BOVINE SPONGIFORM ENCEPHALOPATHY AND CREUTZFELDT–JAKOB DISEASE: IMPLICATIONS FOR PHYSICIANS

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Abstract • Résumé

The appearance of bovine spongiform encephalopathy (BSE) followed by new spongiform encephalopathies and variant Creutzfeldt–Jakob disease (CJD) in the United Kingdom indicates that these diseases may be linked. To give an understanding of this risk, the authors review the literature on the pathogenesis of CJD and BSE and the current findings on how these diseases are transmitted. They also discuss the implications for Canada's food and blood supply and outline previously published recommendations for disease prevention.

L'apparition, au Royaume-Uni, de l'encéphalopathie spongiforme bovine (ESB) suivie de nouvelles encéphalopathies spongiformes et de variantes de la maladie de Creutzfeldt–Jakob indique un lien possible entre ces maladies. Pour aider à comprendre ce risque, les auteurs passent en revue les écrits sur la pathogenèse de la maladie de Creutzfeldt–Jakob et de l'ESB, ainsi que les constatations actuelles sur la transmission de ces maladies. Ils discutent aussi des répercussions sur l'approvisionnement en aliments et en sang au Canada et présentent un aperçu de recommandations déjà publiées sur la prévention des maladies.

The recent report from the United Kingdom of a new variant of Creutzfeldt–Jakob disease (CJD),[1] with putative links to bovine spongiform encephalopathy (BSE), prompted us to search the literature for information on BSE and transmissible spongiform encephalopathies, specifically CJD, and their implications for Canada's food and blood supply.

CREUTZFELDT–JAKOB DISEASE

CJD is the best known of the transmissible spongiform encephalopathies. These diseases affect both animals and humans (Table 1) and share many features,[2] the two most important of which are their transmissibility and the spongiform changes (microscopic spaces or vacuoles in the substance of the brain) visible on neuropathological examination of affected tissue. Other neuropathological hallmarks include astrocytosis, neuronal cell loss and, occasionally, the presence of kuru plaques. These amyloid plaques derive their name from their presence in people with the spongiform encephalopathy kuru and differ from the plaques of Alzheimer disease in their morphological appearance and their inclusion of a different amyloid protein.[2]

CJD has a stable worldwide incidence rate of about 1 per million and an equal male–female ratio.[9,10] Although many epidemiologic risk factors for sporadic CJD have been proposed, none has been definitively linked. Some of the more biologically plausible risk factors for sporadic and iatrogenic CJD include the ingestion of animal brains and a history of surgical procedures.[11–13] A recent analysis of pooled data from several studies demonstrated only two risk factors: a family history of CJD (odds ratio 19) or a history of psychotic disease (odds ratio 9.9).[14] Despite suggestive case reports, there is no evidence for transmission by person-to-person contact.[15–17]

Patients with CJD usually present with a rapidly progressive dementia, myoclonus and periodic sharp wave activity on electroencephalograms (EEGs).[2] Many variants occur, however, and virtually any combination of cortical, subcortical, cerebellar and spinal-cord findings is possible. Myoclonus and EEG changes are not invariably

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present. The initial symptoms are often quite vague, but rapid progression suggests a diagnosis of CJD. The median duration from onset to death is 4.5 months. Death is usually caused by complications of the demented state such as pneumonia and dehydration. A recent study has shown that immunostaining of tonsillar biopsy tissue may be a feasible diagnostic test in living subjects.[18] Although many agents have been tried, there is no effective therapy.[19–22] One report of remission exists.[23]

About 10% of cases of CJD are familial, and approximately 20 mutations leading to the disease have been identified.[24] The mutations are found in the prion protein (PrP) gene. Although the function of PrP is unknown, a neurodegenerative disease was found to develop in aged mice with an experimentally disrupted PrP gene.[25] The two best-known foci of familial CJD, among people in Slovakia and among Libyan Jews in Israel, are associated with a mutation at codon 200 of the PrP gene.[26,27]

The presentation of sporadic CJD is partly determined by a polymorphism at codon 129 of the PrP gene. The biochemical characteristics of the PrP defect determine the clinical presentation of the disease:[28] people homozygous for methionine present with dementia and have myoclonus and periodic sharp wave activity on the EEG, and those homozygous for valine present with ataxia.

Polymorphism at codon 129 is also associated with a risk for iatrogenic CJD. People homozygous for valine are at greater risk for iatrogenic disease, whereas those homozygous for methionine are at greater risk for sporadic disease.[29] About 51% of Caucasians are heterozygous for methionine and valine at codon 129, and only 12% are homozygous for valine.[29,30]

Various medical and surgical therapies and procedures have been linked with CJD.[31] Recipients of human growth hormone and gonadotropin are at increased risk.[32,33] CJD has also been transmitted by surgical instruments,[16,34] stereotactic EEG electrodes,[34] corneal transplants,[35] dura mater[36] and pericardium.[37] Incubation periods are 8 to 20 years for those infected through peripheral inoculation and about 2 years for patients who have undergone neurosurgery.[31]

Most of the transmissible spongiform encephalopathies, even the familial ones such as Gerstmann–Sträussler–Scheinker syndrome, are transmissible to laboratory animals.[38] Fatal familial insomnia is the exception. Intracerebral inoculation of a suspension of brain tissue is the usual method of laboratory transmission. In some circumstances, other tissues (e.g., intestinal tissue[39] and the buffy coat, which contains leukocytes[40–42]) have been found likely to be infective, and other routes (e.g., oral) have been used successfully in transmission experiments.[43] The amount of central nervous system (CNS) tissue required to achieve transmission is many times smaller than the amount of non-CNS tissue required.

Although CJD can be transmitted through blood in the laboratory, a case of transfusion-related CJD has never been confirmed in humans, even in those with hemophilia.[44–48] A case of CJD occurring 1 year after liver transplantation was reported; a donor of albumin, which the transplant patient had received while in hospital, later died of CJD.[47] The 0.5 g of albumin received was minimal and likely insufficient for disease transmission, and thus the occurrence of the CJD in this case was probably coincidental.[49]

Table 1: Transmissible spongiform encephalopathies

Syndrome (year of first report)	Features
Human	
Creutzfeldt–Jakob disease (1920)[2]	Dementia; myoclonus; changes on electroencephalogram
Gerstmann–Sträussler–Scheinker syndrome (1928)[2]	Dementia; ataxia; exclusively familial
Kuru (1957)[3]	Ataxia; tremor; associated with mourning rites among the Fore people of New Guinea
Fatal familial insomnia (1986)[4]	Insomnia; ataxia; myoclonus
Variant Creutzfeldt–Jakob disease (1996)[1]	Low age at onset; ataxia; unique neuropathology
Animal	
Scrapie (sheep and goats) (c. 1750)[5]	Ataxia; pruritus
Transmissible mink encephalopathy (1947)[5]	Ataxia; somnolence
Chronic wasting disease of elk (1980)[5]	Behavioural changes; wasting
Bovine spongiform encephalopathy (1987)[6]	Ataxia; wasting
Spongiform encephalopathy of exotic ungulates (1988)[7]	Ataxia; wasting
Feline spongiform encephalopathy (1990)[8]	Ataxia; behavioural changes

How is Creutzfeldt–Jakob disease transmitted?

The nature of the agent or agents that cause the transmissible spongiform encephalopathies is currently unknown. There are competing theories that either an infective prion protein (PrP) or a virus is responsible; these theories have been discussed in detail in recent reviews.[50,51] The word "prion," derived from *pro*teinaceous *in*fectious particle, was proposed by Prusiner, the originator of the hypothesis that the protein itself is infectious.[52,53]

The prion theory holds that the protein itself is the agent of infection.[53] PrP is a normal constituent of cell membranes and is widely distributed throughout the body. According to the hypothesis, the PrP molecule somehow enters the CNS and induces a conformational change (to a ß sheet) in the host's normal PrP; a chain reaction then occurs, continuing this process. In people with familial disease, PrP is more likely to undergo conformational change spontaneously than it is in other people; sporadic cases can be explained by the hypothesis that the risk of a person's normal PrP undergoing conformational change is 1 in a million.

The proponents of the virus hypothesis have questioned why the process occurs only in the CNS and not in other tissues rich in PrP, and how a protein can be transported unaltered from the gut across the blood–brain barrier to the CNS.[51] Recent work has demonstrated an inverse relation between infectivity and PrP levels in brain homogenates, which suggests that PrP is not necessary to transmit infection.[54] Other researchers have replicated that study and interpreted the results differently, stating that the absence of infectivity was due to the experimental conditions.[55] Numerous reports of viral particles associated with CJD exist.[56] However, nucleic acid associated with CJD infectivity has not been definitively identified, and the agent is resistant to many procedures that inactivate most, though not all, known viruses. Interestingly, some research, which has not been replicated by others, suggests that the agent of CJD may be very commonly carried by humans, though rarely pathogenic.[57]

Although the nature of the infectious agent is controversial, transmission studies of various spongiform encephalopathies have provided insight into the mechanism of infection. In laboratory studies, intracerebral inoculation has been found to be the most efficient means of transmission, although oral dosing and peripheral injection have also been effective.[38,39,42,43] Tissue from the CNS is the most infective, but tissue from the lymphoreticular system and the gut are also infective. Muscle has been shown to be infective only in very high doses, in a single study involving brain inoculation of scrapie.[39] Lateral transmission of scrapie has been reported in sheep;[58] however, vertical transmission to offspring probably does not take place.[59] In three cases of pregnant women with CJD the children have remained healthy.[34,60,61] One mystery of scrapie transmission was recently explained:[62] healthy sheep pastured in fields where sheep with scrapie had previously been developed the disease; hay mites were identified as the probable vector. If replicated, this finding will have important implications for farms with livestock afflicted with scrapie or BSE.

Transmission studies indicate that there is a species barrier: not all animals are susceptible to all transmissible spongiform encephalopathies.[63] There are strains of disease agents that, on serial passage in a particular host, develop stable, unique incubation periods and pathological patterns.[63,64] When a strain known to one species is transmitted to a second species and then injected back into the original host, it may have a new pattern in terms of incubation period and pathological distribution.[63,65] Therefore, it could be difficult to identify the source in an outbreak of spongiform encephalopathy involving a new species.

Infection control

The resistance to sterilization and the infectivity of the agent or agents responsible for transmissible spongiform encephalopathies pose problems for disease prevention.[16,66,67] For disease prevention in operating rooms and autopsy suites, some have suggested that a specific sterilization procedure is sufficient;[68] however, published evidence proves the contrary.[69,70]

Australia's recently released guidelines for infection control of transmissible spongiform encephalopathies[71] recommend the destruction of all surgical and autopsy instruments used on high-risk patients (i.e., those with proven or suspected transmissible spongiform encephalopathy or with a family history of disease). This extends to normally reused equipment such as needles for lumbar puncture and tonometers. For low-risk patients (e.g., recipients of human growth hormone or dural grafts) the instruments must be subjected to intensive decontamination. Because an autopsy of a patient with a spongiform encephalopathy requires special precautions (e.g., opening the skull with the head shrouded to prevent aerosolization) the use of designated autopsy suites, as recommended in Australia,[71] would provide the best service with the least risk.

BSE and implications for Canada's food supply

In 1985 BSE was recognized among cattle herds in the United Kingdom.[6,72] Diseased cows have temperament changes, ataxia and decreased milk production.

BSE has reached epidemic proportions among cattle in the United Kingdom, affecting about 1% of all cattle at the height of the epidemic.[72]

The origin of BSE has been attributed to the use of animal byproducts containing CNS tissue from sheep and cattle in cattle feed, a practice that began in the late 1970s.[72] The BSE outbreak was predictable, given that transmissible mink encephalopathy had been linked to the feeding of infected ruminant tissue (in this case sheep infected with scrapie) to mink.[73] In 1988 the UK government banned the use of ruminant tissue in feed and has claimed that this will lead to the disappearance of BSE in the United Kingdom.[72,74–78] Others, citing evidence for lateral transmission, dispute this claim.[79,80] Fear that BSE may contaminate the human food supply prompted the Specified Bovine Offal Act of 1989, which prevents the use of animal tissue from the CNS, spinal cord, intestine, thymus, tonsils and spleen in the human food supply. Until 1995, this did not apply to animals less than 6 months of age, which is perhaps unfortunate because sheep with scrapie have been found to be infective at as early as 4 months of age.[81] The high-risk foods are "processed" meats that contain offal; bone; mechanically recovered meats; and, apparently, binding agents made from brain homogenates.[82] Whole beef, such as steak or ground beef, is probably not a high-risk food, because muscle has been found to have very low infectivity in scrapie.[39]

Of some concern is evidence that BSE is a risk to the food chain: new transmissible spongiform encephalopathies appeared in the United Kingdom in the late 1980s (feline spongiform encephalopathy and spongiform encephalopathy of exotic ungulates) and were possibly related to the same feed that was implicated in the cases of BSE.[7,8,83] Changes in the production process of pharmaceutical agents, such as heparin and bovine insulin, have been implemented and have likely rendered these products safe.[84]

BSE has crossed the species barrier, and transmission has occurred to numerous species, including pigs.[85] Mice, too, are susceptible to experimentally transmitted BSE; however, in one study, transgenic mice expressing only human PrP were not found to be susceptible;[86] these findings suggest that humans may not be at risk for BSE. There are claims that the lack of epidemiologic evidence linking scrapie and CJD is also evidence that BSE poses no risk,[74] but the relative lack of a species barrier in BSE suggests that the situations are not comparable.

It is difficult to ignore the cases of CJD occurring among cattle farmers in the United Kingdom.[87–89] Three dairy farmers, all of whom had been exposed to BSE, acquired typical CJD. Although the numbers are small and may represent an epidemiologic "blip," it is hard to explain why increased cases would be seen in an occupation theoretically at high risk, if the potential for transmission of BSE to humans exists (both sides of this argument have proponents[90,91]). Against BSE being an occupational risk are data showing no difference in CJD incidence between the United Kingdom and the rest of Europe.[92] Moreover, there has been no increased incidence in Switzerland,[93] which also has a BSE problem.

Stronger evidence that BSE may have entered the human population is the identification in March 1996 of a new variant of CJD.[1] Eleven cases have been reported in the medical literature (10 in the United Kingdom and 1 in France[1,94]), and 1 other case has been confirmed in the United Kingdom.[95] This variant differs from typical CJD in that it affects much younger people (mean age 29 versus 60 years in usual cases of CJD), the presentation is relatively uniform (initial psychiatric symptoms followed by ataxia and eventually dementia), and the neuropathological findings are quite different. Plaques are distributed throughout the cortex and cerebellum and are surrounded by a halo of spongiform changes, an appearance never before recognized (although it may have existed as early as 1981).[96,97] In usual cases of CJD, plaques are rare and, if present, are limited to the cerebellum. One hypothesis to explain why the people with the variant CJD were young rests on the long incubation time for the development of CJD and the phenomenon of protection against infection with one strain of scrapie by pre-existing infection with another.[98] If variant CJD is due to a new agent, then older people who were exposed long before to the agent responsible for the usual form of CJD could be protected against the new agent.[96,99] Although the link is unproven, circumstances suggest that the agent responsible for BSE is most likely the cause of the variant CJD.

Only one case of BSE has occurred in Canada, in an animal imported from the United Kingdom.[100] At that time, all cattle imported from the United Kingdom since 1982 were either destroyed or returned, and most of their offspring and herdmates were destroyed. A control program was implemented in 1990. An autopsy program of neurologically ill cattle was initiated, but no BSE has been discovered.[100] As well, 95% of cattle commercially slaughtered in Canada are examined before death by a veterinarian.[100] Beef has not been imported from the United Kingdom for over 30 years; feed and live cattle from the United Kingdom were banned in 1990. The likelihood of unrecognized BSE in Canadian herds would therefore appear to be very low.

There has never been a proven case of BSE in the United States, and an active autopsy program there, now involving 2800 neurologically ill cattle, has revealed no cases of BSE.[101,102] The United States has also banned imports from the United Kingdom. The suggestion that an outbreak of transmissible mink encephalopathy in Wis-

consin in 1985 was due to cattle with unrecognized BSE being used as feed for mink has not been confirmed.[73]

Implications for Canada's blood supply

In Canada, the incidence rate of CJD has been stable, ranging from 0.60 to 1.21 per million between 1980 and 1993.[103,104] A cluster of cases in Burlington, Ont., did not represent a point-source outbreak; instead, it was due to a combination of sporadic cases and of familial cases among Slovakian immigrants.[105]

Transmissible spongiform encephalopathies are rare; therefore, there is little chance that the infective agent of CJD will contaminate the blood supply. The risk to a person exposed is likely further reduced if he or she does not carry the predisposing genotype (valine at codon 129). Therefore, it seems that one "hit," an uncommon genetic predisposition, and a second, rare "hit," a contaminated blood product, are necessary for transmission of CJD through a blood product.[29,44] Conversely, the risk of CJD among people receiving growth hormone is about 1 in 200 and is related to the duration of therapy.[31,32] In the United States 8 of 1600 people acquired CJD from growth hormone derived from 1.4 million pituitary glands.[32] On these grounds, we believe that the risk of CJD from blood products (which, in experimental transmission from humans to mice, were not consistently infective[106]) must be exceedingly slight. This situation is obviously much different from that involving HIV.

Conclusions

The appearance of BSE followed by new spongiform encephalopathies and variant CJD in the United Kingdom indicates that these diseases may be linked. The human food supply in the United Kingdom likely contained small amounts of BSE-contaminated substances until the more comprehensive regulations were introduced in late 1995. It is predominantly processed foods, not whole meat, that pose a risk. Canada's food supply is likely safe.

The BSE outbreak in the United Kingdom was predictable. To prevent similar occurrences animals should not be fed foods that they naturally would not eat. Recent recommendations from the World Health Organization should be followed by all countries (Table 2).[101,107]

Research into the effects of BSE is urgently required. The results of the surveillance programs in Canada and the United States are comforting and should be continued. A search for spongiform encephalopathies in pigs, poultry and other species in our food chain should be undertaken.

Until there is a better understanding of its epidemiologic characteristics, CJD should become a notifiable disease, with efforts made to confirm every case with pathological evidence. Given the precautions required to prevent infection it will be important to have special autopsy suites for diagnostic confirmation. For similar reasons surgical procedures with reusable instruments should not be performed for soft indications, despite the minimal risk. Physicians must remain vigilant and report any suspected cases.

There is likely little risk of transmission of CJD through blood or blood products, because transmission requires both the rare exposure to contaminated blood as well as an uncommon predisposing genotype. Reasonable measures to prevent any transmission of CJD through blood products include disallowing blood donations from patients with CJD and related spongiform encephalopathies, their families, recipients of human pituitary extracts and, possibly, people who have previously undergone CNS surgical procedures. Notification of recipients of blood products from people later found to have CJD is appropriate, and these recipients should not be allowed to donate blood or organs.

The current epidemic of BSE among cattle herds and the outbreak of variant CJD in the United Kingdom has implications for Canadians. The control measures outlined above should be undertaken, and physicians should suspect CJD in any person presenting with dementia or ataxia, particularly if it has followed a rapid course.

Table 2: Recommendations from the World Health Organization[101,107]

No part of any animal displaying signs of a transmissible spongiform encephalopathy should enter any food chain
All countries should have a BSE* surveillance and notification program
Where BSE exists, any tissue likely to contain the agent of BSE should not enter any food chain
All countries should ban the use of ruminant tissue in ruminant feed
Research on transmissible spongiform encephalopathies should be promoted

*BSE = bovine spongiform encephalopathy.

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