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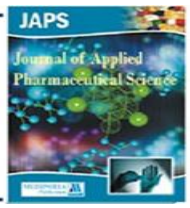

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Prion diseases: A challenge to animal health

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ABSTRACT

Prion diseases are known as transmissible spongiform encephalopathies (TSE), a group of rare, rapidly progressive, and fatal neurologic diseases. The agents responsible for human and animal prion diseases are abnormal proteins (prion or proteinaceous infectious particle) that can trigger chain reactions causing normal proteins in the brain to change to the abnormal protein. These abnormal proteins are resistant to enzymatic breakdown, and they accumulate in the brain, leading to damage. All have long incubation periods followed by chronic neurological disease and fatal outcomes, have similar pathology limited to the CNS include convulsions, dementia, ataxia (balance and coordination dysfunction), and behavioral changes, and are experimentally transmissible to some other species.

Keywords: Bovine spongiform encephalopathy, Chronic wasting disease, Exotic ungulate encephalopathy, Feline spongiform encephalopathy, Mad cow disease, Prion, Scrapie and Transmissible mink encephalopathy.

INTRODUCTION

The word prion, coined in 1982 by Dr. Stanley B. Prusiner, is a *portmanteau* derived from the words *protein* and *infection*, and prion was proposed to "denote a small proteinaceous infectious particle which is resistant to inactivation by most procedures that modify nucleic acids" (Prusiner, 1982). A proteinaceous infectious particle, or prion, is protease resistant, insoluble, forms amyloid fibrils, and has high β-helices (normal proteins are high in α-helices) (Prusiner, 1998). This is in contrast to viruses, which consist of two or three parts: (i) a helical molecule, (ii) protein coat and (iii) sometimes a viral wrapper (Hogan, 2010). Recent studies support the concept of an infectious protein (Legname *et al.*, 2004), and no specific nucleic acid sequence has been identified. Nevertheless, whether the infectious agent or prion is "protein only" remains a subject of debate (Chesebro, 2003). Prions propagate by transmitting a mis-folded protein state: so as with viruses the protein cannot replicate by itself. Instead, when a prion enters a healthy organism, the prion form of a protein induces pre-existing normal forms of the protein to convert into the rogue form. Since the new prions can then go on to convert more proteins themselves, this triggers a chain reaction that produces large amounts of the prion form (Aguzzi, 2008). All known prions induce the formation of an amyloid fold, in which the protein polymerizes into an aggregate consisting of tightly packed β-sheets. Amyloid aggregates are fibrils, growing at their ends, and replicating when breakage causes two growing ends to become four growing ends. The incubation period of prion diseases is determined by the exponential growth rate associated with prion replication, which is a balance between the linear growth and the breakage of aggregates (Masel *et al.*, 1999). This altered structure is extremely stable and accumulates in infected tissue, causing tissue damage and cell death (Dobson, 2001). Due to structural stability the prions are resistant to

formaldehyde, ethanol, proteases, nucleases, and even ultraviolet and ionizing radiation, hydroxylamine and zinc ions (Prusiner, 1982), and making disposal and containment of these particles are very difficult. Furthermore, conditions that are non-denaturing to proteins allow for its separation from other cellular components (Prusiner *et al*., 1980b). The number of possible distinct prion strains is likely far smaller than the number of possible DNA sequences, so evolution takes place within a limited space.

Although the exact mechanism of prion replication remains unclear, the agent is believed to promote the conversion of the cellular prion protein into the abnormal conformer by an autocatalytic or other unidentified process (Telling *et al*., 1996). All known prion diseases affect the structure of the brain or other neural tissue and all are currently untreatable (no natural defense) and universally fatal. PrP^{C} refers to the endogenous form of prion protein (PrP), which is found in a multitude of tissues, while PrP^{Sc} refers to the misfolded form of PrP, that is responsible for the formation of amyloid plaques (Krull *et al.,* 2004) and neurodegeneration (Lauren *et al.,* 2009). The precise structure of the prion is not known, though they can be formed by combining PrP^{C}, polyadenylic acid, and lipids (Deleault *et al.,* 2007). Many different mammalian species can be affected by prion diseases, as the prion protein (PrP) is very similar in all mammals. Due to small differences in PrP between different species it is unusual for a prion disease to be transmitted from one species to another.

ANIMAL PRION DISEASES

The first prion disease, scrapie, was described in the 18th century in Europe. Although it was not shown to be transmissible until 200 years later, it was believed that flocks of sheep and goat could be infected by this disease. Descriptions of other animal prion diseases include Bovine spongiform encephalopathy (BSE) or mad cow disease in cattle, chronic wasting disease (CWD) in white-tailed deer, elk, mule deer and moose, transmissible mink encephalopathy (TME) in mink, feline spongiform encephalopathy (FSE) in cats, Exotic ungulate encephalopathy (EUE) in nyala, oryx and greater kudu, and Spongiform encephalopathy (Not been shown to be transmissible) in ostrich.

SCRAPIE

Scrapie is a naturally-occurring, common disease of sheep and goats, and is present worldwide. The name scrapie is derived from one of the clinical signs 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 clinical signs include excessive lip-smacking, altered gaits, and convulsive collapse (Foster *et al.,* 2001). Symptoms include gait disorders and wool loss; death usually occurs between 6 weeks to 6 months after symptom onset. At present, its routes of transmission remain unclear; however, a hereditary link has been suspected because of a strong genetic element (Parry, 1979). In the 19th century, it was demonstrated that neuronal vacuolation was a characteristic neuropathological feature of the disease, but initial transmissibility studies of scrapie infection were negative. The failure to recognize the long incubation times of the disease was overcome by the inoculation of scrapie into goats (Cuille and Chelle, 1936). The transmissibility of the infectious agent was further confirmed after scrapie was accidentally transmitted into sheep when a Scottish herd was inoculated against a virus with a brain, spleen and spinal cord extract from an infected animal (Gordon, 1946). Since then, scrapie has effectively been transmitted experimentally into other species including laboratory mice (Chandler, 1961), demonstrating that it can cross the 'species barrier'. Scrapie has never been shown to pose a threat to human health (Brown and Bradley, 1998). The mechanism of transmission between animals and other aspects of the biology of the disease are only poorly understood and these are active areas of research. Recent studies suggest that prions may be spread through urine and persist in the environment for decades (Detwiler and Baylis, 2003).

Uptake of prions

Lymph nodes from healthy and infected sheep. Colouring with antibodies shows clear sign of scrapie prions in the intracellular tissue of the infected sheep. The protein enters through the intestines or through cuts in the skin. The prions cause normal proteins of the sheep to fold into the wrong shape. These proteins are gradually accumulated in the body, especially in nerve cells which subsequently die. When the prions are absorbed through the intestines, they first appear in the lymph nodes, especially in Peyer's patches at the small intestine. An experiment has shown that lambs risk being infected through milk from infected ewes (Konold *et al*., 2008). But the lambs in the experiment also infected each other, making it difficult to assess the risk of infection. The experiment did not continue long enough to show that the lambs developed symptoms, merely that the prion was present in the body.

Prevention

A test is now available which is performed by sampling a small amount of lymphatic tissue from the third eyelid (O'Rourke *et al*., 2002). Breeds such as cheviot sheep and suffolk are more susceptible to scrapie than other breeds (Eddie, 2001). Specifically, this is determined by the genes coding for the naturally occurring prion proteins. The most resistant sheep have a double set of "ARR" alleles, while sheep with the "VRQ" allele are the most susceptible. A simple blood test reveals the allele of the sheep and many countries are actively breeding away the VRQ allele. Out of fear of BSE, many European countries banned some traditional sheep or goat products made without removing the spinal cord such as smalahove and smokie (Heim and Kihm, 2003).

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)

BSE is a fatal neurodegenerative disorder in cattle. 'Mad cow disease', as it is also colloquially known, first appeared in the UK in the mid 1980s and evolved into a major epidemic (Anderson *et al*., 1996). In addition to the 'classical' BSE prion, at least two atypical BSE prions can be found in cattle. One has higher

molecular mass fragments than classical BSE and is called 'H-type'; the other has a lower molecular mass and is called 'L-type' or bovine amyloidotic spongiform encephalopathy (BASE). Atypical BSE prions may represent additional strains of BSE or spontaneously occurring prions.

The mean incubation time for BSE is about 5 years. Most cattle were slaughtered between 2 and 3 years of age and therefore did not manifest disease (Stekel *et al*., 1996). Nevertheless, more than 160,000 cattle, primarily dairy cows, have died of BSE over the past decade (Anderson *et al.*, 1996).

BSE is a massive common- source epidemic that may be caused by Meat-Bone-Meal (MBM) fed primarily to dairy cows. The MBM was prepared from the offal of sheep, cattle, pigs, and chickens as a high-protein nutritional supplement. In the late 1970s, the hydrocarbon-solvent extraction method used in the rendering of offal began to be abandoned, resulting in MBM with a much higher fat content (Wilesmith *et al*., 1991). It is now thought that this change in the rendering process allowed scrapie prions from sheep to survive rendering and to be passed into cattle. Alternatively, some bovine prions may have been present before modification of the rendering process, and, with the processing change, survived in sufficient numbers to initiate the BSE epidemic when inoculated back into cattle orally through MBM. The origin of the bovine prions causing BSE cannot be determined by examining the amino acid sequence of PrP^{Sc} in cattle with BSE, because the PrP^{Sc} in these animals has the bovine sequence whether the initial prions in MBM came from cattle or sheep. The bovine PrP sequence differs from that of sheep at seven or eight positions (Prusiner *et al.*, 1993). In contrast to the many PrP polymorphisms found in sheep, only one PrP polymorphism has been found in cattle. Although most bovine PrP alleles encode five octarepeats, some encode six. PrP alleles encoding six octarepeats do not seem to be overrepresented in BSE (Hunter *et al.*, 1994). Brain extracts from BSE cattle cause disease in cattle, sheep, mice, pigs, and mink after intracerebral inoculation (Dawson *et al.*, 1990), but prions in brain extracts from sheep with scrapie fed to cattle produced illness substantially different from BSE (Robinson *et al.*, 1995). Recent statistics argue that the epidemic is now disappearing as a result of this ruminant feed ban (Anderson *et al.*, 1996), reminiscent of the disappearance of kuru in the Fore people of New Guinea (Gajdusek, 1977). Although many plans have been offered for the culling of older cattle to minimize the spread of BSE (Anderson *et al.*, 1996), it seems more important to monitor the frequency of prion disease in cattle as they are slaughtered for human consumption.

Clinical Signs

Bovine spongiform encephalopathy is a neurological disease that usually has an insidious onset in cattle. The symptoms may include gait abnormalities (particularly hind limb ataxia), hyper-responsiveness to stimuli, tremors, and behavioral changes such as aggression, nervousness or apprehension, changes in temperament and even frenzy. The combination of behavioral changes, hyper-reactivity to stimuli and gait abnormalities is highly suggestive of BSE, but some animals exhibit only one category of neurological signs. Pacing, a modified gait in which the legs move in lateral pairs, occurred in 25% of the cattle with BSE in one study, and may be suggestive of this disease. Intense pruritus is not usually seen, but some animals may lick or rub persistently. Nonspecific symptoms include loss of condition, weight loss, teeth grinding (possibly due to visceral pain or neurological disease) and decreased milk production. Decreased rumination, bradycardia and altered heart rhythms have also been reported. The symptoms of BSE usually worsen gradually over a few weeks to six months, but rare cases can develop acutely and progress rapidly. Rapid, acute-onset neurological disease seems to be particularly common in exotic ruminants in zoos. Once the symptoms appear, BSE is always progressive and fatal. The final stages are characterized by recumbency, coma and death (OIE, 2007).

Post Mortem Lesions

Gross lesions are not found in BSE, with the exception of nonspecific signs such as emaciation or wasting. The histopathologic lesions are confined to the CNS. Neuronal vacuolation and non-inflammatory spongiform changes in the gray matter are characteristic of the disease in cattle. These lesions are usually but not always bilaterally symmetrical. Amyloid plaques are not typical of classical BSE, but are associated with atypical L-form BSE prions (OIE, 2007).

Diagnostic Tests

No reliable, specific test for prion disease in live animals is available (Hsich *et al*., 1996), but immunoblotting of the brainstems of cattle for PrP^{Sc} might provide a reasonable approach to establishing the incidence of subclinical BSE in cattle entering the human food chain (Grathwohl *et al*., 1997). Determining how early in the incubation period PrP^{Sc} can be detected by immunological methods is complicated by the lack of a reliable, sensitive, and relatively rapid bioassay. Mice inoculated intracerebrally with BSE brain extracts require more than a year to develop disease.The number of inoculated animals developing disease can vary over a wide range, depending on the titer of the inoculum, the structures of PrP^{C} and PrP^{Sc}, and the structure of protein X. Some investigators have stated that transmission of BSE to mice is quite variable, with incubation periods exceeding 1 year (Lasmezas *et al*., 1997), while others report a low prion titer of 102.7 ID50 units/milliliter of 10% BSE brain homogenate (Taylor, 1991) compared with 107 to 109 ID50 units/milliliter in rodent brain (Prusiner *et al*., 1982). Such problems with the measurement of bovine prions demonstrate the urgent need for Tg mice that are highly susceptible to bovine prions.

Histological examination of the brain is also very helpful in diagnosis, but some animals in early stages of infection have few or no spongiform changes. In addition, BSE can be detected by transmission studies in mice. However, an incubation period of several months often makes this technique impractical for routine diagnosis. Serology is not useful for diagnosis, as antibodies are not made against the BSE agent.

Treatment

There is no treatment for BSE. Suspect animals are usually euthanized for testing.

Prevention

BSE can be prevented by not feeding ruminant tissues that may contain prions to susceptible species. Complete avoidance is generally necessary, as cooking or rendering cannot completely inactivate prions. Many nations have now banned the use of either ruminant or mammalian proteins, with certain exceptions such as milk and blood, in livestock feed. This measure can interrupt transmission of the agent and control BSE epidemics; however, due to the long incubation period, the number of BSE cases may not decline for some time. In addition, countries may place trade bans on the importation of live cattle and certain ruminant proteins from affected countries.

BSE suspects are usually euthanized for testing. These carcasses cannot be used as food and must be destroyed. In the U.K., BSE carcasses are rendered at 133°C (3 bar pressure) for at least 20 minutes. Surveillance can help prevent infected animals from being used in food. Some nations conduct active surveillance of cattle at slaughter (using rapid tests) to detect cases of BSE (OIE, 2007).

CHRONIC WASTING DISEASE (CWD)

Chronic wasting disease (CWD) is a TSE affecting mule deer and elk, predominantly in the USA (Sigurdson and Aguzzi, 2007). It is the only TSE of free-ranging wildlife, affecting white deer, white-tailed deer, Rocky Mountain elk (Williams and Miller, 2002) and moose (Williams, 2005). Experimental evidence has confirmed neuronal vacuolation (Williams and Young, 1980), the accumulation of aggregated prion protein (Spraker *et al.*, 2002) and prion infectivity in the brain (Browning *et al.*, 2004). Moreover, prion protein aggregates are not only found in the central nervous system (CNS), but also in lymphoid tissues, skeletal muscles and other organs. The origin and routes of transmission are unclear (Mathiason *et al.*, 2006). As yet, there is no evidence for CWD transmission to humans.

The epidemiological study further concludes that, "a precaution, hunters should avoid eating deer and elk tissues known to harbor the CWD agent (e.g., brain, spinal cord, eyes, spleen, tonsils, lymph nodes) from areas where CWD has been identified" (Belay *et al*., 2004).

Causative agent

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^{CWD}). The build-up of PrP^{CWD} in the brain is associated with widespread neurodegeneration.

Clinical signs

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. Behavioral changes also occur in the majority of cases, including decreased interactions with other animals, listlessness, lowering of the head, blank facial expression, repetitive walking in set patterns, and a smell like meat starting to rot. In elk, behavioral changes may also include hyperexcitability and nervousness. Affected animals continue to eat grain but may show decreased interest in hay. Excessive salivation and grinding of the teeth also are observed. Most deer show increased drinking and urination.

Diagnosis

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, scientists use a technique called immunohistochemistry to test brain tissue for the presence of the abnormal prion protein to diagnose CWD. A tonsil test has been developed for diagnosis of CWD for living animals, but it has not yet received approval for widespread use. Furthermore, this type of test would not be practical for intensive testing of wild populations.

TRANSMISSIBLE MINK ENCEPHALOPATHY (TME)

Transmissible mink encephalopathy (TME) is a progressive and fatal neurodegenerative disease that affects ranched mink. Most or all of the adult animals on a ranch may be affected, and once an animal becomes symptomatic, death is inevitable. This disease is still poorly understood. It is very rare, outbreaks seem to result from feeding contaminated food 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 (BSE) agent.

Etiology

Mink seem to acquire the TME prion when they eat contaminated feed, but the origin of this agent is still unknown. TME could be caused by the scrapie prion, an agent found in sheep and goats, although this currently seems unlikely. Intracerebral inoculation of mink with U.S. (but not U.K) strains of scrapie can cause neurologic signs, but sheep tissues were not fed to mink in all TME outbreaks, and mink that were inoculated with scrapie prions by feeding did not become ill. Epidemiological investigations suggest that some TME outbreaks were linked to feeding tissues from non-ambulatory (“downer”) or dead cattle, and mink infected orally with BSE prions develop neurologic disease. A recent study in a transgenic mouse line suggests that the TME agent most closely resembles L-type BSE, an atypical BSE

agent that has been reported rarely in cattle. The L-type BSE (or "bovine amyloidotic spongiform encephalopathy") prion has a lower molecular mass than the classical BSE prion.

Strain differences have been reported in hamster-adapted TME prions. Hamsters inoculated with the Hyper (HY) strain become hyperexcitable and develop cerebellar ataxia, but hamsters inoculated with the Drowsy (DY) strain have only progressive lethargy. The DY strain remains pathogenic for mink, but the HY strain can no longer cause disease in this species.

Transmission

TME is thought to be transmitted orally. Outbreaks seem to occur when mink ingest prions in their feed. Studies in hamsters suggest that wounds on the tongue may facilitate the transmission of this agent. During an outbreak, the disease might be able to spread between animals in the same cage by cannibalism: TME prions have been reported in the mesenteric lymph node, spleen, thymus, kidney, liver, intestine and salivary gland of experimentally infected mink that had prions in the CNS. Nevertheless, mink-to-mink transmission is thought to be rare; in at least one outbreak, kits sharing a cage with their dam did not become infected. In addition, adult mink are usually housed individually in cages, making mink-to-mink transmission unlikely. TME is not known to be transmitted vertically, and mink born during one outbreak had no signs of disease the following year. Whether TME prions can survive in the environment is unknown. Other prions have been reported to remain infectious for 2-3 years and possibly longer; however, TME does not seem to recur during subsequent years on the same farm.

Clinical Signs

Transmissible mink encephalopathy causes neurologic signs including behavioral changes. The early clinical signs can be subtle, and may include difficulty eating and 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. Incoordination, circling, clenching of the jaw, and self-mutilation (particularly of the tail) may also be seen. When death is imminent, mink tend to become somnolent and unresponsive; convulsions can occur but are not common. Once the clinical signs appear, TME is always progressive and fatal. Death usually occurs within 2-8 weeks.

In one experiment, mink inoculated orally with the classical BSE agent developed a fatal neurological disease that resembled TME; however, the animals tended to become unusually docile rather than aggressive. Raccoons that are experimentally inoculated with TME prions develop neurologic signs including lethargy, abnormal responses to external stimuli, altered behavior and incoordination.

Post Mortem Lesions

No pathognomonic gross lesions are found in animals with TME; however, the carcass may be dehydrated and the fat deposits can be depleted. The typical histopathologic lesions are confined to the central nervous system. Neuronal vacuolation and non-inflammatory spongiform changes in the gray matter are pathognomonic. Astrocytosis can be seen, but amyloid plaques are not found.

Diagnosis

TME should be suspected in mink that develop progressive, fatal neurologic disease. Although TME has not been reported in raccoons, experimental infections suggest that this species could also be infected. TME have traditionally been diagnosed by histopathology. Currently, disease is usually diagnosed by detecting prions in the central nervous system. Accumulations of prions can be found in unfixed brain extracts by immunoblotting (Western blotting) and in fixed brains by immunohistochemistry. Enzyme-linked immunosorbent assays (ELISAs) have been developed for some prions including BSE, but may need to be validated for TME. Serology is not useful for diagnosis, as antibodies are not made against prions.

Control

There is no vaccine or treatment for TME. Feed that may contain prions, particularly BSE or scrapie, should not be given to mink. Tissues from non-ambulatory cattle should be avoided in mink feed, unless the carcass was tested for BSE. Complete avoidance is generally necessary, as cooking or rendering cannot completely inactivate prions. Mink may be able to acquire TME by cannibalizing infected animals; however, because mink are typically housed in individual cages, this is unlikely to be a concern in most circumstances. Kits housed with their dam do not appear to become infected.

Although there is no evidence that the TME agent is transmitted to mink from the environment, contamination should be avoided whenever possible. Decontamination of prion-contaminated tissues, surfaces and environments is difficult. These agents are highly resistant to most disinfectants (including formalin), heat, ultraviolet radiation and ionizing radiation, particularly when they are protected in organic material or preserved with aldehyde fixatives, or when the prion titer is high. Prions can bind tightly to some surfaces, including stainless steel and plastic, without losing infectivity. Prions bound to metal seem to be highly resistant to decontamination. Few effective decontamination techniques have been published. A 1-2 N sodium hydroxide solution, or sodium hypochlorite solution containing 2% available chlorine, has traditionally been recommended for equipment and surfaces. Surfaces should be treated for more than 1 hour at 20°C (68°F). Overnight disinfection is recommended for equipment. Cleaning before disinfection removes organic material that may protect prions. Recently, milder treatments including a phenolic disinfectant, an alkaline cleaner (KOH with detergents), and an enzymatic cleaner combined with vaporized hydrogen peroxide have been shown to inactivate some prions. These disinfectants may be useful for items that cannot withstand harsher decontamination procedures. Physical inactivation of prions can be carried out by porous load autoclaving at 134-138°C (273-280°F) for 18 minutes at 30 lb/in2. Autoclaving items in water is more effective than autoclaving without immersion. Dry heat is less

effective; hamster-adapted scrapie prions can survive dry heat at temperatures as high as 360°C (680°F) for an hour. A combination of chemical and physical decontamination can be more effective than either procedure alone; chemical disinfection should be carried out first, then the items should be rinsed and autoclaved. Anecdotal evidence suggests that decontamination of contaminated facilities is very difficult. (OIE, 2008)

FELINE SPONGIFORM ENCEPHALOPATHY (FSE)

FSE is a disease that affects the brains and livers of felines. It is caused by proteins called prions. FSE is a prion disease thought to be related to Bovine spongiform encephalopathy (BSE). This disease is known to affect domestic and captive feline species. Lezmi *et al*. (2003) suggested that this infectious agent might be 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.

Clinical signs

Ataxia was observed to last for about 8 weeks in the affected animals. The ultimate result is death of the infected animals.

Epidemiology

This disease was first reported in the United Kingdom in 1990. Up until 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, since 1990, other feline species in zoos were reported to have contracted this disease.

Diagnosis

This disease can only be confirmed at the post-mortem, which includes identification of bilaterally symmetrical vacuolation of the neuropil and vacuolation in neurones. Lesions are likely to be found in basal ganglia, cerebral cortex and thalamus of the brain.

Treatment

This is a terminal condition and there is currently no specific treatment for the disease. (Wikipedia).

EXOTIC UNGULATE ENCEPHALOPATHY (EUE)

EUE is a transmissible spongiform encephalopathy (TSE), or prion disease, identified in infected organs of zoo animals. This subgroup of the TSEs in captive animals was identified in zoo animals in Great Britain including species of greater kudu, nyala, gemsbok, the common eland, Arabian, and Scimitar Oryx, an Ankole-Watusi cow, and an American bison (Contreras *et al.,* 2008). Studies indicate that transmission likely occurred via the consumption of feed supplemented with meat and bone meal, although some animals died after the British ban on ground offal in animal feed. All animals died during the 1990s, with the last death occurring in 1998 (Baird-Parker *et al.,* 2000).

THERAPEUTIC STRATEGIES IN PRION DISEASES

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^{C} to PrP^{Sc}, 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 PrP^{Sc} in prion-infected cell models (Trevitt and Collinge, 2006). However, such models are not stringent screens and these compounds have produced only modest effects *in vivo* (Aguzzi *et al.*, 2001). Targeting endogenous PrP^{C} in mice with early prion infection reverses spongiform change and prevents clinical symptoms, neuronal loss, cognitive and behavioural deficits (Mallucci *et al*., 2007). Strategies to prevent the conversion process may also include the use of antibodies to bind and stabilise PrP^{C} (White *et al*., 2003), 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 PrP^{C} expression in neuroblastoma cells (Tilly *et al.,* 2003) and to prevent PrP^{Sc} accumulation in scrapie-infected cells (Daude *et al*., 2003). 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).

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