

Public health aspects of human and animal spongiform encephalopathies

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الجوانب الصحية العمومية للاعتلالات الدماغية الإسفنجية الشكل في الإنسان والحيوان
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خلاصة أثار هذه المجموعة من الأمراض البشرية والحيوانية المنبثقة كثيراً من الاهتمام والقلق مؤخراً في صفوف المجتمع العلمي وعامة الجماهير على حد سواء . وفي هذه المقالة مناقشة لمختلف جوانب هذه الأمراض فيما يتعلق بالصحة العمومية . فهي تستعرض وبائياتها بين الناس والحيوانات . وتصف الكائنات المسببة لهذه الأمراض . وتتناول بالشرح جوانب التشخيص والباثولوجيا وطرق الوقاية والمكافحة ، مع تبيان الوسائل الكفيلة بتخفيض المخاطر المحدقة بالإنسان والحيوان إلى أدنى ما يمكن .

ABSTRACT This group of re emerging human and animal diseases has recently attracted much attention, as well as concern, both in the scientific world and among the general public. In this paper the various public health aspects of these diseases are discussed. The epidemiology, both in human beings and animals, has been reviewed and the causative agents described. Diagnosis, pathology, prevention and control are addressed, showing how the risk to animals and human beings could be minimized.

Les encéphalopathies spongiformes humaines et animales: aspects de santé publique

RESUME Ce groupe de maladies qui font leur réapparition chez l'homme et l'animal a dernièrement attiré beaucoup d'attention et suscité également une vive inquiétude, tant au sein de la communauté scientifique que dans le grand public. Le présent article examine les divers aspects de santé publique de ces maladies. L'épidémiologie, tant chez le sujet humain que chez l'animal, y est analysée et les agents étiologiques y sont décrits. Le diagnostic, la pathologie, la prévention et la lutte sont autant d'éléments qui sont abordés, montrant comment le risque pour l'homme et l'animal pourrait être minimisé.

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Spongiform encephalopathies in animals

Scrapie

Scrapie is a disease mainly affecting sheep between two and five years of age. It can also affect goats. It was reported in Britain nearly 300 years ago. It is the only type of spongiform encephalopathy that is known to exist as an endemic infection of its natural host (sheep). Transmission is predominantly maternal/fetal (during pregnancy transplacentally or during parturition). The age of onset thus gives an idea of the incubation period, which is usually three or four years.

Other spongiform encephalopathies

Transmissible mink encephalopathy is a rare disease of farm-reared mink associated with feeding of animal wastes contaminated with the agent. It is not transmitted transplacentally or perinatally. In the United States, chronic wasting disease occurs in mule deer and elk. In the United Kingdom, cats are affected by feline spongiform encephalopathy.

Bovine spongiform encephalopathy

Bovine spongiform encephalopathy (BSE) first came to the attention of the scientific community in November 1986 with the appearance of a newly recognized form of neurological disease in cattle in the United Kingdom. From 1986 until now, approximately 160 000 cases of the disease have been confirmed in cattle in the United Kingdom. It has been reported from four other European countries (Ireland, Switzerland, Portugal and France), where it occurred indigenously, and from a few others that imported cattle from the United Kingdom, but the disease has not become endemic.

Epidemiological studies in the late 1980s suggested that the source of the disease was cattle feed prepared through the

recycling of cattle carcasses, a procedure that was introduced in 1981.

It is still unknown how BSE started in cattle. Some scientists believe that the causative agent was introduced into the cattle food chain from the carcasses of sheep infected with scrapie, with the causative agent of scrapie in sheep crossing the species barrier to infect cattle. Others believe that the epidemic developed from unrecognized infections in cattle and that the recycling of infectious material quickly amplified the problem.

It is important to note that the number of cases in Britain reached a peak of 37 000 cases in 1992, then started to decrease rapidly: it was down to about 13 000 in 1995. This decrease reflects the impact of bans on the use of offal in cattle feed in 1989 and 1991. However, the impact was less than expected because of nonconformity with the ban, and some of the cattle that were born after the ban (approximately 25 000) fell ill with the disease. Most of these were born in 1988 and 1989, then rates decreased, and there have been no cases among cattle born after 1993, as shown in the table below giving the number of cases by year of birth of the cattle:

1988	1989	1990	1991	1992	1993
10 988	10 132	2928	793	30	3

To date, there is no firm evidence to confirm maternal or horizontal transmission among cattle. This is supported by the fact that the incidence of BSE in any herd has never exceeded 3%. However, the question of transmission will hopefully be answered by an ongoing closed herd study.

Symptoms in cattle include nervousness, kicking, heightened sensory perception and abnormal gait (high stepping and pelvic limb ataxia). If not destroyed, the animal devel-

ops a swaying gait, itching, anorexia and weight loss and behavioural problems. In advanced stages, the infected beast stands away from the rest of the herd with its legs widely spaced and with low head carriage. It also exhibits severe muscular twitches. Injuries are common because of repeated falling, and death is preceded by an inability to stand and coma. The abnormal motor nerve control coupled with aggressiveness has earned the disease the name of "mad cow disease". It is actually an inappropriate name as the cow does not go mad.

So far there has been no recorded transmission of any of the animal spongiform encephalopathies to humans.

Spongiform encephalopathies In humans

There are four known naturally occurring spongiform encephalopathies in humans.

Kuru

Kuru was detected at high incidence in the 1950s in a specific population group, the Fore, in the Papua New Guinea highlands. The spread was due to the tribe's unusual mourning rites, in which the brains of the dead were removed and children and women were exposed to infectious tissue; hence the agent was transmitted.

It is a disease of the central nervous system manifested by cerebellar ataxia, loss of coordination, shivering, tremors, rigidity and progressive wasting.

An important observation was that the milk of mothers suffering from kuru was apparently not infectious, as shown by the fact that of the 450 cases of kuru that occurred among breast-feeding mothers, none of their children was affected. As well, the injection of milk from infected females into chimpanzees did not prove to be infectious.

When this mourning practice was stopped in the late 1950s, the disease disappeared gradually and is now rare. Cases that have occurred recently indicate that the incubation period could be as long as 30 years.

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) was first described in the 1920s. It has been reported from all over the world in a sporadic form with an average incidence of between 0.5 and 1 per million population. It occurs in all countries at the same rate (whether they have RSE or not), and vegetarians suffer at the same rate as others. It is a neurodegenerative disorder of insidious onset, beginning with mental deterioration and confusion, which develops into a rapidly progressive dementia. Cerebellar dysfunction, movement disorders (ataxia and later on myoclonus) and loss of balance are the second-most common manifestations. Some cases have visual affection even from the start of illness. Death usually occurs within a few months after the appearance of symptoms, and 90% die in less than a year. Routine laboratory studies indicate normal cerebrospinal fluid, and there is no fever. The electroencephalogram is characteristic, with periodic high voltage complexes. Almost all cases occur in persons above the age of 40 years (most commonly between 55 and 75 years), and there is evidence of a possible hereditary factor as shown by a positive family history of presenile dementia in 10% of the cases. The pattern of inheritance is probably due to mutation of the prion protein (PrP) gene. Both sexes are equally affected.

The occurrence of Creutzfeldt-Jakob disease is also associated with treatment with gonadotrophic and growth hormones prepared from human pituitary glands.

With respect to transmission, there is no evidence that Creutzfeldt Jakob disease spreads from one person to another under

natural conditions. There is, however, evidence of increase in the number of iatrogenic cases (62 cases among recipients of human growth hormone worldwide and 20 among recipients of human dura mater or corneal grafts). Epidemiological evidence indicates that blood transfusion is unlikely to be a risk factor. In the iatrogenically induced cases, manifestations started between three and seven years after the use of growth hormones, and after an average of one and a half years following cerebral inoculation with dura mater grafts.

Gerstmann-Sträussler-Scheinker disease

Gerstmann-Sträussler-Scheinker disease is believed to be a familial disease with hereditary predisposition. It differs from Creutzfeldt-Jakob disease in being of a longer duration of illness with more slowly progressive dementia and/or cerebral ataxia.

Familial fatal insomnia

Discovered only recently, fatal familial insomnia presents initially with sleeping difficulties and disturbance of the autonomic nervous system, followed by insomnia and dementia.

Recent developments

During 1995, the Creutzfeldt-Jakob disease surveillance unit in Edinburgh, Scotland, noted an increase in the number of cases of Creutzfeldt-Jakob disease in general, and identified 10 cases that had a different clinical picture from usual. In contrast to typical cases of sporadic Creutzfeldt-Jakob disease, these variant cases had the following characteristics:

- The majority were clustered around their mid and late twenties; two were in their late teens and one was aged 42 years.

The average age was 26.3 years, compared to 64 in the classical type.

- Most of them presented with psychiatric disorders. Forgetfulness and memory disturbances appeared in the late stages.
- The course of illness is prolonged (average 13 months compared to 6 months in the classical type).
- The characteristic electroencephalogram changes seen in classical Creutzfeldt-Jakob disease were not found.
- The brain pathology of those who died (eight out of the 10) showed a different pathological profile. The key histological feature is the presence of numerous widespread kuru-type amyloid prion protein (PrP) plaques surrounded by vacuoles in all sections examined. The cerebellum and occipital lobes were severely involved. These plaques have not been found in sections taken from people with classical Creutzfeldt-Jakob disease. Immunocytochemistry for PrP using two monoclonal PrP antibodies (KG9 and 3F4) showed strong staining of these plaque-like lesions. Other PrP depositions were also seen.

Patients' medical histories, genetic analysis and consideration of other possible causes were reviewed by the UK Advisory Committee on Spongiform Encephalopathy; the Committee concluded:

Although there is no direct evidence of a link, on current data and in the absence of any credible alternative, the most likely explanation at present is that these cases are linked to exposure to BSE before the introduction of the specified bovine offal ban in 1989.

The statement did not implicate any specific mode of transmission. However, the fact that this pathology has not been seen before points to the possibility of a new risk

factor. What this factor is, no one can tell. A link has not yet been proven between the newly recognized variant of Creutzfeldt-Jakob disease in the United Kingdom and the effect of exposure to BSE agent. Further data on these variant cases are needed to clarify any possible relationship.

It is expected that there will be more cases of this newly identified variant but it is not believed that a massive epidemic will occur.

The causative agents

The causative agents of transmissible spongiform encephalopathies are described as unconventional filterable agents, the nature of which is not fully understood. There is a big debate on the exact nature of the agents. They were first described as slow viruses, then as self-replicating proteins and more recently as prions. A prion is thought to be a kind of protein that can exist in more than one form. The prions responsible for spongiform encephalopathies are somehow able to change the structure of harmless isoforms in the central nervous system to harmful forms. The mechanism by which propagation of such prions damages cells is not known. Transmissible spongiform encephalopathies are now called prion diseases with reference to the causative agent.

Prions have proved to be highly stable agents, resisting heating to normal cooking temperature and even higher, such as temperatures used for sterilization. They can resist freezing and drying, X-irradiation and many chemical disinfectants.

Diagnosis

At present there is no reliable diagnostic test that indicates infection. Prions, unlike bac-

teria and viruses, are poorly immunogenic, which makes early diagnosis difficult.

At present, diagnosis is essentially based on the detection of the pathological changes that can be seen during post-mortem microscopic examination of the brain, in the form of spongiform changes in specific parts of the brain. These changes occur only late and may not always be present. Two other methods are used in the diagnosis of BSE, especially in cases where the brain tissues are liquified, namely examination for evidence of scrapie-associated fibrils and immunoblotting for PrP.

The absence of a reliable early diagnostic test is a great handicap in being able to better understand this disease.

Distribution of the infectious agent in animal tissues

As the infectious agent has not been isolated, it has not been possible to determine its natural history or concentration in animal tissues.

At present, the most sensitive test is to challenge another animal of the same species with a tissue extract. But, again, the incubation period is very long in cattle. Transmission to mice following inoculations has been used as a proxy for the presence of the agent and by implication the possible risk to human health. These studies have shown that brain tissues of the diseased animals have very high concentrations of infective material, which can easily cross the species barrier. The incubation period in mice depends on the dose and route of administration. Intracerebral inoculation is 40 000–100 000 times more efficient than oral challenge.

Because asymptomatic naturally infected cattle cannot be identified during the incubation period, a study is being carried out to determine the development of infectivity fol-

lowing oral exposure of young calves (four months) to a single large dose (100 grams) of affected cattle brain. Some of the challenged and control animals are killed every four months starting two months after the challenge. Various tissues are collected and inoculated parenterally into susceptible mice, which are monitored while alive, and their brains examined after death. At the time of writing, five kills had been made, and the following observations were noted:

- No calves showed signs of disease before slaughter, i.e. an incubation period of at least three years.
- Infectivity was found in the distal ileum of challenged calves starting six months after the challenge.
- No infectivity was found in any other tissue before one year.

The study is still going on but so far there is no evidence of infectivity in red meat.

As well, it has not been possible to transmit the disease to mice who were fed on milk taken from affected cows. More studies are, however, needed to allow a full risk assessment of various tissues.

Transmission studies have shown that BSE can be transmitted to many animal species. The incubation period was different between challenging orally or parenterally.

Human Involvement

Human involvement in BSE might be possible because of the following:

- The causative agent of BSE, which was thought to affect only cattle, has now been transmitted experimentally to many other animals: sheep, goats, mice and marmosets, and recently to other species, including cats. It could, therefore, theoretically have also crossed the species barrier to humans.

- By the time the first clinical cases were recognized in cattle, many thousands were already incubating the disease. Most of these apparently healthy cattle entered the human food chain in the 1980s.
- The inability to neutralize the agent effectively during food processing and cooking means that, in all probability, most humans who have consumed beef products since the start of the BSE epidemic will have been exposed to the agent. The risk to humans is very much related to the product consumed as the concentration of the agent in various tissues is clearly different.

What we all hope is that the human species barrier is great and hence it obstructs at least small concentrations. We also know that human exposure would have been mostly through the oral route, which is a relatively inefficient challenging route.

Taking into account the fact that since 1989 there has been a ban on cattle tissues known to have high concentrations of the causative agent (central nervous system, tonsils, spleen, etc.) and that transmission studies so far have not indicated infectivity of skeletal muscle tissues, it is expected that the risk from eating beef obtained from countries with endemic BSE is at present much less than it was before 1989. The problem, if any, was what happened in the past. It is sincerely hoped that human involvement has been limited, and that the problem will now be halted by the measures being taken.

In view of the fact that there are no diagnostic tests to detect infection early and the incubation period is long, it is very difficult to assess the impact of BSE on human health with any degree of accuracy. Unless a breakthrough in early diagnosis occurs, it will be many years before we can be sure that public health has not been compromised

by BSE when it was widespread in cattle with no control measures (during the 1980s).

Prevention and control

It is extremely important that control measures to protect human health be rigorous and comprehensive but they must also be objective. During the crisis that resulted from the announcement made by the UK Minister of Health on 20 March 1996 of a possible link between some cases of Creutzfeldt-Jakob disease and exposure to BSE, the response of some authorities was more emotional than logical; for example, calling for a total prohibition on eating beef. As much as it is very important not to under-react, it is also important not to overreact. Now people are coming to grips with the problem, and logic is returning after the gradual fading of the emotions.

Some people are looking for zero risk, which is always extremely difficult if not impossible to achieve in our daily lives, but we must make every effort to minimize any risk.

Minimizing the risk in animals

The solution is to eliminate exposure of cattle to BSE through feed. Scientific evidence indicates that this is the only route for natural infection. Therefore:

- No part of any animal that has shown signs of BSE should enter any food chain (human or animal). To this effect, all countries must ensure mandatory killing and safe disposal of affected animals in a way that guards against the agent's entering the food chain. The procedure to be used for rendering should effectively inactivate BSE agents.
- Countries where BSE exists should not permit tissues that are likely to contain

the BSE agent to enter any food chain (animal or human).

- All countries should establish surveillance and compulsory notification of BSE. The success of such a system will depend on instituting a system of compensation for the owners, preferably 100% of the value of the destroyed stock.
- All countries should ban the use of ruminant tissues for making feed for ruminants and all other animals. Those importing animal feed should ensure that it does not contain ruminant tissues.
- Research should be supported, particularly in the field of diagnosis and epidemiology as well as cross species infectivity to allow for a full risk assessment.

Minimizing the risk in humans

It must first be remembered that available scientific information so far indicates four main guiding principles:

- The risk, if any, to humans would arise essentially from exposure to certain tissues of infected animals or products prepared from these tissues. Significant infectivity is likely to be present only in the central nervous system and in certain organs of the lymphoreticular tissues. It is satisfying to note that since 1989, the country where the disease is endemic, namely the United Kingdom, has banned the use of brain, spinal cord, thymus, spleen and intestine of cattle origin (bovine offal) in foods for human consumption.
- None of the food processing technologies such as heat treatment (cooking, pasteurization or sterilization), freezing, drying, acidification, fermentation or irradiation are fully effective for inactivating the infectious agent.

- Milk is considered safe even in countries with high incidence of BSE. There is evidence from other animal and human spongiform encephalopathies to suggest that milk will not transmit these diseases.
- Exposure to BSE agent from beef and beef products has been substantially reduced by measures taken by the United Kingdom. In animal studies, the skeletal muscles of beef, even from affected cattle, have not shown any detectable infectivity. The safety of beef and beef products will be further enhanced by the implementation of measures that minimize risk in cattle.

Therefore prevention will depend on:

- Excluding potentially infective tissues from being a source of human food. Countries where BSE exists should not permit such tissues to enter the human food chain.
- Preventing occupational transmission, by taking special precautions when handling or processing potentially infected material. Care should be taken to avoid injuries, especially with instruments that have been in contact with bovine offal. Occupational histories of Creutzfeldt-Jakob disease show evidence of increased risk among dairy farmers in the United Kingdom. However, statistical analysis shows that the increase is both in countries with BSE and in many countries without BSE; so it could be concluded that if this increase is significant, other factors, such as exposure to insecticides, may be behind this increase.
- Prevention of hypothetical risks from medicinal products and medical devices derived from bovine material by:
 - Careful selection of source material and ensuring that bovine materials destined for the pharmaceutical industry should only be obtained from

countries that have a surveillance system for BSE in place and from which no cases of BSE have been identified;

- Avoiding tissues with maximum infectivity titres, such as tissues from the brain, pituitary and intestine from duodenum to rectum;
- Apply procedures capable of removing or reducing infectivity such as autoclaving at 138 °C for 18 minutes and removal of proteins by precipitation. In this regard, gelatin is considered safe for human consumption since its preparation involves a chemical extraction process that is capable of making it safe.

Applying the above measures will contribute to minimizing the risk to humans but no one can be sure that they will be fully preventive, particularly as we still do not understand many things about spongiform encephalopathies in humans. Therefore, more studies are needed on Creutzfeldt-Jakob disease and its new variant.

International measures

The Office of International Epizootics recommends the following with respect to BSE:

- A veterinary administration be authorized without restriction to limit the import directly or indirectly of milk, milk products, semen, hide and skin originating from healthy animals from countries where BSE has been reported.
- There be conditions for the importation of cattle, of embryos and ova and of fresh meat and meat products from cattle that vary according to whether the country has high or low incidence of BSE. Certification of compulsory notification, antemortem inspection, slaughtering and complete destruction of affected cattle and certification that nerve and lymphat-

ic tissues are removed from carcasses are required.

The above measures are spelled out in Chapter 3.2.13 of the Office of International Epizootics International Zoo-Sanitary Code on Bovine Spongiform Encephalopathy.

Action taken by WHO

After the identification of BSE, and in order to continue to assess possible hazards of BSE to humans, WHO held three meetings on spongiform encephalopathies in 1991, 1993 and 1995, and participated in another meeting in 1994 organized by the Office of International Epizootics. These meetings reviewed the existing state of knowledge on spongiform encephalopathies to evaluate possible means of transmission and to identify risk factors for infection. The main purpose was to review the possible human public health implications of BSE and ways of minimizing the risks of possible transmission to humans by various methods, including medicinal products.

The conclusions of these meetings of scientists as of May 1995 were that the epidemiological evidence in Europe did not indicate a change in the incidence of Creutzfeldt-Jakob disease that could be attributed to BSE and that the risk of transmission to humans had been minimized after the introduction of precautionary measures in farms and slaughterhouses and in the meat processing industry. It was, however, indicated that mammals, including humans, are potentially susceptible to BSE if sufficiently exposed to its agent.

In light of the new information on 10 cases of variant Creutzfeldt-Jakob disease reported in March 1996, a WHO meeting of international experts in neurology, BSE, epidemiology, veterinary science, and public health met on 2 and 3 April 1996 in Geneva to review the situation and make further technical and public health recommendations. They stressed the necessity to strictly implement the recommendations related to reducing the risks of BSE transmission to cattle and humans.