Bovine Spongiform Encephalopathy

Mad Cow Disease, BSE

Last Updated: August 2016

Importance

Bovine spongiform encephalopathy (BSE) is a fatal neurodegenerative disease, caused by a prion, that mainly affects cattle. Other ruminants, cats, nonhuman primates and humans are occasionally affected; this disease is called feline spongiform encephalopathy (FSE) in cats, and variant Creutzfeldt-Jakob disease (vCJD) in people. BSE is primarily acquired by eating prion-containing tissues from an infected animal. Cooking and standard disinfection procedures do not destroy this agent. Infected animals or people do not become ill for years; however, the disease is always progressive and fatal once clinical signs develop. BSE was first reported in the United Kingdom in the 1980s. Its origins are unknown; however, the recycling of ruminant tissues into ruminant feed amplified BSE prions and caused an explosive epidemic in the U.K. This epidemic peaked in 1992, with almost 1,000 new cases diagnosed each week. BSE also spread to many European countries, North America, parts of Asia and possibly other areas of the world. Control measures, including restrictions on ruminant feed, have now greatly decreased its prevalence, and cases have become uncommon or rare in many areas. Many countries have also passed new regulations to prevent BSE-containing tissues from entering human food supplies.

As a result of increased surveillance, BSE prions that differ from the prion causing 'classical' BSE have been identified at very low levels in cattle populations. The leading hypothesis, at present, is that these atypical prions arise spontaneously in cattle. Some experiments suggest that an atypical prion might have given rise to the BSE epizootic when it was amplified in cattle feed.

Etiology

BSE is a member of the transmissible spongiform encephalopathies (TSEs), a group of neurodegenerative disorders caused by prions, infectious proteins that appear to replicate by converting a normal cellular protein into copies of the prion. The cellular protein, which is called PrP^{c}, is found on the surface of neurons. Pathogenic isoforms of PrP^{c} are designated PrP^{res} (The 'res' refers to the proteinase K-resistant nature of prions, compared to normal PrP^{c}). PrP^{Sc} or PrP^{TSE} are other names for this protein. Prions that cause different diseases (e.g. BSE or scrapie) are considered to be different strains of PrP^{res}.

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' BSE or H-BSE; the other has a lower molecular mass and is called 'L-type' BSE or L-BSE. The disease caused by the latter organism has also been termed 'bovine amyloidotic spongiform encephalopathy (BASE).' Atypical BSE prions are thought to represent additional strains of BSE. Currently, the most likely hypothesis is that they arise spontaneously in cattle, similarly to some prion diseases in other species (e.g., spontaneous Creutzfeldt-Jakob disease in humans). L-BSE and H-BSE have been reported to change to a classical BSE phenotype on passage in some types of mice. This has led to the suggestion that one of these prions may have originally given rise to the BSE epidemic after amplification through the food chain.

Species Affected

BSE mainly occurs in cattle, but the host range of this prion is unusually broad compared to most prions. Rare clinical cases have been reported from goats; exotic ruminants in zoos, including nyala (*Tragelaphus angasi*), kudu (*Tr. strepsiceros*), gemsbok (*Oryx gazella*), eland (*Taurotragus oryx*), Arabian oryx (*O. leucoryx*), scimitar-horned oryx (*O. dammah*), ankole cattle and North American bison (*Bison bison*); various felids including housecats, cheetahs (*Acinonyx jubatus*), pumas (*Felis concolor*), ocelots (*F. pardalis*), tigers (*Panthera tigris*) and Asian golden cats (*Catopuma temminckii*); and captive lemurs, which were apparently infected in contaminated feed. (The feline spongiform encephalopathy factsheet contains details on infections in felids.) Sheep become ill after experimental inoculation, but no naturally acquired cases have been reported in this species. European red deer (*Cervus elaphus elaphus*) can also develop clinical signs if they are fed a high dose of prions; however, this species does not seem to easy to infect, as only one of 6 orally

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inoculated red deer became infected. Mink (*Mustela vison*) and cynomolgus macaques (*Macaca fascicularis*) are also susceptible to oral inoculation. Common marmosets (*Callithrix jacchus*) and squirrel monkeys (*Saimiri sciureus*) have been infected by intracerebral inoculation; however, their natural susceptibility to BSE is unknown, as this method bypasses normal species barriers to prions. Pigs could be infected by simultaneous intracranial, intravenous and intraperitoneal routes or by intracerebral inoculation alone, but short-term feeding trials did not cause disease. One study reported that sea bream (*Sparus aurata)* seemed to be susceptible to oral inoculation.

L-BSE can infect sheep and cynomolgus macaques by intracerebral inoculation, but there are currently no reports of their susceptibility by ingestion. However, L-BSE has been transmitted to lemurs by the oral route, with the development of neurological signs. Mice have been infected with L-BSE and H-BSE by intracerebral inoculation.

Zoonotic potential

Humans occasionally develop variant Creutzfeldt-Jakob disease after eating prion-containing tissues from an infected animal. To date, all known cases have been caused by the classical BSE prion. Whether H-BSE and L-BSE can cause disease in people is still uncertain. Some studies in laboratory models, but not others, have suggested that humans may be susceptible to L-type BSE.

Geographic Distribution

Cases of classical BSE have been reported in indigenous cattle in some European countries, Canada, Israel and Japan. Some of these countries may have eradicated this disease, as it has not been reported in some time. Classical BSE was documented only in imported cattle in some nations, including the U.S., the Falkland Islands and Oman. Other countries, such as Iceland, Australia and New Zealand, seem to have remained completely free of classical BSE. The presence or absence of this disease cannot be determined in countries without adequate surveillance programs.

Atypical BSE prions have been reported in Europe, the U.S., Canada, Japan and Brazil, as the result of surveillance programs for BSE. They are also likely to exist in other countries.

Transmission

BSE is usually transmitted when an animal or human ingests tissues containing the BSE prion. Young animals may be particularly susceptible: some studies suggest that most cattle become infected with BSE during the first six months of life. Sheep are, likewise, most susceptible to experimental (oral) inoculation during the first few months of life, especially during the first few weeks. In cattle, the prions are thought to replicate initially in the Peyer's patches of the ileum, then are transported via the peripheral nerves to the central nervous system (CNS). Prions have been found in the brain of cattle as soon as 16-24 months after infection.

The highest prion concentrations occur in the CNS (both the brain and spinal cord) and in the ileum. However, very sensitive detection methods have also found this agent in lymphoid tissues associated with the jejunum and colon, various nerve ganglia, peripheral nerves and adrenal glands, and in the optic nerve and retina. The accumulation of BSE in peripheral nerves, nerve ganglia and adrenal gland seems to coincide with or follow prion accumulation in the CNS. However, one group detected BSE in the jejunum as soon as 4 months after oral inoculation. There have been rare reports of BSE prions or infectivity in other locations, such as the tonsils; bone marrow; mesenteric lymph nodes; the esophagus, abomasum and rumen of one animal (possibly in nerve endings); sensory receptors (muscle spindles) of muscles but not myofibrils; one muscle sample (probably associated with the endings of the sciatic nerve); the tongue and nasal mucosa of cattle in the terminal stages of the disease; and even in concentrated saliva. These studies have generally used very sensitive techniques, found very small quantities of prions, and reported that these tissues contain prions only in animals with clinical signs. In cattle, BSE prions do not seem to occur in the spleen or lymphatic tissues other than those associated with the gastrointestinal tract. Most studies have also not detected BSE in muscles. While one group reported evidence of its presence in a few plasma samples from cattle, others have not detected these prions in bovine blood. Epidemiological evidence and transmission studies suggest that BSE is not transmitted in milk, semen or embryos.

There is no evidence that BSE is transmitted horizontally between cattle; however, there is an unexplained increase in the risk of BSE among the offspring of infected animals. In one study, calves seemed to be more likely to develop BSE when the dam was in the later stages of infection (i.e., nearer to the onset of clinical signs). These observations have led to speculation that vertical transmission might be possible in cattle. If this occurs, it seems to be rare, and the route is unknown.

In experimentally infected sheep, BSE prions are more widely disseminated in the body than in cattle. They are readily found in many lymphoid tissues including the spleen, lymph nodes and gut-associated lymphoid tissue (GALT), as well as in the CNS. Blood-borne transmission has been demonstrated in this species. A number of ewes (18%) also transmitted BSE to their lambs in an experimental flock. The lambs were more likely to become infected if the dam was in the later stages of the disease. Prions were not found in the placenta, except in one stillborn lamb, and the live lambs were thought to have been infected shortly after birth. One lamb born to an BSE-negative sheep became infected; however, such horizontal transmission appears to be rare. In this experimental flock, a low transmission rate suggested that sheep would not maintain BSE long-term.

Prions in the environment are not thought to be significant in the epidemiology of BSE. Nevertheless, there have been concerns about their possible longevity in sources such as buried carcasses. In one study, infectivity was reported to persist for at least 265 days in sewage or phosphate buffered saline, under laboratory conditions. BSE prions detected by immunoblotting disappeared sooner than infectivity, and could not be found in sewage by 150 days. Other prions (e.g., the agents of scrapie and chronic wasting disease) can also persist in the environment for prolonged periods, and hamster-adapted scrapie prions have been shown to survive in the soil for at least 3 years. Prions are reported to remain infectious after passage through the digestive systems of birds (crows) and mammals (coyotes).

Atypical BSE

In cattle, some studies report that the tissue distribution of atypical L-BSE and H-BSE seems to resemble that of classical BSE, with prions detected mainly in the CNS. (There are, however, some differences in the pattern of distribution within the brain.) H-BSE and L-BSE have also been found in peripheral nerves, nerve ganglia and sensory receptors (muscle spindles) in some studies, and L-BSE was detected in the adrenal gland. In one study, prions were found in the muscles of L-BSE infected cattle by immunostaining, and infectivity was detected in muscle homogenates with a highly sensitive mouse bioassay. Whether vertical transmission can occur is not known. One calf born to a cow in the late stages of infection with L-BSE was not infected.

Transmission to humans including iatrogenic spread

In humans, variant Creutzfeldt-Jakob disease usually results from eating BSE prions in contaminated animal tissues. Several patients were infected via blood transfusions from asymptomatically infected individuals, and highly sensitive prion detection techniques have found BSE prions in the blood of some symptomatic patients. There is also the potential for transmission by routes such as transplantation or the use of prion-contaminated equipment during surgeries. In humans, vCJD (BSE) prions can be found in the CNS, the retina and optic nerves, various nerve ganglia and lymphoid tissues. Prions in lymphoid tissues are particularly common in the spleen, tonsils, appendix and other GALT; however, they may also be found in other lymph nodes. Although very sensitive techniques have detected prions in the urine of some vCJD patients, there is no evidence that this disease can be transmitted during casual contact.

Origins of the BSE epidemic

The origins of BSE are not well understood. This disease was first reported in the 1980s, but it was probably present in cattle since the 1970s or earlier. The two most popular hypotheses are that BSE originated as a spontaneous PrP^c mutation in cattle, or that it came from a mutated scrapie prion that contaminated ruminant feed. Other sources suggest that BSE might have originated from a wildlife population or a human TSE agent. Once the BSE agent entered cattle populations, it was amplified by recycling tissues from infected cattle into ruminant feed supplements, mainly as meat-and-bone meal (MBM). MBM is a rendered concentrate derived from animal offal and carcasses. While rendering cannot completely inactivate prions even under optimal conditions, the epidemic may have been facilitated by changes in rendering practices that allowed more prions to survive.

Disinfection

Complete decontamination of prion-contaminated tissues, surfaces and environments can be difficult. These agents are very resistant to most disinfectants, including formalin and alcohol. They are also resistant to heat, ultraviolet radiation, microwave irradiation 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. Hamster-adapted scrapie prions are commonly used to assess prion disinfection methods; however, some studies have reported that BSE prions are more resistant to decontamination (e.g., to heat) than other prions.

Few prion decontamination techniques have been published and confirmed to be effective for routine use. A 1-2 N sodium hydroxide solution, or a sodium hypochlorite solution containing 2% available chlorine (20,000 ppm), has traditionally been recommended for equipment and surfaces. Surfaces should be treated for more than one hour at 20°C (68°F). Overnight disinfection is recommended for equipment. Cleaning before disinfection removes organic material that may protect prions. Experimentally, some milder treatments have also been effective against certain prions, under some conditions. They include a specific phenolic disinfectant, various alkaline and enzymatic detergents (although the efficacy of specific agents within these classes varies), hydrogen peroxide gas plasma, radiofrequency gas plasma, sodium dodecyl sulfate plus acetic acid, copper plus hydrogen peroxide, and others. New commercial decontaminants have been developed for prions, though published tests of their efficacy vary. Some laboratories pre-treat tissues with formic acid (98%) to decrease infectivity before sectioning tissue blocks.

Physical inactivation of prions (e.g., on surgical instruments) can be carried out by porous load autoclaving at 134°C (273°F) for 18 minutes at 30 lb/in^2. Some reviews also recommend 132°C (269°F) for 1 hour (gravity displacement sterilizer). Tissue films containing prions are more difficult to decontaminate by steam after they have dried, and human guidelines for surgical instruments recommend that, after use, they be kept moist or wet until

decontamination is performed. The cleaning agent used before autoclaving should also be chosen with care, as certain agents (e.g., some enzymatic treatments) can increase the resistance of prions to steam sterilization. Some types of samples cannot be decontaminated effectively even at the recommended temperatures. For example, tissue macerates containing BSE were reported to require wet heat sterilization at ≥ 155°C (311°F) for 20 minutes, and resisted even these temperatures if the sample was dehydrated. Dry heat is less effective than moist heat; hamster-adapted scrapie prions can survive dry heat at temperatures as high as 360°C (680°F) for an hour, and one group even reported that infectivity survived incineration at 600°C (1112°F). A combination of chemical and physical decontamination can be more effective than either procedure alone, and effective combinations of chemical agents (e.g., NaOH) and autoclaving have been published. Even the harshest combination of chemical and physical disinfection is not guaranteed to destroy all prions in all types of samples. While the risk of transmitting vCJD on surgical instruments decontaminated with prion-specific techniques is thought to be very low, disposable equipment and instruments may be recommended during certain medical procedures.

Anecdotal evidence and a recent study on scrapie suggest that decontaminating contaminated facilities, especially sites such as animal pens, can be very difficult. Incineration is commonly used for carcasses, but two studies found that composting may reduce or eliminate BSE and other prions in tissues, while another suggested that soil microorganisms might degrade prions in buried carcasses. In one of the two composting studies, BSE was found to be more resistant to decomposition than the prions that cause chronic wasting disease and scrapie.

Infections in Animals

Incubation Period

The incubation period for classical BSE is estimated to be 2 to 8 years in cattle, and might be longer than a decade in a few instances. Published incubation periods in sheep fed BSE prions have ranged from approximately 1.5 years to more than 6 years. Other reported incubation periods in animals, after oral inoculation, are 4 years, 9 months in one European red deer, 15 months in mink and several years in experimentally infected macaques.

Clinical Signs

Cattle with classical BSE

Bovine spongiform encephalopathy is a neurological disease that usually has an insidious onset in cattle. The clinical signs may include gait abnormalities (particularly hindlimb ataxia) and difficulty negotiating obstacles, low carriage of the head, hyperresponsiveness to stimuli, tremors and behavioral changes such as aggression, nervousness or apprehension, changes in temperament, and even frenzy. A combination of behavioral changes, hyperreactivity to stimuli, and gait abnormalities is highly suggestive of BSE, but some animals exhibit only one category of neurological signs. Behavioral signs are often noted initially, and reluctance to be milked is reported to be a common early sign in dairy cattle. 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 in cattle, but some animals may lick or rub persistently. Nonspecific signs 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 signs of BSE usually worsen gradually over a few weeks to several 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 clinical signs appear, BSE is always progressive and fatal. The final stages are characterized by recumbency, coma and death.

Cattle with atypical BSE

The features of atypical BSE in cattle are still incompletely understood. H-BSE and L-BSE have usually been found in asymptomatic cattle during routine surveillance, in fallen stock (‘downer’ cattle) or at emergency slaughter. H-BSE in one 13-year-old cow was characterized by a change in behavior (unusual fear), while neurological signs were reported in a 19-year-old zebu bull (*Bos indicus*) with H-BSE at a zoo.

Experiments (all using intracerebrally inoculated cattle) have reported varying clinical signs, with some researchers concluding that L-BSE can be distinguished clinically from classical BSE, and others reporting that the spectrum of clinical signs overlaps. One group reported that Friesian and Alpine brown cattle infected with an Italian isolate of L-BSE developed an illness primarily characterized by inactivity, "mental dullness" (e.g., decreased alertness), and muscle atrophy, which could be distinguished from classical BSE. The animals in this study were reported to be hyperresponsive to tactile facial stimuli, but not to light or sound. In this experiment, the same breeds inoculated with classical BSE prions developed behavioral changes (e.g., aggressiveness, bellowing), as well as postural abnormalities and hyperresponsiveness to stimuli. Another group found that, in Holstein-Friesian cattle inoculated with German isolates of H-BSE and L-BSE, the initial signs seemed to be more nonspecific and subtle in atypical BSE (e.g., weight loss and loss of condition), but the differences were not sufficient to unambiguously distinguish these forms from classical BSE. These cattle were hyperresponsive to acoustic and visual stimuli as well as tactile facial stimuli. Other clinical signs also appeared similar to classical BSE. A third experiment used Danish

Holstein/ Aberdeen Angus crosses inoculated with an Italian L-BSE strain and an H-BSE strain. Both "dull" and "nervous" forms of the illness were reported in this study; however, dullness was uncommon, and many cattle became hyperreactive to external stimuli, including tactile and facial stimuli. Behavioral, sensory and motor signs were all seen. In this study, the cattle tended to develop dysmetria and have difficulty in rising, but none progressed to permanent recumbency (unlike animals with classical BSE that develop ataxia). A study that used a Japanese L-BSE isolate in Holstein cattle reported decreased activity, hyperresponsiveness to stimuli, ataxia mainly of the hindlegs, difficulty rising and little aggression.

Sheep with classical BSE

Various neurological signs have been reported in experimentally infected sheep. In one study, Cheviot sheep mainly developed ataxia with minimal pruritus, and died in a few days to a week. In indigenous French breeds, clinical signs included ataxia and intense pruritus with loss of fleece. These animals deteriorated slowly and died in approximately 3 months. A third study mainly used Suffolk and Romney sheep, but also included a few individuals of other breeds, and reported that the clinical signs were similar in all animals. Pruritus was detected in all clinically affected sheep (however, it should be noted that this sign was also reported in 29% of the sheep that did not have evidence of BSE at slaughter). Other signs in some animals included behavioral changes, teeth grinding, movement abnormalities including tremor and ataxia, hyperresponsiveness to auditory stimuli or decreased menace response in a few animals, and weight loss or loss of body condition. Altered behavior combined with ataxia and pruritus were detected in 40% of these sheep.

Goats with classical BSE

The few BSE cases documented in naturally infected goats were discovered during routine surveillance at slaughter. One goat was a scrapie suspect. Neurological signs have been reported in experimentally infected animals. In one study, the disease was characterized by ataxia and tremors, and progressed rapidly in intracerebrally inoculated goats; however, the signs in orally inoculated goats were mainly lethargy and weight loss, which progressed to recumbency over 3 weeks. Ataxia was not seen in orally inoculated goats, and neither intracerebrally nor orally inoculated goats had signs of pruritus. In another study, intracerebrally inoculated Saanen goats developed abnormalities in movement (e.g., ataxia, tremors, postural deficits and especially hypermetria) and hyperresponsiveness to stimuli. Over the course of the experiment, sniffing and nibbling of the animal handlers and instruments changed to aversive behavior, and these signs became more pronounced with time. One goat carried its head low when undisturbed and was inappetent. Other signs in some animals included pruritus, an absent menace response, teeth grinding and weight loss.

Other species

Neurological signs have also been reported in other species inoculated experimentally with BSE. Weight loss preceded behavioral signs (fear, restlessness) and other neurological signs (e.g., stereotypic head movements, abnormal flicking of the ears) in one red deer. This animal also developed audible mouth breathing and ptyalism. In mink, the clinical signs included decreased appetite, lethargy and neurological signs, which mainly consisted of hindlimb ataxia, sometimes progressing to hindleg paralysis. Hyperexcitability and hyperaggressiveness, which are common in transmissible mink encephalopathy, were not seen in these animals.

Nonhuman primates developed neurological signs, and had gradual weight loss in the later stages of the disease. Some orally inoculated, subclinical cynomolgus macaques gained weight, compared to uninoculatd animals, at a time when prions were accumulating in the gastrointestinal tract.

Post Mortem Lesions

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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 infections with the classical BSE prion or H-BSE, but are associated with L-BSE prions. Similar spongiform changes occur in experimentally infected sheep and macaques.

Diagnostic Tests

There is no live animal test for BSE. This disease is usually diagnosed by detecting prions (PrP^{res}) in the CNS. Sampling of the whole brain is mainly done at the level of the obex; however, the brainstem can be sampled through the foramen magnum for some purposes (e.g., for surveillance with rapid tests). Immunoblotting or immunohistochemistry are the most specific assays. A number of rapid diagnostic tests based on enzyme-linked immunosorbent assays (ELISAs), automated immunoblotting (Western blotting) and lateral flow assays are also available. Rapid tests allow large numbers of samples to be screened, and are often used in surveillance and slaughter testing. Positive samples in rapid tests are traditionally confirmed with immunohistochemistry or immunoblotting. However, the World Organization for Animal Health (OIE) states that confirmation of positive results with a second BSE rapid test is acceptable under some circumstances (details are available in the OIE Manual of Diagnostic Tests and Vaccines and at http://www.tse-lab-net.eu/documents/tse-oie-guide.pdf). In autolyzed brains, BSE may also be diagnosed by finding characteristic prion fibrils called scrapie-associated fibrils (SAF) with electron microscopy; however, this test has low sensitivity. Histological examination of the brain can be

very helpful in diagnosis (although it is not generally used as the sole confirmatory test), but some animals in the early stages of infection have few or no spongiform changes.

Most tests used for BSE diagnosis are relatively insensitive and cannot detect prions in the brain until 3-6 months before the onset of clinical signs. Highly sensitive assays, including protein misfolding cyclic amplification (PMCA) and quaking-induced conversion (QuIC) or real-time quaking-induced conversion, may be able to identify prions sooner. These techniques detect tiny amounts of prions by their ability to convert PrPc (the normal cellular protein) into prions *in vitro*. They are being investigated for diagnostic use, but have not yet been formally evaluated for surveillance programs. BSE can also be detected by inoculation into mice (rodent bioassays); however, an incubation period of several months makes this technique impractical for routine diagnosis. Serology is not useful, as antibodies are not made against the BSE agent.

Atypical prions (H-BSE or L-BSE) can be detected with the same tests, including rapid tests, as classical BSE. The distribution patterns of H-BSE and L-BSE in the brain differ somewhat from that of classical BSE, as well as from each other; however, these prions can also be found in the obex. Atypical prions can be differentiated from classical BSE prions by their properties in tests such as immunoblotting. H-BSE has higher molecular mass fragments than classical BSE. It also reacts with a monoclonal antibody to an N-terminal epitope that is not found in classical BSE after proteinase K cleavage. L-BSE has a lower molecular mass than classical BSE prions. Its glycosylation pattern differs from classical BSE, and it has an unusual deposition pattern in the brain characterized by amyloid plaques.

BSE in small ruminants must be distinguished from scrapie, a far more common prion disease in these species. In most cases, this can be accomplished with conventional prion tests. However, BSE is more difficult to distinguish from certain atypical (CH1641) scrapie prions. A limited number of assays such as PMCA, certain special types of immunoblots, PrPSc profiling or epitope mapping can differentiate the latter two agents.

Treatment

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

Control

Disease reporting

Veterinarians who encounter or suspect BSE should follow their national and/or local guidelines for disease reporting. This disease is reportable in most countries. In the U.S., state or federal veterinary authorities should be informed immediately.

Prevention

Some countries test cattle, and sometimes sheep and goats, at slaughter to detect cases of BSE. In most cases, testing in healthy cattle and/or small ruminants intended for human consumption is targeted at animals over a certain age. At one time, Japan tested all cattle, regardless of age. Testing requirements for high-risk animals (e.g., nonambulatory cattle or those with neurological signs) are usually more stringent. Some countries only (or mainly) test high risk animals. As the prevalence of BSE has decreased, even nations that once tested most or all cattle have scaled back their testing requirements.

When an infected animal is identified, the affected herd is usually quarantined, and the source of the infection investigated. Cohorts of an infected animal (e.g., animals born or raised in the same herd for the first year of life) are often euthanized and tested, as they are likely to have been exposed to the same feed at the time of highest susceptibility. Due to the increased risk of BSE in the offspring of infected cattle, these animals may also be traced and euthanized.

Classical 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. The specific bans, and protein sources prohibited, vary with the country. In some countries, bans also apply to other animal feeds, or even to fertilizer. The latter measures can help prevent cross-contamination and accidental exposure of cattle to BSE prions. While feed bans can interrupt transmission and control BSE epidemics, the number of cases may not decline for some time because the incubation period for this disease is so long. In addition, countries may place trade bans on the importation of live cattle and certain ruminant proteins from affected countries.

If atypical BSE represents sporadic (genetic) cases, this form of the disease cannot be eradicated. However, feed bans may help prevent these prions from being amplified in ruminant populations.

Negligible, controlled and uncontrolled risk classifications for classical BSE

The OIE recognizes countries as of "negligible risk" or "controlled risk" for classical BSE, if they conduct surveillance and traceback programs that meet OIE standards, and also fulfill certain other criteria (e.g., feed bans, laboratory support, BSE awareness programs for people who work with livestock). Countries with negligible risk have either had no cases of classical BSE in indigenous animals, or any infected animals were born more than 11 years ago, while those classified as controlled risk have had more recent BSE cases. Countries that do not meet the standards for either negligible risk or controlled risk are

classified as "undetermined risk." Atypical BSE is currently not considered in this system.

Morbidity and Mortality

Although some cases of classical BSE have been diagnosed in cattle as young as 22 months, the peak incidence occurs in 4-6 year-old-animals, and this disease is rare in animals less than 30 months of age. Dairy cattle have been predominantly affected. Nearly all L-BSE and H-BSE prions have been found in cattle older than 8 years. One exception was an L-BSE prion reported from a 23-month old steer in Japan, and another was a case thought to be H-BSE in a 6.5 year-old animal in Switzerland. BSE is always fatal once the clinical signs appear.

At one time, the estimated prevalence of classical BSE in various countries ranged from more than 100 cases per million cattle to fewer than 2 cases per million. BSE epidemics were reported in several European countries. The first outbreak occurred in the U.K., where more than 180,000 cases have been confirmed since the 1980s. The U.K. epidemic peaked in 1992, with nearly 1,000 new cases confirmed each week, and an annual incidence of approximately 2-3% in affected herds. As a result of control measures (particularly feed bans), the incidence declined to approximately 5-10 new cases per week in 2004, then to 7 to 11 cases each year between 2009 and 2011, and 0-3 cases per year between 2012 and 2016. The peak of the epidemic curve occurred later in countries where feed bans were established later; however, classical BSE has now become rare or apparently absent in many nations. Some countries outside Europe also had cases of classical BSE. Japan, which tested all healthy cattle at slaughter until 2005, and cattle > 21 months of after this time, found 36 cases between 2001 and 2009, and none since that time. Canada and the U.S. have focused their test programs on high risk cattle (e.g., those with signs that could be consistent with BSE), although the U.S. conducted more extensive testing in 2004-2006. Canada has detected approximately 20 BSE cases altogether, with the most recent classical BSE case identified in 2015, and the U.S. has reported one case of classical BSE in an animal imported from Canada.

As of 2016, approximately 100 animals infected with L-BSE or H-BSE have been identified worldwide. The majority of these animals were asymptomatic, and identified mainly during surveillance programs for classical BSE. The incidence of atypical BSE appears to be much lower than classical BSE. Its prevalence in France and Germany may be as low as 1 case per 3 million adult cattle. Small numbers of cases were also reported from Japan, Brazil and North America, including three cases in the U.S.

Only two BSE cases have been published, to date, in goats, and no naturally acquired cases have been seen in sheep, despite their susceptibility to experimental infection. Some cases in small ruminants might have been misdiagnosed as scrapie, particularly before BSE surveillance was extended to these species. Surveillance conducted in Europe suggests that the prevalence of BSE is currently very low in sheep, if it occurs at all. Estimates of the maximum proportion of sheep TSE cases that could be BSE range from 0.7% to 5%. Experimentally infected sheep that are genetically resistant to scrapie seem to have some resistance to BSE after intracerebral inoculation, but are not immune to infection or disease. However, some studies suggest that these sheep (e.g., the ARR/ARR genotype) might be completely resistant to oral inoculation.

Infections in Humans

Incubation Period

The incubation period for vCJD is difficult to establish with certainty; however, the average incubation period is estimated to be 11 to 12 years, and some people have remained asymptomatic for up to 16 years before developing symptoms. In three cases transmitted in blood transfusions, the incubation period was 6 to 8.5 years. For comparison, some other human prion diseases have similar median incubation periods, but have been reported up to 40 years after exposure.

Clinical Signs

The symptoms of vCJD are broadly similar to the sporadic (genetic) form of CJD, but usually appear in younger patients. The first signs are usually psychiatric symptoms, such as anxiety, depression, insomnia, social withdrawal, delusions and/or persistent painful sensory symptoms. In most patients, frank neurological signs such as gait disturbances, ataxia, incoordination, memory loss, slurring of speech and tremor appear a few months later; however, neurological signs coincide with or precede psychiatric symptoms in a minority. Cognitive function gradually deteriorates. Involuntary movements (e.g., chorea, dystonia, myoclonus), visual disturbances and dementia typically develop late in the course of disease. Most patients die within two years.

All of the known clinical cases, to date, have occurred in people with a certain genotype (see Morbidity and Mortality, below). Some authors have noted that, if other genotypes are more resistant but not actually immune to vCJD, their symptoms and/or the progression of the disease might differ from the syndrome described so far.

Diagnostic Tests

A tentative diagnosis may be made before death by the history, clinical signs and cortical atrophy on magnetic resonance imaging (MRI) of the brain. The electroencephalogram (EEG) is usually normal, and only rarely develops the characteristic abnormalities seen in sporadic CJD (f it occurs at all, this is seen late in the disease.) A definitive diagnosis can be made by finding prions in tonsil biopsies with immunoblotting (Western blotting) or immunohistochemistry. In other cases, the

diagnosis is made by microscopic examination of brain tissue, usually at necropsy. Numerous amyloid plaques surrounded by vacuoles are found in vCJD; such plaques are seen in only 5-10% of cases of sporadic (genetic) CJD. Large amounts of prion protein can be found around the plaques by immunohistochemistry. Highly sensitive prion techniques (e.g., PMCA, QuIC) can detect BSE prions in the blood of some vCJD patients and are being examined as potential antemortem and blood screening tests. Prions have also been found in the urine of some patients.

Treatment

No treatment is available, other than supportive care. While various drugs have been tried, none have been demonstrated to be effective, to date.

Control

Variant Creutzfeldt-Jakob disease can usually be avoided by not eating tissues from BSE-infected or potentially BSE-infected animals. Animals with clinical signs consistent with BSE (e.g., neurological signs, downer cattle) cannot be used as human food in many countries. Tissues that have a high risk of transmitting BSE in cattle (specified risk materials or SRM) are no longer allowed to enter the human food chain in many countries. They generally include the brain, spinal cord, associated bones and some associated nerve ganglia; tonsils; and various portions of the spinal cord (e.g., currently, the distal ileum in the U.S., and the last 4 meters of the small intestine, the cecum and mesentery in the E.U.). Surveillance of animals at slaughter, using rapid tests, can help prevent meat from infected animals from reaching the human food supply. (While most sources do not consider meat alone to be of risk, it could become contaminated with prions from neurological or GI lymphoid tissues during processing.) Slaughter and processing techniques that have a high risk of contaminating muscle tissues with CNS (e.g., mechanically separated meat) have been prohibited in many countries. In the E.U., some slaughter regulations now apply to sheep and goats, as well as cattle.

Special prion decontamination techniques, or the use of disposable surgical instruments, can reduce the risk of person-to-person transmission during surgeries. In addition to the risks from neurological tissues in vCJD suspects, there are concerns that some asymptomatic people may have BSE prions in tissues such as the appendix or tonsils. Transmission in blood cannot be completely prevented with the current techniques; however, many countries restrict blood donations from people with a significant risk of having been infected during the BSE epidemics. Some countries have also taken other measures, such as universal leucodepletion of blood, to reduce the risk of vCJD. Prion filters have been developed to reduce infectivity in plasma, but are still being evaluated and are not in wide use. Some countries import fresh frozen plasma from low-risk countries for patients without dietary exposure to BSE (e.g., patients born after 1996 in the U.K.).

Although laboratory or abattoir-related cases have not been reported, veterinarians and laboratory workers should always take precautions when conducting necropsies on BSE suspects or handling tissues; BSL-3 is the recommended level of protection. Because prions can survive in the environment for years and are difficult to disinfect, contamination of surfaces and equipment should be avoided as much as possible. Disposable plastic-coated paper sheets can be used to protect tables and other surfaces. Disposable instruments and work clothing may also be used.

Morbidity and Mortality

To date, vCJD has usually been seen in young patients. The reason is unknown, but it is possible that children and adolescents are more susceptible to infection and/or have a more rapid progression of disease than adults. The median age of onset is 26 years (range 12 to 74 years); in contrast, it is 65 years (range 15 to 94 years) in the sporadic (genetic) form of Creutzfeldt-Jakob disease. Once symptoms develop, vCJD is always fatal.

As of May 2016, 228 cases of vCJD have been reported worldwide. This includes 178 cases in the U.K., 27 cases in France, and < 5 cases each in various European, North American, Asian and the Middle Eastern countries. With the exception of the French cases, the vast majority (185 people) had resided in the U.K. for more than 6 months during the peak of the BSE epidemic, and are likely to have been infected there. The number of vCJD cases diagnosed in recent years has been falling. The incidence in the U.K. peaked in 2000, when 28 cases were diagnosed, and gradually fell to 5 cases per year in 2005. There were 2-5 cases per year between 2006 and 2011, and only two additional cases were diagnosed between 2012 and 2016. To date, all people with confirmed clinical cases have been homozygous for methionine at codon 129 in the PrP^{C} protein (M/M). One person who was heterozygous for methionine/valine at this codon (M/V) was infected in a blood transfusion, but did not develop vCJD symptoms, and died of unrelated causes after 5 years. A possible, but unconfirmed, clinical case occurred in a M/V individual in 2009. It is not yet known whether people with resistant genotypes (V/V or M/V) are unlikely to develop vCJD, or simply have a longer incubation period.

The number of people who have been infected asymptomatically, and the percentage of those likely to develop vCJD, are still unclear. Based on the pattern of infection in the U.K, some sources suggest that, at most, 70 additional cases can be expected. However, some studies that have examined lymphoid tissues, such as the tonsils or appendix, suggest that from 1 in 2000 to 1 in 10,000 people in the U.K. may be infected subclinically. This includes a recent, large scale survey, which found BSE prions in 0.05% of appendix samples archived between 2000 and

2012. This study found that V/V individuals seemed to be overrepresented among those with BSE prions, and the M/V genotype was also seen. Whether these people will ever develop vCJD is not known.

Internet Resources

Canadian Food Inspection Agency
http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/bse/eng/1323991831668/1323991912972

Centers for Disease Control and Prevention
http://www.cdc.gov/prions/bse/index.html

European Commission. TSE/BSE
http://ec.europa.eu/food/food/biosafety/tse_bse/index_en.htm

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.html

The National Creutzfeldt-Jakob Disease Surveillance Unit, United Kingdom.
www.cjd.ed.ac.uk

United Kingdom. Department for Environment Food and Rural Affairs. Bovine Spongiform Encephalopathy
https://www.gov.uk/guidance/bse

United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service. Bovine Spongiform Encephalopathy
http://www.usda.gov/wps/portal/usda/usdahome?navtype=SU&navid=BSE

United States Food and Drug Administration. Bovine Spongiform Encephalopathy
http://www.fda.gov/animalveterinary/guidancecomplianceenforcement/complianceenforcement/bovinespongiformencephalopathy/default.htm

World Health Organization. Bovine Spongiform Encephalopathy
http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

Acknowledgements

This factsheet was written by Anna Rovid Spickler, DVM, PhD, Veterinary Specialist from the Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) provided funding for this factsheet through a series of cooperative agreements related to the development of resources for initial accreditation training.

The following format can be used to cite this factsheet.
Spickler, Anna Rovid. 2016. *Bovine Spongiform Encephalopathy*. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

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* Link is defunct