nor98 and other atypical scrapie agents have been detected in a number of European countries. Nor98 was diagnosed for the first time in U.S. sheep in March 2007. It has no zoonotic importance (Colby and Prusiner, 2011).

### 2.5.2. Bovine Spongiform Encephalopathy

Bovine spongiform encephalopathy (BSE) is a transmissible spongiform encephalopathy (TSE) of cattle. Classical BSE is associated with ingestion of BSE-contaminated feedstuffs. H- and L-type BSE, collectively known as atypical BSE, differ from classical BSE by displaying a different disease phenotype and they have not been linked to the consumption of contaminated feed. BSE possibly originated as a result of feeding cattle meat-and-bone meal that contained BSE-infected products from a spontaneously occurring case of BSE or scrapie-infected sheep products. There is strong evidence and general agreement that the outbreak was then amplified and spread throughout the United Kingdom cattle industry by feeding rendered, prion-infected, bovine meat-and-bone meal to young calves (Gray *et al.*, 2016). It has zoonotic importance.

### 2.5.3. Chronic Wasting Disease of Deer and Elk

Chronic wasting disease of Deer and Elk (CWD) was initially reported in 1980 as a TSE in captive

research deer in Colorado and Wyoming. The disease origin still remains completely obscure. Since 1980, cases of CWD in free-ranging Mule Deer (*Odocoileus hemionus*), Whitetailed Deer (*O. virginianus*), and Rocky Mountain elk (*Cervus elaphus nelsoni*) have been detected in the same region of Colorado and Wyoming. Recently, increased surveillance efforts across the United States and Canada have startlingly revealed CWD in adjacent states (Nebraska, New Mexico, and Utah) but also distant (Wisconsin, Illinois, Canada) from this original endemic region. Thus far, CWD is only known to occur in North America and in South Korea. That said, international testing for CWD has been minimal with the exception of a CWD surveillance program in Germany (Sigurdson, 2008). It has no zoonotic importance, but transmitted within species by the dead bodies remained in the environment.

#### 2.5.4. Feline Spongiform Encephalopathy

Feline spongiform encephalopathy (FSE) is a neurodegenerative disease, affects domesticated cats (housecats) and captive wild cats including Cheetahs, Pumas, Ocelots, Tigers, Lions and Asian golden Cats. Most cases have been seen in the United Kingdom. In addition, a few infected housecats have been found in Norway, Switzerland, Northern Ireland and Liechtenstein. Infected zoo cats have been reported from Australia, Ireland, France and Germany. Once the symptoms appear, this disease is invariably fatal. FSE was first reported in 1990 and was apparently transmitted to individual cats in BSE contaminated feed (CFSPH, 2007).

As the BSE epidemic has declined and controls have been feeding high risk bovine tissues to animals FSE has become increasingly rare. However this disease has a long incubation period and occasional cases continue to be reported in house cats and zoo animals. The lesion pattern emphasizes the spongy, change in the cerebrum, the corpus striatum, thalamus and cerebral cortex (CFSPH, 2007). It has no zoonotic importance except cases of intra species transmission.

#### 2.5.5. Transmissible Mink Encephalopathy in Mink

Transmissible mink encephalopathy is a progressive and fatal neurodegenerative disease that affects ranched mink. Most of the adult animals on a ranch may be affected and once an animal exhibits clinical signs, death is inevitable. This disease is still poorly understood. It is very rare, with only a few outbreaks reported in the U.S.A. and other countries. Outbreaks seem to result from feeding contaminated containing prions to mink; however, the origin of these prions is unknown. Recent evidence suggests they might be an unusual variant of the bovine spongiform encephalopathy agent (Comoy *et al.*, 2013). Several

outbreaks of TME were reported in United States of America between 1947 and 1985; no cases have been documented in the U.S.A. since that time. The incubation period is 6 to 12 months in ranched mink. The early clinical signs can be subtle, may include difficulty in eating, swallowing and changes in normal grooming behavior. Affected mink often soil the nest or scatter feces in the cage. Later, animals may become hyperexcitable and bite compulsively. Affected mink often carry their tails arched over their backs like squirrels. Once the clinical signs appear, TME is always progressive and fatal. Death usually occurs within 2-8 weeks (CFSPH, 2008). It has no zoonotic importance.

### Conclusion and Recommendations

The normal, cellular PrP (PrPC) is converted into PrP (Sc) through a post translational process this leads to the progress of prion disease in different species of animals including humans. The formation of infectious agent is unknown, but with cascades of molecular mechanisms which cause degeneration of the nervous system the disease is manifested by spongiform encephalopathies. The diseases can be transmitted within and between species by several mechanisms, including ingestion, iatrogenic transmission, mother to offspring and blood transfusion. Using Meat Bone Meal for cattle feed pose a problem in the livestock industry, some of the diseases have zoonotic importance like BSE. Based on the above conclusion the following recommendations are forwarded.

- Avoid feeding of Meat Bone Meal,
- Slaughtering/culling of infected animals (shoat case) and
- Disinfection using alcohol and proper use of equipment's.

### Corresponding Author:

Dr. Ayalew Negash  
College of Veterinary Medicine and animal science,  
University of Gondar, P.O. Box.  
196, Gondar, Ethiopia  
Telephone: (+251) 966751899  
E-mail: [drayalewdvm@gmail.com](mailto:drayalewdvm@gmail.com)

### References

1. Aguzzi, A., Glatzel, M., Montrasio, F., Prinz, M., Heppner, F. 2001. Interventional strategies against prion diseases: *Nat Rev Neurosci*.2: 745-749.
2. Aguzzi, A., Calella, A.M. 2009. Prions: protein aggregation and infectious diseases: *Physiol Rev*. 89:1105-1152.
3. Arun, B., Shah, R. R. 2002. Prion and viruses 5th edition chapter 27. Prion diseases. Pp. 213-222.

4. Asuni, A.A., Guridi, M., Sanchez, S., Sadowski, M.J. 2015. Antioxidant peroxiredoxin 6 protein rescues toxicity due to oxidative stress and cellular hypoxia in vitro, and attenuates prion-related pathology in vivo: *Neurochem Int.*90:152-65.
5. Bakkebo M.K., Mouillet-Richard, S., Espenes, A., Goldmann, W., Tatzelt, J., Tranulis, M.A. 2015. The Cellular Prion Protein: A Player in Immunological Quiescence. *Front Immunol.* 2(6):450.
6. Baron, T. 2002. Identification of inter-species transmission of prion strains: *J Neuropathol. Exp. Neurol.* 61(5):377-383.
7. Brandel, J.P., Heath, C.A., Head, M.W., Levasseur, E., Knight, R., Laplanche, J.L., Langeveld, J.P., Ironside, J.W., Hauw, J.J., Mackenzie, J. 2009. Variant Creutzfeldt Jakob disease in France and the United Kingdom Evidence for the same agent strain: *Ann Neurol.*65:249-256.
8. CFSPH, 2007. The center for food security and public health (CFSPH). Feline Spongiform Encephalopathy. Iowa State University. [www.cfsph.iastate.edu/ Fact sheet s/ pdfs/ feline\\_spongiform\\_encephalopathy](http://www.cfsph.iastate.edu/Fact%20sheet%20s%20pdfs/feline_spongiform_encephalopathy) (accessed date April 2016).
9. CFSPH, 2008. The center for food security and public health. Transmissible Mink Encephalopathy. Iowa State University. [http://www.cfsph.iastate.edu/Factsheets/pdfs/Transmissible Mink Encephalopathy](http://www.cfsph.iastate.edu/Factsheets/pdfs/Transmissible%20Mink%20Encephalopathy) (accessed date April 2016).
10. Claudio, S., Nikunj, S. 2011. The intricate mechanisms of neurodegeneration in prion diseases: *Trends Mol Med.* 17(1): 14–24.
11. Claudia, Y., Acevedo, M., Holger, W. 2014: Review on The Structure of Human Prions: From Biology to Structural Models. Department of Biochemistry and Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Canada: *J. Vir.* 6: 3875-3892.
12. Cohen, E., Avrahami, D., Frid, K., Canello, T., Levy, Lahad, E., Zeligson, S., Perlberg, S., Chapman, J., Cohen, O.S., Kahana, E., Lavon, I., Gabizon, R. Snord, A.2013. A molecular marker and modulator of prion disease progression: *J. Vet. Path.* 8(1):456-459.
13. Colby, D.W., Prusiner, S.B. 2011. Prions: *J.Biol.* 3(6):1-22.Cold Spring.
14. Comoy, E.E., Mikol, J., Ruchoux, M.M., Durand, V., Luccantoni-Freire, S., Dehen, C., Correia, E., Casalone, C., Richt, J.A., Greenlee, J.J., Torres, J.M., Brown, P., Deslys, J.P. 2013. Evaluation of the zoonotic potential of transmissible mink encephalopathy: *Patho.* 2(3):520-32.
15. Emmanuel, A., Asante, Michelle, S., Andrew, G., Richard, Houghton. 2015. A naturally occurring variant of the human prion protein completely prevents prion disease: *Nature.* 522: 478–481.
16. Fraser, J.R.2002. What is the basis of transmissible spongiform encephalopathy induced neurodegeneration and can it be repaired? *Neuropathol Appl Neurobiol.* 28:1–11.
17. Gossner, A.G., Hopkins, J. 2015. The effect of PrP (Sc) accumulation on inflammatory gene expression within sheep peripheral lymphoid tissue. *Vet Microbiol.* 181(34):204-11.
18. Gray, J.G., Graham, C., Dudas, S., Paxman, E., Vuong, B., Czub, S. 2016. Defining and Assessing Analytical Performance Criteria for Transmissible Spongiform Encephalopathy-Detecting Amyloid Seeding Assays: *J Mol Diagn.* 18(3):454-67.
19. Haldar, S., Tripathi, A., Qian, J., Beserra, A., Suda, S., McElwee, M., Turner, J., Hopfer, U., Singh, N. 2015. Prion protein promotes kidney iron uptake via its ferrireductase activity: *J Biol Chem.* 290(9):5512-22.
20. Jackson, G.S, Murray, I., Hosszu, L.L., Gibbs, N., Waltho, J.P.,Clarke A.R. 2001. Location and properties of metal binding sites on the human prion protein:*Proc: Natl Acad Sci. USA* 98:8531–8535.
21. Jianhui, W., Xiaochun, W., Xiaobin, G., Joachim, B., Alexander, O., Vortmeyer. 2015. Prion Diseases and their Prpsc-Based Molecular Diagnostics: *J Neur Neurosci Proc: Natl. USA.* 95: 13363–13383 .
22. Mallucci, G., Collinge, J.2005. Rational targeting for prion therapeutics: *Nat Rev Neurosci.* 6: 23-34.
23. Mallick, R.L., Kumari, S., Singh, N., Sonkar, V.K., Dash, D. 2015. Prion protein fragment induces prothrombotic state by raising platelet intracellular calcium and microparticle release: *J. Neur. Sci.* 4(9):300-11.
24. Martin, S.F., Burón, I., Espinosa, J.C., Castilla, J., Villalba, J.M., Torres, J.M. 2007. Coenzyme Q and protein/lipid oxidation in a BSE-infected transgenic mouse model: *Free Radic Biol Med.* 142(11):1723-9.
25. Moore SJ, Smith JD, Greenlee MH, Nicholson EM, Richt JA, Greenlee JJ 2016. Comparison of Two US Sheep Scrapie Isolates Supports Identification as Separate Strains: *Vet Pathol.* 6:345-349.
26. Mukund, S., Londhe, N., Mahajan, K., Rajender, P., Gupta, Renu, M., Londhe, Lala, L. R. 2012: Review on prion diseases in animals with emphasis to Bovine Spongiform Encephalopathy

- University of Veterinary & Animal Sciences, Haryana, India. 5(7):443-448.
27. NCJDSRU CJD, 2014. National CJD Research & Surveillance Unit Data and Reports. Latest NCJDSRU CJD Monthly Statistics. Available from: <http://www.cjd.ed.ac.uk/documents/figs.pdf> (accessed date may 2016)
  28. Patrick, V. Z., Erik, M. 2000. How reassurance undermine precautions: a review. *prions res. USA.* 158-167.
  29. Perrier, V., Solassol, J., Crozet, C., Frobert, Y., Mourton-Gilles, C., Grassi, J., Lehmann, S. 2004. Anti-PrP antibodies block PrPSc replication in prion-infected cell cultures by accelerating PrPC degradation: *J.Neurochem.*89: 454-463.
  30. Pierluigi, G., Ignazio, C., Silvio, N., Qingzhong, K., Wen-Quan, Z., Witold, K. 2011. Molecular biology and pathology of prion strains in sporadic human prion diseases: *Acta Neuropat.* 121(1): 79-90.
  31. Prusiner, S.B. 1997. Prion Diseases and the BSE Crisis: *Sci.* 278 (5336): 245-251.
  32. Radostits, O.M., Blood, D.C., Gay, C.C., Hinchcliff, H.E. 2005. Mastitis In Veterinary Medicine. A text book of the diseases of cattle, sheep, pigs, goats and horses. 9th edn, WB Saunders Co Ltd., London.
  33. Sebastian, B. 2003. CNS Pathogenesis of prion disease. MRC Prion Unit, Department of Neurodegenerative Diseases, Institute of Neurology. London, UK: *J.Neuro.Dis.*5:567-573.
  34. Sigurdson, C.J. 2008. A prion disease of cervids: chronic wasting disease: *Vet Res.*8 (56)39: 41.
  35. Singh, A., Haldar, S., Horback, K., Tom, C., Zhou, L., Meyerson, H., Singh, N. 2013. Prion protein regulates iron transport by functioning as a ferrireductase: *J Alzheimers Dis.*35(3):541-52.
  36. Singh, N. 2014. The role of iron in prion disease and other neurodegenerative diseases: *J.Patho.Inf.Pathog.*10 (9): 18.
  37. Solfrosi, L., Criado, J.R., McGavern, D.B., Wirz, S. 2004. Crosslinking cellular prion protein triggers neuronal apoptosis in vivo. *J.Viro.*303: 1514-1516.
  38. White, M.D., Farmer, M., Mirabile, I., Brandner, S., Collinge, J., Mallucci, G.R. 2008. Single treatment with RNAi against prion protein rescues early neuronal dysfunction and prolongs survival in mice with prion disease: *Proc. Natl. Acad. Sci. USA.* 105: 10238-10243.
  39. Yuan, F., Yang, L., Zhang, Z., Wu, W., Zhou, X., Yin, X., Zhao, D. 2013. Cellular prion protein (PrPC) of the neuron cell transformed to a PK-resistant protein under oxidative stress, comprising main mitochondrial damage in prion diseases: *J Mol Neurosci.*56 (2):219-24.
  40. Yun, S.W., Gerlach, M., Riederer, P., Klein, M.A. 2006. Oxidative stress in the brain at early preclinical stages of mouse: scrapie. *Exp Neurol.*201 (1):90-8.
  41. Younan, N.D., Nadal, R.C., Davies, P., Brown, D.R., Viles, J.H. 2012. Methionine oxidation perturbs the structural core of the prion protein and suggests a generic misfolding pathway. *J Biol Chem.* 28:28263-28275.

1/17/2021