

PRIONS AND PRION DISEASES

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ABSTRACT

A prion is a small infectious particle, which resist inactivation by procedures that modify nucleic acids. Transmissible spongiform encephalopathies (TSEs also known as prion diseases) are a group of progressive conditions that affects the brain and nervous system of humans and animals and are transmitted by prions. Unlike other kinds of infectious diseases that are spread by microbes, the infectious agent in TSEs is a specific protein called prion protein (PrP). TSEs are unique diseases in that they can be inherited, occur spontaneously (sporadic TSE) or can be spread through infection. The clinical signs of the disease in humans vary, but commonly include personality changes, psychiatric problems such as depression, lack of coordination and/or an unsteady gait (ataxia). Patients also may experience involuntary jerking movements called myoclonus, unusual sensation, insomnia, and confusion or memory problems. In the later stages of the disease, patients may have severe mental impairment (dementia) and may lose the ability to move or speak. Well known prion diseases include scrapie (in sheep and goat), bovine spongiform encephalopathy (BSE or mad cow disease) and Creutzfeldt- Jakob disease (CJD). Less well known prion diseases include the transmissible mink encephalopathy (TME) (in mink), chronic wasting disease (CWD) (in mule, deer and elk), feline spongiform encephalopathy (FSE) (in cats), Gerstmann-Straussler-Scheinker syndrome (GSS), Alpers syndrome, and fatal familial insomnia (FFI). Six of these affect humans: CJD, GSS, FFI, mad cow disease known as (new) variant CJD, (nvCJD), Alpers syndrome and kuru. These conditions form a spectrum of diseases with overlapping signs and symptoms. There is currently no treatment that can cure or control TSEs.

Key words: prions, transmissible spongiform encephalopathy

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INTRODUCTION

Several slowly progressive neurological diseases are caused by a group of infectious agents called prions designated PrP, a protease resistant protein of molecular mass 27-30KDa(1,2).

A prion has been defined as a small proteinaceous infectious particles (PrP) which resist inactivation by procedures that modify nucleic acids(3). A Prion is a molecule of a normal body protein that have changed its three dimensional configuration. The normal protein is called PrP^C (for cellular). This is a transmembrane glycoprotein normally found at the surface of certain cells (e.g neural

and hematopoietic stem cells). Its secondary structure is dominated by alpha helices (probably 3 of them). It is soluble and therefore easily digested by proteases. The protein is encoded by a

gene designated in humans as PRNP and located on chromosome 20. On the other hand, the abnormal, disease producing protein is called a PrP^{Sc} (for scrapie). This protein has the same amino acid sequence as the normal protein, that is, their primary structures are identical but its secondary structure is dominated by beta conformation. It is insoluble in all but the strongest solvents and is also highly resistant to digestion by protease. When PrP^{Sc} comes in contact with PrP^C, it converts the PrP^C into more copies of itself. These molecules bind to each other forming aggregates. However it is not yet clear if these aggregates are themselves the cause of the cell damage or are simply a side effect of the underlying disease process(4).

Prion proteins occur in the brains of all mammals so far studied. However their normal function is

not well understood, but recent research on mice that lack the PrP gene, which encodes the prion protein suggest that it protects the brain against dementia and other degenerative problems associated with old age(5).

Extensive studies on this agent have so far failed to identify any nucleic acid associated with the infectious materials, yet biochemical studies to date cannot conclusively rule out the requirement for nucleic acid for infectivity. Whether or not prions contain RNA or DNA, their known biological and physical properties can best be described and appreciated in comparison with those of other small infectious agents (e.g. RNA species)(6).

Prion diseases are often called transmissible spongiform encephalopathies (TSE) because of the postmortem appearance of the brain with large vacuoles in the cortex and cerebellum (3). These large vacuoles cause mental and physical abilities to deteriorate and myriad tiny holes appear in the cortex causing it to appear like a sponge (hence spongiform), which becomes visible when brain tissue obtained at autopsy is examined under a microscope. The disorders cause impairment of the brain including memory changes, personality change and problems with movement that worsen with time (7).

TSEs are a group of progressive conditions that affects the brain and nervous system of humans and animals. They are unique diseases in that they can be inherited, occur spontaneously ("sporadic" TSE) or can spread through infection(8). Most TSEs are sporadic and occur in an animal with no prion protein mutation. Inherited TSE occurs in an animal carrying a rare mutant prion allele, which expresses prion proteins that contort by themselves into the disease causing conformation.

Transmission occurs when healthy animals consume tainted tissues from others with the disease(8). The transmission of disease depends on the abnormal prion being similar enough to the host prion to be able to 'lock in' to its structure and convert it. Transmission works best between animals of the same species(5). Prions cannot be transmitted through the air or through touching or most other forms of casual contact. However they can be transmitted through contact with infected tissues, body fluids or contaminated medical instruments. Normal sterilization procedures such as boiling or irradiating materials fail to render prions non infective(9).

Inherited prion diseases include Creutzfeldt-Jakob (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) and Alpers syndrome. Infectious prion diseases include kuru, scrapie, bovine spongiform encephalopathy (BSE) or "mad cow disease", CJD and variant Creutzfeldt- Jakob disease (vCJD). Sporadic prion diseases include CJD and FFI(4).

Examples of prion diseases of humans include: CJD, GSS, FFI,vCJD, kuru and Alpers syndrome. Prion diseases of animals include: scrapie (sheep and goat), transmissible mink encephalopathy (TME) (mink), chronic wasting disease (CWD) (elk, mule, deer), bovine spongiform encephalopathy (BSE) (cow) and feline spongiform encephalopathy (FSE) (cats)(3).

In view of the rising cases of neuropathological syndromes worldwide and their concomitant fatal consequences, this study was designed to draw attention of the Nigerian health care providers and indeed, Nigerian public, to the existence of these rare neurodegenerative disorders that are hitherto without any known treatment, and which may have been responsible for the mental disability

(commonly referred to as old age sickness), shortly before death, of many old people.

PATHOGENESIS

Ingested prions may be absorbed across the gut all at Peyer's patches. These are a part of the mucosal associated lymphoid tissue (MALT). It is thought that the MALT presents microorganisms to the immune system in a contained and ideal fashion, facilitating a protective immune response. Prions could be taken up in the same way. Lymphoid cells then phagocytose the particle and travel to other lymphoid sites such as lymph nodes, the spleen and tonsils. The prion can replicate in these sites. Many of these sites are innervated and eventually the prion gains access to a nerve and then propagates back up the axon to the spinal cord and eventually the brain (3).

GENETIC BASIS OF PRION DISEASES

Familial forms of prion diseases are caused by inherited mutations in the PRNP gene. Only a small percentage of all cases run in families, however. Most cases are sporadic, which means they occur in people without any known risk factor or gene mutations.

The PRNP gene provides the instruction to make a protein called the prion protein (PrP). Normally this protein maybe involved in transporting copper into cells. It may also be involved in protecting brain cells and helping them communicate. 24 point mutations in this gene cause cells to produce an abnormal form of the prion protein, known as PrP^{Sc}. This abnormal protein builds up in the brain and destroys nerve cells, resulting in the signs and symptoms of the diseases (10). Familial forms of prion disease are inherited in an autosomal dominant pattern, which means that one copy of the altered gene in

each cell is sufficient to cause the disorder. In many cases, an infected person inherits the altered gene from one infected parent (11).

CHARACTERISTICS OF DISEASES

The degenerative tissue damage caused by human prion diseases (CJD, GSS, Alpers syndrome and Kuru) are characterised by four features: spongiform change, neuronal loss, astrocytosis and amyloid plaque formation. These features are also shared with prion diseases in animals(12). The clinical signs in humans vary, but commonly include personality changes, psychiatric problems such as depression, lack of co-ordination and/or an unsteady gait (ataxia). Patients also may experience involuntary jerking movements called myoclonus, unusual sensations, insomnia, confusion, or memory problems. In the later stages of the disease, patients may have severe mental impairment (dementia) and may lose the ability to move or speak(13).

DIAGNOSIS

Neuropathological features have formed the basis of the histological diagnosis of human prion disease for many years, although it was recognised that these changes are enormously variable both from case and within the central nervous system in individual cases (11). However not all encephalopathies are caused by prions as in the cases of PM1 (caused by the JC virus), CADASIL (caused by abnormal NOTCH3 protein activity), and Krabb disease (caused by deficiency of enzyme galactosylceramidase). PSL-, which is a spongiform encephalopathy, is also probably not caused by a prion, although the adulterant, which causes it among heroin smokers, has not yet been identified (7,8,10). This, combined with the highly variable nature of prion disease pathology,

is why a prion disease cannot be diagnosed based solely on a patient's symptoms (9).

Another hindrance to a successful diagnosis of the disease is the fact that although their infectious natures and small size suggest similarities to conventional viruses, no prion has been observed, even by electron microscopy (1). However an approach towards successful diagnosis has been made by Montagna *et al.*, (12) According to the research the abnormally folded proteins that cause prion disease have been found to expose a side chain of amino acids which the properly folded protein does not expose. Antibodies specifically coded to this side chain amino acid sequence were also found to stimulate an immune response to the abnormal prion and leave the normal protein intact. The research concluded that while assisting in diagnosis, that the discovery could also be helpful in formulating a vaccine that could be used to control the disease.

APPROACHES TO TREATMENT

PrP over expression facilitates the development of prion diseases. For treatment therefore it follows that knowledge of the agents which reduce PrP expression will delay the onset of the diseases. In this case agents, which bind and stabilize the PrP^C conformation may be beneficial. Similarly agents destabilizing the PrP^{Sc} may also be effective. In addition agents, such as Congo red, which interfere with the putative PrP^C - PrP^{Sc} interaction might similarly be effective. Chemicals affecting the endocytosis, exocytosis, intracellular trafficking and degradation of proteins and in particular PrP may also be effective (3).

Another approach towards treatment concern gene therapy, where by the gene for encoding protease-resistant protein is considered to be an error in several species, and therefore something to be

inhibited (12). As our knowledge of the structure of PrP however increases, the chances of rationally deducing effective therapeutics based on these ideas also increases.

PRION DISEASES

Creutzfeldt-Jakob disease (CJD) was first described by two German neurologists, Hans Gerhard Creutzfeldt and Alfons Maria Jakob. Some of the clinical findings described in their first papers do not match current criteria for Creutzfeldt-Jakob disease, and it is considered highly likely that at least two of the patients in their initial studies were suffering from a different disorder (14). Many Americans first learned about the disease when the famed choreographer, George Balanchine died of it in 1983(15).

Creutzfeldt-Jakob disease is a very rare and incurable degenerative neurological disorder (brain disease) that is ultimately fatal. It is the most common of the transmissible spongiform encephalopathies (TSEs)(16). Typically, onset of symptoms occurs at about age 60. Three major categories of the disease exist. These are the sporadic, hereditary and acquired CJDs (17).

The prion that is believed to cause CJD exhibits at least two stable conformations. One, the native state, is water-soluble and present in healthy cells. As at 2006, its biological function was unknown. The other conformational state is very poorly water-soluble and readily forms protein aggregates (18). The CJD prion is dangerous because it promotes refolding of native proteins into the diseased state. Subsequently the number of misfolded protein molecules will increase exponentially and the process will lead to a large quantity of insoluble prions in affected cells. This mass of misfolded proteins disrupts cell function and cause cell death. Once the prion is transmitted, the defective proteins invade the

brain and get produced in a self-sustaining feedback loop, causing exponential spread of the prion, and the patient usually dies within a few months although a few patients have been known to live as long as two years (19).

Although CJD is the most common human prion disease, it is still rare and only occurs about one out of every one million people. It usually affects people aged 45-75, most commonly appearing in people between the ages of 60-65. The exception to this is the more recently recognized "variant" CJD (vCJD), which occurs in younger people (20). Some cases of CJD are clustered in certain families, and the fact that some of these families also have an apparently higher incidence of Alzheimer's disease has led to the supposition that the two diseases may be related (6).

The first symptoms of CJD is rapidly progressive dementia leading to memory loss, personality changes and hallucinations. This is accompanied by physical problems such as speech impairment, jerky movements (myoclonus), balance and coordination dysfunction (ataxia), and changes in gait, rigid posture, and seizures. The duration of the disease varies greatly but sporadic CJD can be fatal, killing its victims within months, or even weeks (21). In most patients, these symptoms are followed by involuntary movements and the appearance of a typical diagnostic electroencephalograph tracing (22).

The symptoms of CJD are caused by the progressive death of the brain nerve cells, which are associated with the build-up of abnormal prion proteins. When brain tissue from a CJD patient is examined under a microscope, many tiny holes can be seen where whole areas of nerve cells have died. The word "Spongiform" in transmissible spongiform encephalopathies refers to the spongy appearance of the brain tissue (19).

There is currently no single diagnostic test for CJD. The first concern is to rule out treatable forms of dementia such as encephalitis or chronic meningitis. The only way to confirm a diagnosis of CJD is by brain biopsy. Because a correct diagnosis of CJD does not help the patient, a brain biopsy is discouraged unless it is needed to rule out a treatable disorder (17).

There is no treatment that can cure or control CJD. Currently treatment is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relieve pain, and the drugs clonazepam and sodium valproate may help relieve involuntary muscle jerks (17). However search for viable treatment has continued (21).

The defective CJD protein can be transmitted by human growth hormone (HGH) products, corneal grafts, dural grafts or electrode implants (acquired or iatrogenic form: iCJD). Less than 5% of CJD cases are iatrogenic; it can be inherited (hereditary or familial form: fCJD). Familial cases are associated with a gene mutation and make up about 10-15% of all CJD cases; or it may appear for the first time in the patient (sporadic form: sCJD). Sporadic cases have an unknown cause and occur through out the world at the rate of about one per million which account for 85-90% of CJD cases (4,23).

Humans can contract the disease by consuming material from animals infected with the bovine form of the disease. The only cases to arise thus far have been vCJD, although there are fears - based on animal studies- that consuming beef or beef products containing prion particles can also cause the development of classic CJD. There is no evidence of CJD transmission through blood or blood products (21).

INHERITANCE AND GENETICS OF CJD

As already pointed out, 10-15% of the cases of CJD are inherited; that is the patient comes from a family in which the disease has appeared before. The disease is inherited as an autosomal dominant. This means that the patients have inherited at least one copy of a mutated PRNP gene. Some of the most common mutations are: a change in Codon 200 converting glutamic acid (E) at that position to lysine (K) (thus designated "E200K"), a change from aspartic acid (D) at position 178 in the protein to asparagine (D178N) when it is accompanied by a polymorphism in the gene encoding valine at position 129(4).

A new variant form of CJD (usually called **variant Creutzfeldt-Jakob Disease (vCJD)**) or **new variant Creutzfeldt -Jakob Disease (nvCJD)** is a rare and fatal human neurodegenerative condition. Like Creutzfeldt-Jakob disease, vCJD is classified as a **Transmissible Spongiform Encephalopathy (TSE)** because of characteristic spongy degeneration of the brain and its ability to be transmitted. However unlike the traditional forms of CJD, vCJD has affected younger patients (average age of 29 years as opposed to 65 years), has a relatively longer duration of illness (median of 14 months as opposed to 4-5 months) and is strongly linked to exposure, probably through food, to a TSE of cattle called **Bovine Spongiform Encephalopathy (BSE)** or mad cow disease

vCJD is a new disease that was first described in March 1996(15,23).

Early in the infection, patients usually experience psychiatric symptoms, which most commonly result in a form of depression or less often a schizophrenia-like psychosis. Unusual sensory

symptoms, followed by ataxia and myoclonus usually occur with dementia appearing in the final stages of the illness (14).

There is no available, completely reliable diagnostic test for use before the onset of symptoms. However magnetic resonance scans, tonsillar biopsy and cerebrospinal fluid analysis are all useful diagnostic tests. Currently the diagnosis of vCJD can only be confirmed following pathological examination of the brain (18). vCJD is strongly linked to exposure to the BSE agent. BSE is a TSE affecting cattle and was first reported in the U.K in 1986. From October 1996 to November 2002, 129 cases of vCJD were reported in the U.K, six in France and one each, in Canada, Ireland, Italy and the USA (14). In 2005 five people died from vCJD in the U.K (16).

In 2004, a possible transmission of vCJD through blood transfusion was reported, though to date no case of vCJD has ever developed in recipients of any blood. However in reaction to the report some countries prohibited donations of blood from persons who have resided in countries with higher risk of BSE (23,24).

Gerstmann-Straussler syndrome (GSS) is a very rare, usually familial, fatal neurodegenerative disease that affects patients from 20 to 60 years of age (25). This prion disease is caused by the inheritance of a **PRNP gene with a mutation encoding most commonly, leucine instead of proline at position 102 (P102L)** or valine instead of alanine at position 117 (**A117V**). The disease is strongly associated with homozygosity for a polymorphism at position 129 (both residues being methionine). Brain extracts from patients with GSS can transmit the disease to Monkeys, apes and transgenic mice containing a portion of

the human PRNP gene. Transgenic mice expressing the P102L gene develop the disease spontaneously⁽⁴⁾. GSS occurs typically in the 4th-5th decade, characterised by cerebella ataxia and concomitant motor problems, dementia less common and disease course lasts several years to death. It was originally thought to be familial, but it is now known to occur sporadically as well (3).

Kuru (also known as laughing sickness due to the outbursts of laughter that marks its second phase), the first slow infectious disease of humans to be identified, was first noted in Papua New Guinea in the early 1900s. By the 1950s most of the women and many of the children were being attacked by a fatal neurological disorder that began by causing its victims to giggle uncontrollably. The syndrome baffled American epidemiologist Carleton Gajdusek, who analysed soil, drinking water, food, and even ashes in the fires in search of the etiologic agent and its mode of transmission. After months of inquiry, Gajdusek discovered that the tribe was cannibalistic. As an expression of respect for their dead relatives, the survivors would consume portions of the corpses, including the brain. Years after preparing the brains for cooking, the women and children would begin the fatal giggles. Kuru (shaking death in the language of the Fore) was subsequently shown by Gajdusek to be caused by a previously undiscovered type of pathogen, originally called a slow virus because of its 2-to-20-years incubation period. The agent now recognised as a prion is transmitted by eating the infected neurological tissue of someone who has died from the laughing death or by cutaneous inoculation of the virus while preparing the brain. The tribe's extinction was avoided when they were persuaded to abandon their cannibalistic tribute to the dead (26,1,6).

The kuru epidemic reached its height in the 1960s. Between 1957 and 1968, over 1,100 of the South Fore died from disease. The vast majority of the victims were women. Infact, eight times more women than men, contracted the disease. It later affected small children and the elderly at a high rate as well. This disproportion was later traced to the distribution of the corpse's remains between the sexes. The males got the "good" parts of the corpse, which usually consisted of the muscles and fatty organs. The females and children got the "bad" parts, which included the brain and other less desirable parts. Thus, the women and children directly ingested the prion, leading to a much higher occurrence rate of the disease⁽²⁷⁾.

SYMPTOMS OF KURU:

1. The ambulant stage, which is accompanied by unsteadiness of stance, gait, voice, hands, and eyes; deterioration of speech; tremor; shivering; loss of coordination in lower extremities that moves slowly upward, and dysarthria.
2. The sedentary stage: at this stage the patient can no longer walk without support, more severe tremors and ataxia (loss of coordination of the muscles), shock-like muscle jerks, emotional liability, outbursts of laughter, depression, and mental slowing. It is important to note that muscle degeneration does not occur at this stage, and tendon reflexes are usually still normal.
3. The terminal stage, which is marked by inability to sit up without support, more severe ataxia, tremor and dysarthria (slurring of speech), urinary and faecal incontinence, difficulty in swallowing (dysphasia), and deep ulceration appear.

Cerebella dysfunction is the cause of these conditions (28).

Knowledge of the dynamics of kuru has continued to grow even though the disease all but disappeared with the termination of cannibalism in Papua New Guinea (29).

Fatal familial insomnia (FFI) is a very rare autosomal dominant inherited disease of the brain. The dominant gene responsible has been found in just 28 families worldwide; if only one parent has the gene, the offspring have a 50% chance of inheriting it and developing the disease. The disease's genesis and the patients' progression into complete sleeplessness is untreatable, and ultimately fatal (12). People with this rare disorder have inherited a PRNP gene with asparagines instead of aspartic acid encoded at position 178 (D178N); and the susceptibility polymorphism of methionine at position 129 of the PRNP gene. The mutation changes the shape of the protein so that it becomes a prion and makes other normal protein molecules change to the abnormal shape. This causes plaques to develop in the thalamus, the region of the brain responsible for regulation of sleep. This first results in insomnia, and then progresses to more serious problems over time (4).

The Italian doctor, Ignazio Rioter in 1979, who discovered two women from one family who apparently died of insomnia, first detected FFI. Family records showed a history of seemingly related deaths. When another member of the family fell ill in 1984, his deterioration was studied and after his death, his brain was flown to the U.S for further investigation (30).

The age of onsets is variable, ranging from 30 to 60, with an average of 60. Death usually occurs between 7 to 36 months from onset. The

presentation of the disease varies from within the same family (27).

The disease has four stages, taking 7 to 18 months to run its course:

1. The patient suffers increasing insomnia, resulting in panic attacks and phobias. This stage lasts for about four months.
2. Hallucinations and panic attacks become noticeable, continuing about five months.
3. Complete inability to sleep is followed by rapid loss of weight. This lasts about three months.
4. Dementia, turning unresponsive or mute over the course of six months. This is the final progression of the disease, and the patient will subsequently die.

There is no cure or treatment for FFI; hopes rest on the so far unsuccessful gene therapy. Sleeping pills have no effect (12).

Alpers syndrome, first described more than 70 years ago, is a rare, progressive neurodegenerative disorder that occurs in infants and children. It is an autosomal recessive, developmental mitochondrial DNA depletion disorder characterized by deficiency in mitochondrial DNA polymerase gamma (POLG) catalytic activity, refractory seizures, neurodegeneration and liver disease (31). The birth incidence is believed to be between 1/100 000 and 1/250 000. Most patients with Alpers syndrome are asymptomatic at birth and develop normally for weeks to years before the onset of symptoms. About 80% present in the first two years, and 20% present between 2 and 25 years of age (32).

First signs of the disease, which include intractable seizures and failure to meet meaningful developmental milestones, usually

occur in infancy. Primary symptoms of the disease are developmental delay, progressive mental retardation, hypotonia (low muscle tone), spasticity (stiffness of the limbs), and dementia. Seizures may include *epilepsia partialis continua*, a type of seizure that consists of repeated myoclonic (muscle) jerks. Optic atrophy may also occur, often leading to blindness. And, although physical signs of chronic liver dysfunction may not be present, many patients suffer liver impairment leading to liver failure (33). The prognosis for individuals with liver disease is poor. Those with the disease usually die within their first decade of life. Liver failure is usually the cause of death, although cardio respiratory failure may also occur (34).

Prenatal diagnosis is now available by POLG DNA testing in couples with a previously affected child and known genotype (32).

There is no cure for Alpers' disease and, currently, no way to show its progression. Treatment is symptomatic and supportive. Anticonvulsants may be used to treat the seizures (35). Physiotherapy, avoidance of group settings that promote the spread of common seasonal, childhood respiratory infections and attention to good nutrition can help to ease symptoms and reduce the frequency of neurodegenerative episodes, but are not proven to improve the overall severe prognosis (32).

Chronic wasting disease (CWD) is a transmissible spongiform encephalopathy (TSE) of deer, elk, (wapiti), and moose. First recognized as a clinical "wasting" syndrome in 1967 in mule deer in a wildlife research facility in Northern Colorado, it was identified as a TSE in 1978. CWD is typified by chronic weight loss leading to death. There is no known relationship between

CWD and other TSE of animals or people. Although there have been reports in the popular press of humans being affected by CWD a study by the CDC failed to find any relationship (36).

Most cases of CWD occur in adult animals. The disease is progressive and always fatal. The most obvious and consistent clinical sign of CWD is weight loss over time. Behavioural changes also occur in the majority of cases, including decreased interaction with other animals, listlessness, lowering of the head, blank facial expression, and repetitive walking in set patterns. In elk, behavioural changes may also include hyper excitability and nervousness. Affected animals continue to eat grain but may show decreased interest in hay. Excessive salivation and grinding of teeth also are observed. Most deer show increased drinking and urination (37).

The agent responsible for CWD is a prion, an abnormal form of a normal protein, known as prion protein (PrP), most commonly found in the central nervous system (CNS), and is capable of spreading to the peripheral nervous system (PNS), thus infecting meat, or muscle, of deer and elk. The abnormal prion protein infects the host animal by promoting conversion of normal cellular prion protein (PrP^C) to the abnormal prion form (PrP^{Sc}). The build up of PrP^{Sc} in the brain is associated with widespread neurodegeneration (14).

Research is being conducted to develop live animal diagnostic tests for CWD. Currently, definitive diagnosis is based on postmortem examination (necropsy) and testing. Gross lesions seen at necropsy reflect the clinical signs of CWD, primarily emaciation. Aspiration pneumonia, which may be the actual cause of death also, is a common finding in animals

affected with CWD. On microscopic examination lesions of CWD in the central nervous system resemble those of other TSEs. In addition, a technique called immunohistochemistry has been developed to test brain tissue for presence of the abnormal prion protein to diagnose the disease (38).

The origin and mode of transmission of the prions causing CWD is unknown, but recent research indicates that prions can be excreted by deer and elk and is transmitted by eating grass growing in contaminated soil^(39,40). Animals born in captivity and those born in the wild have been affected with the disease. Based on epidemiology, transmission of CWD is thought to be lateral or from animal to animal; although maternal transmission may occur, it appears to be relatively unimportant in maintaining epidemics. Research has recently shown that an infected deer's saliva is also able to spread the CWD prions (37).

Scrapie, the first TSE to be studied, was described in sheep and goats in the 18th century, precisely in 1732. However it is still found in most parts of the world despite attempts to eradicate the agent by destroying infected flock (4,6).

Scrapie is a fatal, degenerative disease that affects the nervous system of sheep and goats. It is one of several transmissible spongiform encephalopathies (TSEs), which are related to bovine spongiform encephalopathy (BSE or "mad cow disease") and chronic wasting disease of deer. Like other spongiform encephalopathies, scrapie is believed to be caused by a prion (5).

The name scrapie was derived from one of the symptoms of the condition, wherein affected animals will compulsively scrape off their fleece

against rocks, trees or fences. The disease apparently causes an itching sensation in the animals. Other symptoms include excessive lip smacking, strange gait and convulsive collapse (6,13).

Scrapie is infectious and transmissible among similar animals in feed contaminated with nerve tissue and so one of the most common ways to the disease (since it is incurable) is to quarantine and destroy those affected. However it tends to persist in flocks and can also arise apparently spontaneously in flocks that have not previously had cases of the disease. The mechanism of transmission between animals and other aspects of the biology of the disease are only poorly understood. Recent studies suggest that scrapie agents may be spread through urine and persist in the environment for decades⁽⁴¹⁾. Scrapie agent, in the form of extracts from infected brains, has been passed experimentally to mice, hamsters, ferrets, mink, and monkeys, but apparently is not infectious for humans, Chimpanzees or rabbits (6).

Feline spongiform encephalopathy (FSE) affects felines. It is a prion disease thought to be related to bovine spongiform encephalopathy (BSE). It is known to affect domestic and captive felines⁽²⁵⁾. Lezmi *et al.*, (2003), suggested that this infectious agent might spread by both haematogenous and nervous pathways. Like BSE, this disease can take several years to develop. It is probable, but not proven, that the affected animals contract the disease by eating contaminated bovine meat⁽²⁷⁾.

The clinical signs include ataxia that was observed to last for about 8 weeks in the affected animals. The ultimate result is death of the infected animals (42).

The disease was first reported in the United Kingdom in 1990. Uptil about 5 years ago, there were reports of 87 FSE cases (only domestic cats) in the UK, one in Norway, one in Northern Ireland and one in Switzerland. However in 1990, other feline species in zoos were reported to have contracted the disease (43).

FSE can only be confirmed at the postmortem, which includes identification of bilaterally symmetrical vacuolation of the neutrophil and neurons. Lesions are likely to be found in basal ganglia, cerebral cortex and thalamus of the brain (18).

FSE unfortunately is a terminal condition and currently there is no specific treatment for the disease (38).

Bovine spongiform encephalopathy (BSE) commonly known as mad cow disease is a fatal, neurodegenerative disease of cattle, which infects by mechanism that surprised biologists on its discovery in the late 20th century. While having never killed cattle on a scale comparable to other livestock diseases, such as foot and mouth disease and rinderpest, BSE has attracted wide attention because it seems possible to transmit the disease to humans; it is thought to be the cause of variant Creutzfeldt-Jakob disease (vCJD), sometimes called new variant Creutzfeldt-Jakob disease (nvCJD), a human brain wasting disease.

An epidemic of BSE began in Great Britain in 1985 and before it was controlled, over 170,000 cattle were sickened by it. Its origin appears to have been cattle feed that contained brain tissue from sheep infected with scrapie; and feed that had been treated in a new way that no longer destroyed the infectiousness of the scrapie prions (25). The use of such food was banned in 1998

and after peaking in 1992, the epidemic declined quickly (8).

Cattle, like most other animals, are herbivores. In nature, cattle eat grass or grains. In modern industrial cattle farming, various commercial feeds are used, which may contain ingredients including antibiotics, hormones, pesticides, fertilizers and protein supplements. BSE began when meat and bone meal were used as protein supplements in cattle feed in Europe shortly before 1986(5).

Following an outbreak of BSE in Britain, 155 people (up till 2004) acquired and died of a disease with similar neurological symptoms subsequently called vCJD or (new) variant Creutzfeldt-Jakob disease. This is a separate disease from "classical" Creutzfeldt-jakob disease, which is not related to BSE and has been known since the early 1900s. Of the 155 cases of vCJD in humans so far, 148 occurred in the United Kingdom, 6 in France, and one in Italy (25).

For many of the vCJD patients, direct evidence exists that they had consumed tainted beef, and this is assumed to be the mechanism by which all affected individuals contracted it. Disease incidence also appears to correlate with slaughtering practices that lead to the mixture of nervous system tissue with hamburger and other beef. It is estimated that 400,000 cattle infected with BSE entered the human food chain in the 1980s. Although the BSE outbreak was eventually brought under control by killing all suspected cattle populations, people are still being diagnosed with vCJD each year (though the number of new cases currently seems to be dropping). This is attributed to the long incubation period of prion diseases, which are typically measured in years or

decades. As a result the full extent of the human vCJD outbreak is still not fully known (11). The scientific consensus is that infectious BSE prion material is not destroyed through normal cooking procedures, meaning that contaminated beef foodstuffs prepared “well done” may remain infectious (10,13).

In 2004 researchers reported evidence of a second contorted shape of prions in a rare minority of diseased cattle. In other words, this implies a second strain of BSE prion. The finding of a second strain of BSE prion raises the possibility that transmission of BSE to humans has been under estimated, because some of the individuals diagnosed with spontaneous or “sporadic” CJD may have actually contracted the disease from tainted beef. So far nothing is known about the relative transmissibility of the two disease strains of BSE prion (15).

The tests used for detecting BSE vary considerably as do the regulations in various jurisdictions for e.g. when and which cattle, must be tested. For instance, in the EU the cattle tested are older (30 months +), while many are slaughtered earlier than that. At the opposite end of the scale, Japan tests all cattle at the time of slaughter.

Testing animals before slaughtering is difficult as the altered prion protein has very small level in blood or urine, and no other signal is found. Currently the only reliable test is examination of tissues during autopsy (44). No particular medication has been found to control BSE, but to contain the disease, all suspected cattle are killed and cremated and the carcass buried (3).

CONCLUSION

Unconventional transmissible agents cause a group of human and animal fatal neurodegenerative disorders. They result in spongiform change, neuronal loss, reactive gliosis and amyloid plaque formation in the affected brain. Extensive investigations on the nature of the infectious agent in these disorders have so far failed to reach any conclusion. The prion hypothesis that states that the transmissible agent is composed entirely of PrP^{Sc} has gained much favour at present since it appears to explain many of the transmissible and genetic aspects of these remarkable diseases. PrP^{Sc} is derived from a large precursor host glycoprotein (PrP^C), which is normally expressed in neurones and is encoded by gene on chromosome 20 in humans. Human prion disease occur as sporadic, familial and acquired diseases. The commonest of these is sporadic CJD, the underlying cause for which is not known. Familial prion diseases occur as inherited disorders, which are invariably associated with mutations or insertions in the human prion protein gene. A large body of evidence exists to support the claim that susceptibility to both iatrogenic and sporadic human disease is controlled by a naturally occurring polymorphism at Codon 129 in the PrP gene. Individuals who are homozygous at this Locus accounts for the large majority of CJD patients. A new variant form of CJD has been identified in the UK, which is causally linked to exposure to the BSE agent.

Since prions cause fatal diseases with no known forms of remission or recoveries, preventive measures must be taken to safeguard human and animal lives. To do this effectively no part or product of any animal that has shown signs of a TSE should enter any human or animal food chain.

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