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Prions and Transmissible Spongiform Encephalopathies

D.J. Wise¹ and **G.R. Carter²**

¹Department of Biology, Concord University, Athens, West Virginia, USA. ²Professor Emeritus of the Department of Medical Sciences and Pathobiology, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia, USA.

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Glossary

Prions are proteinaceous infectious particles that cause chronic degenerative, neurological, invariably fatal diseases of animals and humans referred to as transmissible spongiform encephalopathies (TSE). The animal TSEs are the following:

Scrapie

Bovine spongiform encephalopathy

Feline spongiform encephalopathy

Transmissible mink encephalopathy

Chronic wasting disease of mule deer and elk

Spongiform encephalopathy in captive ruminants

Historical

Scrapie has been recognized as a distinct disease entity for at least 300 years (it was formally recognized in England in 1732). The nature and etiology of Kuru, a human TSE transmitted by ritual cannibalism, was elucidated in the 1970s. The human TSE Creutzfeldt-Jakob disease (CJD) has been known for many years. Bovine spongiform encephalopathy (BSE) was recognized in Britain in 1986.

William Hadlow is credited as the first to make the connection between kuru and scrapie. Carleton Gajdusek received the Nobel Prize in 1976 for his work correlating human (kuru and Creutzfeldt-Jakob disease) and animal TSEs. Prusiner was awarded the Nobel prize in 1997 for his discovery of prions. He had introduced the appellation "prion" in 1982.*

* Poser CM. Notes on the history of prion diseases. Part I. Clinical Neurology and Neurosurgery 2002; 104:1-9. - PubMed

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Prion Characteristics

- The proteins involved are thought to be derived from a post-translational modification of a normal cellular protein with unknown function. The normal cellular protein is designated PrP and the prion PrP with a superscript associated with a particular disease, for example PrP^{sc} in scrapie.
- The protein involved is approximately 254 amino acids in length. Its function is not known. In humans, the PrP gene is located on the short arm of chromosome 20.
- They multiply or reproduce by converting the normal cellular protein PrP to the PrP^{sc} the infectious form via a conformational change.

- Prions are particularly resistant to: 135°C for 18 minutes, ionizing radiation, ultraviolet light, concentrations of formaldehyde that kill viruses, and nonionic and non-denaturing anionic detergents. They are sensitive to urea, phenol, sodium dodecyl sulfate (SDS), sodium hypochlorite and other agents that denature proteins.
- Prions do not elicit antibodies in the host they infect; however, antibodies can be raised against them in other animals.
- Agents of TSEs can be transmitted to laboratory animals by various injection routes. However, prions show a marked restriction of host range. For example, PrP^{sc} will readily passage in sheep, but will only rarely infect other species such as mice, hamsters, and certain primates. All attempts to transmit scrapie to guinea pigs, rats, and chimpanzees have failed to date. Maintenance of prions in cell culture is also very difficult, although low titers of PrP^{sc} have been maintained in a mouse L cell line.
- Prions are partially resistant to proteases and have strong tendency to form aggregates or polymers.
- Antibodies to prions allowed the visualization of rod structures in infected brains, which consisted of filaments or fibrils made up of prion protein. Amyloid plaques were shown to be made up of these fibrils.
- Amyloid plaques and fibrils are located between nerve cells, presumably released following destruction of cells.

Transmissible Spongiform Encephalopathies of Animals

Scrapie

Cause

A prion. Several polymorphisms of the PrP gene have been identified and associated with differences in susceptibility to scrapie in breeds of sheep. These polymorphisms result in the production of amino acid substitutions in PrP.

Occurrence

This fatal neurological disease affects sheep and goats. The disease is endemic in the United Kingdom, but less common in other European countries. It has been eradicated from Australia and New Zealand. It occurs rarely in North and South America. The disease was first diagnosed in the United States in Michigan in 1947.

Transmission

The agent of scrapie is transmitted both vertically in family lines of flocks and horizontally by direct or indirect contact with infected placenta (e.g., ingestion, abrasions).

Pathogenesis

The scrapie prion is found in the spleen, mesenteric and retropharyngeal lymph nodes, placenta, intestine, ovary and palatine tonsil where it replicates and reaches the CNS via fibers of the autonomic nervous system. As the disease progresses high concentrations of the infectious prion accumulate in the brain. When clinical signs appear death usually occurs within six months.

Clinical & Pathologic Features

Scrapie is a non-febrile, insidious disease with a long incubation period with the peak incidence of signs at 3 - 4 years. In infected animals the agent may be detected in lymphoreticular tissues as early as eight months of age and in the CNS at about two years. Clinical signs may appear as early as three and a half years. Initial signs are restlessness, excitability, and grinding of the teeth. Later signs are tremors, intense pruritus resulting in shedding of wool and laceration of the skin, and convulsions. Death occurs from several weeks to several months after onset of signs.

Changes are seen microscopically in neurons of the medulla, pons, midbrain and spinal cord. There are single or multiple vacuoles surrounded by zones of cytoplasmic degeneration in neurons. Similar spongiform changes may also be seen in the neuropil of the CNS and peripheral nervous system. Fibrils and amyloid plaques are commonly seen in the brain.

Diagnosis

- Clinical specimens: Brain and spinal cord.
- Clinical signs are suggestive of scrapie but definitive diagnosis requires histological examination of brain tissue.
- Supportive is finding characteristic fibrils with electron microscopy.
- Other procedures used to confirm the diagnosis are immunoblotting to detect PrP^{sc}, and immunohistochemical staining of PrP^{sc}.
- Some of the methods used for the diagnosis of variant CJD (see below), including demonstration of the agent in tissue of the palatine tonsil, are being explored.

Prevention

- This is best accomplished by removing affected animals and maintaining closed flocks.
- In countries where the disease is notifiable, affected flocks are quarantined and slaughtered (particularly bloodline-related animals) or depopulation is carried out.
- Measures are implemented to prevent importation of infected animals.
- In some countries, the frequency of the disease is such that only gradual elimination is feasible.
- Genetics is being used as a tool in eradication of scrapie. This is accomplished by eliminating susceptible bloodlines.

Several polymorphisms of the PrP at several codons are associated with resistance to the disease. No such polymorphisms have been identified in goats.

Bovine Spongiform Encephalopathy

(Mad cow disease)

Cause

A prion that is not considered host species-specific. It has been concluded that the prion involved was acquired by eating contaminated (scrapie prion) meat and bone meal derived from slaughterhouse offal. A change had been made in the rendering process that allowed survival of the scrapie agent. Factors involved in the extent of the epidemic were no doubt the fact of the endemicity of scrapie and large proportion of sheep tissues and offal in the meat-bone meal supplement. Subsequently the supplement also contained offal and tissues from cattle with BSE.

Occurrence

It is estimated that more than 170,000 cases were confirmed in Britain prior to eradication. More than 99% of the laboratory confirmed cases of BSE have occurred in Great Britain. A small number of cases attributed to the importation of British cattle were identified in Switzerland, France, Portugal and Ireland. Eight cases have been identified in Canada and three cases in the USA, one of which was traced to an affected herd in Canada.

Transmission

This occurred orally through the eating of the meat-bone meal supplement referred to above. There was no evidence of horizontal or vertical transmission.

Clinical & Pathologic Features

The pathogenesis is probably roughly analogous to other TSEs, but details are not yet clear. Following exposure to the agent of BSE, there is a long incubation period prior to development of clinical signs. The average time appears to be about four to five years. Affected cattle display clinical signs associated with progressive CNS dysfunction, including behavioral changes, incoordination and hypersensitivity to various stimuli. The disease is uniformly fatal within 1 - 6 months after the onset of signs.

Diagnosis

- Clinical specimens: Fresh or formalin-fixed brain tissue.
- Diagnosis of BSE is based on clinical signs and the subsequent demonstration of the characteristic spongiform changes in the brain by histopathologic examination.
- Prion fibrils can be observed in brain extracts with electron microscopy.
- Immunohistochemical staining of tissues for the prion protein.
- Immunoblotting employing monoclonal antibodies to demonstrate the proteinase K resistant prion of BSE.
- There is an urgent need for a reliable live animal diagnostic test. One approach has involved olfactory and tonsillar biopsies and monoclonal antibodies.
- The rapid screening test used by the United States Department of Agriculture is the TeSeE® test (Bio-Rad Laboratories), which is an ELISA-based test for the BSE-specific prion protein. The company also produces similar tests for the detection of chronic wasting disease and scrapie.

Prevention

- All protein derived from ruminants must be excluded from cattle feed.
- BSE is a reportable disease in most countries. Its occurrence, even one case, can have a devastating effect on the cattle industry. Quarantine and slaughter of the herd is usually carried out.
- Affected cattle are incinerated. Decontamination of premises is carried out with a strong solution of sodium hydroxide or sodium hypochlorite.

Feline Spongiform Encephalopathy

Cause

This is presumed to be the same as that causing BSE and scrapie of sheep and goats, viz. a self-replicating protein, referred to as a prion.

Occurrence

Since 1990 more than 80 cases of feline spongiform encephalopathy (FSE) have been reported from Great Britain. One case has been reported from each of the following countries: Northern Ireland, Norway, and Liechtenstein. Nine cases have involved cheetahs and two in lions. Three of the nine cases in cheetahs occurred abroad but originated in Britain. FSE has not been reported from North, South, or Central America.

Given the strict regulations for the control of scrapie and BSE the disease in cats, even in Great Britain, should markedly

decline.

Transmission

It is presumed that cats acquire the infectious agent by eating infectious bovine, ovine, or goat tissue most likely in prepared cat foods, raw meat or table scraps. It is not known if transplacental transmission takes place and it seems unlikely that cat-to-cat transmission occurs.

Clinical Features

The incubation period is not known, but is presumed to be long as is the clinical course. The disease is seen most frequently in cats 2 - 7 years of age. Signs include behavioral changes, salivation, hyperesthesia, muscular tremors and ataxia. All cases terminate fatally.

Diagnosis

- Clinical specimens: Brain and spinal cord.
- Although the long course and clinical signs may suggest FSE, a definitive diagnosis can only be made after necropsy.
- The changes observed in the brains of cats with FSE are indistinguishable from those seen in brains of cattle with BSE. The former differs somewhat from the changes seen in sheep with scrapie. Characteristic histological changes include vacuolation of the grey matter neuropil and neurons. Fibrils of the kind seen in the brain in scrapie and BSE can be seen in the brain of cats with FSE by electron microscopy.
- Detection of the prion protein involved is not carried out in most veterinary diagnostic laboratories.

Prevention

With the near eradication of BSE it seems very unlikely that its prion will be found in cat food.

Transmissible Encephalopathy of Mink

Transmissible encephalopathy of mink (TEM) is an insidious neurologic disease characterized by a long incubation period (eight months or longer) and clinical signs of hyperirritability, loss of weight, ataxia, compulsive biting, somnolence, and ultimately death in about 2 - 6 weeks.

There are no gross necropsy lesions, but characteristic spongiform changes in the brain are noted histologically. These spongiform changes are essentially identical to those observed in the brain of sheep with scrapie and with the spongiform encephalopathies of other animals, including cattle. Mink are thought to be infected by eating contaminated meat from ruminants. Cannibalism and fighting may spread the agent among other mink.

Chronic Wasting Disease of Deer and Elk

Chronic wasting disease (CWD) was first recognized as a clinical syndrome in a farm-reared mule deer in Colorado in 1967. That the disease was a TSE was confirmed in 1978. Clinical features and pathology were similar to other animal TSEs. The disease has subsequently been seen in captive and wild deer, and elk in western states of the U.S., Wisconsin and Minnesota, and two western Canadian provinces. Like other TSEs the incubation period is long with progressive loss of condition, striking weight loss and always followed by death.

Efforts are being made to eliminate the disease from some herds by quarantine and removal of positive animals. As yet, there is no evidence of transmission of the disease to humans or to domestic cattle and sheep.

Spongiform Encephalopathy in Captive Ruminants

During the outbreak of BSE in Britain in 1986, spongiform encephalopathy was observed in some captive wild ruminants including nyala, oryx and greater kudu. These cases were attributed to the feeding of the same kind of dietary supplement that gave rise to BSE*.

*Quinn et al. Veterinary Microbiology and Microbial Disease. Blackwell Science 2002. - Available from amazon.com -

Human Transmissible Spongiform Encephalopathies

- Creutzfeld-Jacob Disease (CJD)
- Variant CJD (vCJD)
- Kuru
- Gertsmann -Straussler-Sheinker Syndrome
- Fatal Familial Insomnia

Creutzfeld-Jacob Disease

This human TSE is rare with a worldwide incidence of approximately one in a million. It appears spontaneously, but also with a familial association of ~10%. The means of transmission, except for iatrogenic transmission, is unknown. Means of iatrogenic transmission include corneal transplant, via intracerebral electrodes, surgical operations with contaminated instruments, dura mater grafts, and treatment of children and teenagers with growth hormone extracted from the hypophysis (pituitary gland) of people dying of CJD. Most cases are seen in people 50 - 70 years of age. The course of the

disease is about six months and the average age of death is 58.

Variant Creutzfeld-Jacob Disease (vCJD)

This is the human TSE attributed to consumption of meat from cattle with BSE. It was identified in Britain in 1996. However, the mode of transmission and the factors that affect vCJD susceptibility are not understood. Ways in which vCJD differs from CJD are:

- Early age of onset, an average of 27 years as compared to > 50 for CJD.
- Presentation is psychiatric as opposed to neurological symptoms.
- The typical electroencephalogram appearances of CJD are absent.
- In vCJD flower-like amyloid plaques are seen.
- The period of illness prior to death is 13 months compared to three months for CJD.
- In the UK from 1994 through 2003, 104 deaths were confirmed to be from vCJD. However, the number of reported cases has been decreasing in recent years. Only two human cases of vCJD have been diagnosed thus far in the USA and they are thought to have originated in the United Kingdom. In the USA, CJD deaths among persons < 30 years of age are fewer than five deaths per billion per year.

Procedures for the diagnosis of vCJD are the same as those used for the diagnosis of BSE.

Kuru

This human TSE occurred among the Fore tribes of New Guinea as a result of ingesting human brains of the dead during ritual cannibalism, a rite of mourning for their dead. Death occurred within a year after the onset of symptoms.

Gertsmann-Straussler-Sheinker Syndrome

This is a very rare form of CJD that appears to result from a mutation in the prion gene.

Fatal Familial Insomnia

This human TSE is considered a variant of CJD. It was found recently in patients with a prion gene mutation of an amino acid change at position 178. The first symptoms are loss of sleep, followed by hallucinations and death in less than a year.

Glossary

Neuropil: A network of axons and dendrites of neuroglial cells in mainly the central nervous system.

Polymorphisms: Refers to multiple alleles for a particular gene within a population.

Proteinase K: An endolytic serine protease that cleaves peptide bonds at the carboxylic sides of aliphatic, aromatic or hydrophobic amino acids.

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