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Transmissible spongiform encephalopathies or Prion protein diseases and public health

by

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Abstract

Prion diseases are transmissible neurodegenerative disorders of humans and animals. The prion protein (PrPc) gene is expressed to some extent in many cell types but principally in neurons. Normal PrPc may contribute in the protection of neurons and is protease sensitive. Abnormal prions consist of a post-translationally modified form of PrP, PrPsc, which is partly protease resistant. PrPsc is a protein with high resistance to inactivation by irradiation, heat and harsh chemical treatments. It is currently proposed that PrPsc is an infectious protein that propagates by inducing the normal PrPc to become the abnormal PrPsc. PrPsc causes transmissible spongiform encephalopathies (TSE), an unusual group of degenerative brain diseases that can be transmitted by inoculation or ingestion of diseased brain or other tissues. The human diseases occur in an inherited, acquired and sporadic form. Transmission of prion diseases between species is limited by a species barrier, dertermined in part by the degree of sequence homology between the host PrP and inoculated PrPsc. The epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom is a new disease that has affected over 160,000 cattle and has presumably arisen from

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dietary exposure to PrPsc from sheep with scrapie. Until shown otherwise we must assume that oral consumption of infectious BSE protein is a new factor for Creutzfeldt-Jakob (CJD) disease in man. Early diagnostic markers for the disease to facilitate the diagnosis and to screen blood and organ donors are not available. The control of the disease relies on measures to eradicate the spread of BSE by banning the use of ruminant tissues in ruminant feed and slaughter and rendering procedures to ensure inactivation of prions of all infected animals. The control of nvCJD is based on reduction of exposure to BSE by banning a variety of tissues for consumption. A surveillance worldwide is increased for both BSE and nv-CJD and the WHO update regularly recommendations to limit the risk of transmitting the disease.

Keywords

BSE, Creutzfeldt-Jakob disease, Prion, NvCJD, Scrapie

Introduction

Transmissible spongiform encephalopathies (TSE) are a group of degenerative brain diseases that are transmitted by unconventional agents. Both in humans and animals, they induce strictly neurological diseases, that are always fatal after a long clinically silent incubation period. These diseases include scrapie in sheep, spongiform encephalopathy (BSE) in cattle, and Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Straussler-Scheinker syndrome (GSS) and iatrogenic TSE in humans. TSE occur in many different animal species, including humans, various nonhuman primates, mice, hamsters, rats, guinea pigs, minks, goats, cattle, pigs, elk, mule deer, cats, and a variety of exotic felines and bovids in zoo. There is now a tremendous interest of the media due to the recent belief that the mad cow disease could be transmitted via the food chain in human and cause a variant form of CJD.

The discovery of the prion concept

Scrapie has been recognized as a disease in sheep in Europe and has been described for the first time in 1738(1), but the etiology of the disease remained unknown for more than two centuries. In 1939 Cuillé and Chelle (2) have shown that scrapie could be transmitted by inocula-

tion. However, the mechanism of natural transmission of scrapie remains uncertain. Initially, there was a belief that scrapie was a virus-like transmissible disease because an ultrafiltrate could transmit the disease. As the incubation period was 6 month or longer, the disease was described as a "slow virus disease" and the agent as a "slow virus" (3, 4). An important experimental approach to better characterize the causative agent was done by assessment of the biophysical and biochemical properties of the TSE agents. These experiments rely on an *in vivo* infectivity assay. Initially the assay involves inoculation of groups of susceptible animals with serial dilutions of samples to be tested. Recipient animals (mostly mice) are then followed for development of clinical neurologic disease signs typical of TSE for an appropriate period of time. The assay is extremely slow, requiring 2 to 8 months in most cases and the need to inoculate at least 60 animals for the estimation of the infectivity of one sample (5). An important boost was given to the TSE research by using the Syrian hamster as recipient animal (6). With this animal the incubation period is proportional to the amount of causative agent inoculated, so that with fewer animals and in shorter time information is given (7). However, with both methods important properties of the agent were discovered. First, the transmissible agent can pass through filters with an average pore diameter of 20 to 100 nm, suggesting a size range consistent with many conventional viruses (8). However, the scrapie-agent is particularly resistant to ultraviolet and ionizing radiation, and to chemical inactivation with formaldehyde (3). Biochemical analysis of pelleted scrapie brain extracts enriched for infectious agent led to the finding of a new protease-resistant protein, known as PrP or prion protein (9, 10). The word is actually derived from **Pro**teinaceous **in**fectious particle or **proin**, but the word was changed into **prion**, because this sounds better (11). After the initial discovery of PrP in purified scrapie brain extracts, the identification of the partial aminoacid of this protein led to the cloning of PrP cDNA from mouse and hamster scrapie-infected brain (12-14). However, PrP mRNA was not specific for scrapie, but was also expressed at equal levels in normal brain of uninfected animals. So the prion protein is a normal protein that has a M.W. of 22-36 kD. It is a GPI-linked cell surface protein that is expressed on brain, heart and lung and activated lymphocytes. PrP^c is conserved in the different mammalian species studied so far. In man, the gene is encoded on chromosome 20 and consists of 253 amino-acids, which comprises four principal regions: a N-terminal region with repeat sequences, a second region encompassing the transmembrane domain, a third region with two possible glycosylation sites and a C-terminal region with an anchor site for glycosylphosphatidyl-inositol (GPI).

The normal function of the PrP was mysterious, as PrP null mice with a disrupted gene for PrP, were born normal and had no apparent pathology. Nevertheless, when these mice were observed for longer periods they developed symptoms of ataxia and histological analysis of their brain showed loss of Purkinje neuronal cells (15). Therefore, we may conclude that PrP is normally expressed in birds and mammals and plays a protective role in the survival of Purkinje neuronal cells. Importantly, the PrP null mice, are no longer susceptible to inoculation with the prion agent (16).

A clue for the pathogenesis of the disease came from the observation that in pathological tissue, unlike the normal PrP the pathological prion is resistant to protease (17). So the disease is caused by a transition of the normal protease sensitive PrP, referred to as PrP^{c}, "the cellular form of the prion protein", into a protease-resistant form referred to as PrP^{sc}, "the scrapie form of the prion protein". Depending on the books, the Pr^{Sc} stands for all pathological forms of the prion protein and also for the Creutzfeldt-Jakob, BSE, etc... or other authors use the term PrP^{SC}, PrP^{CJD}, PrP^{BSE}, for respectively the protein in scrapie, Creutzfeldt-Jakob disease and bovine spongiform encephalitis (18).

The normal PrP^{c} is formed by the neurons, migrates through the Golgi-apparatus where it is glycosylated and finally reaches the cell membrane. The metabolic half-life of the protein is 3-6 h, as the protein is taken-up by endocytosis and degraded in the endosomes by proteolysis (19-21). The susceptibility of the PrP is due to the tertiary and quaternary structure of the protein. PrP consists for 42% out of α-helix structures without notable β-sheet structures, in sharp contrast is PrP^{sc} with a lower% of α-helix (30%) but importantly 43% of the protein has a β-sheet structure, which renders it resistant to protease degradation (22).

Mechanisms of pathological prion formation

The conversion of normal protease sensitive PrP^{c} into abnormal protease-resistant PrP^{sc} is an important feature of TSE pathogenesis. Due to the conversion, the normal turn-over of the protein is hampered and the abnormal protein accumulates in the neurological tissue, which leads to neuronal degeneration and typical hole formation. It is still a matter of debate whether the disease is caused by "the protein only" or that a separate agent is also important in the transmission of the disease.

The "protein only" hypothesis implies that the abnormal protein associates with a normal protein to form homodimers and induce the normal protein to undergo conformational change into the abnormal protein. In that way, the abnormal protein is the onset of a domino-effect that induces abnormal shaping of the existing proteins. However, the protein only theory is still controversial, and different arguments are challenging this view. Most important problems are that infectious fractions tested so far are not true protein, but contain nucleic acids and the lack of explanation for the existence of scrapie strains (23). Therefore, Weissmann has proposed an unified theory for prion propagation. The infectious particle is called holoprotein and consists of a PrPsc termed apoprion and a still unidentified nucleic acid termed coprion. The apoprion is responsible for the neuropathology and the coprion for the infectivity and strain differences. However the coprion has until now not been identified and many researchers doubt that it exists (24).

Epidemiology and clinical disease in humans

In humans, TSE diseases are subdivided into three groups: infectious, familial and sporadic. Diseases of all three groups can be transmitted to primates by ingestion, inoculation of diseased infectious brain tissue. However, these groups differ in the apparent manner in which the disease was acquired in the first place.

Kuru and iatrogenic TSE are transmitted to patients by exposing to TSE agent by contact with brain tissues or extracts contaminated by TSE agent. For kuru this occurs during the handling and ritual cannibalism of brain tissue of relatives who died from kuru (25). Iatrogenic TSE cases have been induced by transplantation of corneal or dural tissue from patients with TSE or by neurosurgery using instruments incompletely sterilized following use on TSE patients or by inoculation of growth hormone extracted from pituitary glands from large groups of individuals (18). In this situation the extracts were apparently contaminated with brain tissue from undiagnosed TSE patients. The clinical findings in kuru and iatrogenic TSE consists primarily of cerebellar ataxia. Mutation of the PrP gene is not found in this group of patients. Susceptibility may be influenced by variant PrP genotypes, such as Val-Met, Met-Met, and Val-Val at PrP codon 129, which segregate in the normal population (26).

Sporadic CJD

Sporadic CJD is the main clinical disease that falls into TSE diseases. CJD occurs at an incidence of 1 in 2 million people worldwide.

In this group there is no strong association with a mutant PrP allele nor is there any epidemiological evidence for exposure to TSE agent. The age of onset is usually between 50 and 70 years, but can range as low as 16 and as high as 80 years. The primary clinical symptom is usually dementia with confusion, memory loss and bizarre behavior. The EEG often shows a disease specific pattern (27).

Familial TSE

Familial TSE are associated with the presence of an autosomal dominant genetic alteration of the PrP gene. Different mutations at different sites of the gene have been reported. Clinical disease usually begins at an early age and is of long duration. Findings are variable and include dementia, ataxia and myoclonus (28).

A new variant form of TSE

Bovine spongiform encephalopathy (BSE), known as mad cow disease, was discovered in 1986 and taking into account an incubation period ranging from 20 months to 18 years, the infection started in 1981-82 (29, 30). The disease is a new disease that affected the cattle in Great-Britain, because calves received meat-and-bone meal that carried the prion agent. The infection was introduced only after 1980 because of a new production method for meat-and-bone meal. This meal is produced by rendering discarded animal fat, bones, offal, whole carcasses, and other material from bovine, ovine, porcine, poultry, and other sources. This meal was incorporated into cattle feed since the 1940. The raw materials were broken down and processed in several systems at temperatures ranging from 100°C to 150°C for varying periods. Up to 1980 a hydrocarbon extraction step was included to increase the tallow yield so that the extracted meal product contained less than 1% fat. Finally the product was treated with pressurized steam to remove the residual solvent. Apparently, this treatment was able to inactivate the TSE agents. The solvent extraction and solvent recovery steps were omitted in the late 1970's and early 1980s because the market for tallow declined (31). It is likely that the outbreak of BSE was derived from scrapie-infected sheep as a result of an increase in the dose of the TSE agent due to the change in the processing of the meal-and-bone meal. Until now 165,000 cattle have been affected by the disease and it is likely that about $1x10^6$ out of the $12x10^6$ cattle in the UK have been infected. Less than 50

cases of BSE were reported in cattle bred in the UK and imported into Canada, Denmark, the Falkland Islands, Germany, Ireland, Italy, Oman, and Portugal. This figure is low in comparison with more than 50,000 cattle that had been exported from the UK.

In Switzerland 234 cases of BSE have been reported in native cattle, for the other countries (France, Ireland, the Netherlands and Portugal) only a few cases have been diagnosed in native cattle. In Belgium one case has been reported recently in 1997. The infection is probably due to ingestion of meat-and-bone meal from the UK. Again, the few cases are in contrast with the large quantities (71 kilotonnes) of the food that has been exported (29).

Measures to control the disease

In June 1988, BSE was made a notifiable disease. In July 1988 a ban on the supply and use of ruminant-derived protein in ruminant feed was installed. In August 1988, the compulsory slaughter and carcasses of all cattle suspected having BSE was ordered (32).

Transmission of BSE to other species

The BSE agent is transmissible by parenteral injection of infected brain homogenate into cattle, sheep, goats, pigs, mink, marmosets and mice, but not pigs. Orally transmission to sheep and goats were possible with 0.5 g of brain (29).

Resistance of BSE agent

The infectivity of 10% homogenates of BSE-infected bovine brain is not eliminated by filtration through 50 nm filters, by autoclaving at 121°C for 15 min. The scrapie agents withstands alcohol or glutaraldehyde. It can be inactivated by exposure for 1 hour to sodium hypochlorite providing 2% chlorine, or by exposure to 1N or 2N NaOH for 2 hours (33, 34).

BSE and the new variant form of Creutzfeldt-Jakob disease

There is now a great concern in the fact that in the UK a new clinico-pathological type of CJD, new variant CJD (nvCJD) has been reported. This disease is putatively linked on epidemiological grounds with dietary exposure to BSE. To date, 24 nvCJD cases have been neuro-patho-

logically confirmed in the UK and one in France. The features of this nvCJD were young age at onset (mean age 27 years) and early onset of behavioral signs superseded after a few months by devastating neurological dysfunction including ataxia and involuntary movements. Electroencephalographic findings characteristic of CJD were absent. The disease is characterized by progressive dementia and by the inexorably fatal clinical course that lasted typically more than 1 year. Eight out of eight patients were homozygous for methionine at codon 129 for PrP. Evidence in support of a causal link between BSE and nvCJD is provided by experimental transmission of BSE to macaques, and by the pattern of glycoforms seen in PrP from brain extracts of patients that is similar to that seen in mice experimentally infected with BSE (32).

Infectivity of tissue in scrapie and BSE.

Challenging mouse by intra-cerebral injection of different tissues from sheep and BSE infected animals showed that for the sheep the most infectious organs were brain and spinal cord, followed by ileum, lymph nodes, proximal colon, spleen and tonsil, to a lesser degree sciatic nerve, thymus, lung, pancreas, bone marrow, distal colon, whereas blood clot, heart muscle, kidney, mammary gland, colostrum, skeletal muscle, milk, serum and testis were not infectious in this assay. In cattle, brain tissue, spinal cord and retina were the most infectious tissues, followed by distal ileum, whereas sciatic nerve, colon, thymus bone marrow, liver, lung, blood, heart muscle, pancreas, kidney, mammary gland, milk, serum skeletal muscle, testis were not able to transmit the infection in mice (35).

Species barrier

Apparently, although scrapie is endemic in sheep, the scrapie agent has not been transmitted to man. But the agent has been transmitted in cattle. The basis of species barrier is considered by Prusiner as the difference in aminoacid sequence between the PrP in donor species and in the recipient species. Bovine and ovine PrP differ at seven positions and bovine and human at more than 30 positions. Bovine PrP gene sequence might be slightly closer to the human than the sheep sequence. However, it is possible that the overall difference in sequence is not so important, but that homology at specific sites is more critical to allow dimerization between the PrPs and subsequent conformational change.

In this respect, it was reported that bovine and human PrP share some critical homologies. However, transmissibility studies of BSE to transgenic mice expressing the human PrP and no mouse PrP shows that up to 500 days the species barrier holds firm. Moreover in mice expressing both human and mouse PrP, only the mouse PrP is transformed and the human PrP remains unaffected (36). These data have to be interpreted with caution, because, the transgenic mice express a human PrP with valine at codon 129, and all cases of nvCJD examined so far have been homozygous for methione at codon 129.

How big is the threat?

For the moment, we even do not know if the nvCJD is caused by oral ingestion of contaminated food. The infectious pathway remains mysterious. Recently, it has been shown that nvCJD prions accumulate in the lymphoid tissue of the tonsil (37). This indicates that prions might reach the nervous tissue using the immune system as vehicle. In line with these observations, it has been shown that after intraperitoneal and even intracerebral infection of mice infectivity of the spleen can be demonstrated 4 days after challenge. The nature of the cells that allow prion propagation is unknown but follicular dendritic cells could be those cells as nude mice without a good functioning T cell system are able to propagate the infection, whereas SCID mice with no B and T cells and also impaired follicular dendritic cells fail to do so (38).

It is now 10 years since BSE was recognized, probably within 1-3 years we will be able to estimate whether the nvCJD cases mean the start of an epidemic. Too many questions about the load of the prion in the food, the efficiency of transmission through ingestion, the influence of food preparation and conservation on the infectivity and the species barrier and the genetic influence on it are unanswered to give us a fair idea on the future of the infection rate in man.

Diagnosis of nvCJD.

A definitive diagnosis of transmissible spongiform encephalopathy requires histopathological examination of a brain biopsy speciem. In 1986 Harrington et al (39, 40) Identified two proteins on two-dimensional gel electrophoresis, witch provided a sensitive specific marker for the diagnosis of Creuzfeldt-Jakob disease. These markers have been iden-

tified as 14-3-3 proteins and an immunoassay has been developed.The test is now under evaluation to diagnose patients with nvCJD. 14-3-3 proteints are not the prion proteins, but the presence of 14-3-3 proteins in the cerebrospinal fluid of patients with dementia should point to neuronal injury and might be an indirect marker for the diagnosis of nvCJD. A more definitive diagnosis can be made by the detection of protease-resistant prion protein on immunoblotting. However, for the moment analysis of tissue from the central nervous system is required to pervorm these tests. More sensitive immunoassays might allow detection of the protein in lymph nodes and other lymphoreticular tissues. Particular stimulating was the discovery that nvCJD is associated with a specific pattern of protease-resistant PrP on Western blot analysis. Inportantly, this assay seems to be positive in tonsillar tissue (37).

Measurements to limit the risk of transmission of CJD.
1. Risk of transmission of BSE in cattle via the food chain.

Following measures were taken in the U.K.

Ban of the supply and use of ruminant derived protein in ruminant feed, July 1988

Compulsory slaughter and disposal of carcasses of all cattle suspected of having BSE, August 1988

Destruction of all milk from suspect animals, 1989

Bans on specified bovine offals (SBO) for human consumption in UK, November 1989

SBO feed ban for all animals and birds, September 1990

Ban on the use of mechanically recovered meat from bovine vertebral column for human food, December 1995

Meat from all cattle over 30 months old should be deboned in approved licensed facilities, supervised by the Meat Hygiene service before being offered for sale, March 1996.

Most cases have occurred in Holstein Friesian dairy cattle and have been exposed as calves. There is no evidence that cattle to cattle transmission is sufficient to maintain the epidemic. The principle animal health control measures are bans on the feeding of ruminant derived protein to ruminant animals and on the use of SBO for feeding to any species of animal or birds.

2. Measures to reduce possible human risks from disease

Human health is protected by compulsory slaughter and destruction of suspect animals, and a ban on the use of their milk, and by prohibiting the use of SBO in food. The SBO are those tissues which, in clinically healthy cattle incubating BSE, might conceivably harbour infectivity. These are the use of brain, spinal cord, tonsil, thymus, spleen and intestine, and the head except for the tongue.

European Union decisions to reduce the risk of transmission.

Ban on export of cattle born before 18 July 1988 and offspring of affected and suspected animals, 28 July 1989.

Restriction of export of cattle to those under six months, which are slaughtered before that age, 1 March 1990.

Disease made notifiable to European Commission, 1 April 1990.

Prohibition of sale for human consumption of meat of bovine animals slaughtered in the U.K., 27 march 1996.

3. Measures to limit transmission of prions by tissue handling

Prions are not contagious in the usual sense. Successful transmission requires both specific material (an infected individual's tissue, from or adjacent to central nervous system) and specific modes, mainly penetrating contact with the recipient. Nevertheless, specific safety precautions are mandatory to avoid accidental transmission and to decontaminate any infectivity. Autopsy is essential for definite diagnosis of these disorders. The following measures have been proposed in a consensus report published recently in brain pathology (41).

Following measures were proposed:

1. the personnel should wear safety gloves; special care should be taken to avoid accidental penetrating wounds.

2. the formaldehyde-fixed brain is processed on a table covered by a disposable plastic sheet and cut on layers of cellulose sheets (to be discarded by burning with infectious hospital waste).

3. to deactivate CJD infectivity, it is recommended to soak tissue blocks for histology (not more than 5 mm in thickness) in concentrated (95-100%) formic acid for one hour, followed by fresh formaldehyde solution for at least 48 hours. However, this makes the tissue block brittle and more difficult to cut. Without this step, paraffin blocks may still be infectious

4. all instruments, gloves etc. which came into contact with potentially infectious material must be decontaminated. Instruments that were contaminated by formaldehyde-fixed, non-formic acid-treated tissue are not decontaminated by autoclaving but should be immersed in 2N NaOH for one hour.

5. tissue remnants, cuttings debris and contaminated formaldehyde solution should be discarded within a plastic container as infectious hospital waste by burning.

6. accidents involving parenteral exposure to material or contaminated wastes from TSE should be recorded

Decontamination procedures

7. Steam autoclaving (glassware, instruments, safety, gloves, etc.) 134°C recommended for 1 hour
8. Chemical decontamination of nonautoclavable materials and surfaces
   a) 2N NaOH (80 g per liter) for one hour is recommended, alternatively, 1 N NaOH may be used for two hours. Do not use NaOH for aluminium material.
   b) Alternatively 5% NaOCl (at least 20.000 ppm free chloride, fresh solution) for 2 hours.
   c) Some laboratories use boiling of instruments in 3% SDS for at least 3 min as another option, either alone or in combination with autoclaving for one hour.

4. Measurements to reduce possible human risks by the use of blood or blood products.

At the moment there is no evidence that CJD has been transmitted to humans by blood or blood components. No cases of transmission

have been reported so far. However, the USA FDA in its December 11 position recommends the market withdrawal of blood derivates when the donor is diagnosed with CJD, has two non-iatrogenic familial cases of CJD, is a recipient of dura mater transplant or has received human pituitary-derived growth hormone, whether or not the donors are known to be at risk for CJD. Blood donors receive a questionnaire to identify donors at increased risk for CJD by asking for family history of CJD in relatives, treatment with pituitary growth hormone or dura mater graft.

Conclusions

In the light of new information on the human cases of nvCJD, a WHO meeting of international experts has been organised in Geneva on 2-3 april 1996 (42). The experts concluded the following:

Recommendations
Bovine Spongiform Encephalopathy:

1. No part of any animal which has shown signs of TSE should enter any food chain, human or animal. All countries must ensure the slaughter and safe disposal of TSE-affected animals so that TSE infectivity cannot enter any food chain. All countries should review their rendering procedures to ensure that they effectively inactivate TSE agents.

2. All countries should establish continuous surveillance and compulsory notification for BSE according to recommendations established by the Office International des Epizooties in Paris. In the absence of surveillance data, the BSE status of a country must be considered as unknown.

3. Countries where BSE exists in native cattle should not permit tissues that are likely to contain the BSE agent to enter any food chain, human or animal.

4. All countries should ban the use of ruminant tissues in ruminant feed.

5. With respect to specific products:

   * Tests on milk from BSE-infected animals have not shown any BSE infectivity, and there is evidence from other animal and human spongiform encephalopathies to suggest that milk will not transmit these diseases. Milk and milk products, even in countries with a high incidence of BSE, are therefore considered safe.

* Gelatin is considered safe for human consumption since its preparation involves a chemical extraction process that destroys BSE infectivity.

* Tallow is likewise considered safe if effective rendering procedures are in place.

6. With respect to medicinal products, which differ from food in that they can be injected as well as taken orally, measures to minimize the risk of transmitting the BSE agent were developed at a previous WHO consultation in 1991 and continue to be applicable.

   * As more information becomes available these measures will be reviewed and strengthened if necessary.

   * The importance of obtaining materials destined for the pharmaceutical industry from countries which have a surveillance system in place and which report either no or sporadic cases of BSE is reiterated.

   * Removal and inactivation procedures contribute to the reduction of the risk of infection. But it must be recognized that the BSE agent is remarkably resistant to physico-chemical procedures which destroy the infectivity of common micro-organisms.

7 Research on TSE should be promoted, especially on rapid diagnosis, agent characterization, and epidemiology of TSEs in humans and animals.

Variant Creutzfeldt-Jakob Disease (V-CJD):

1 The geographic distribution of V-CJD, although reported at present only in the UK, needs to be further investigated.

2 While the most likely hypothesis at present for this newly recognized variant is exposure to the BSE agent, further data from scientific studies on these variant cases are urgently required to establish a link. More monitoring and surveillance studies on all forms of CJD are required throughout the world, modelled on current European collaborative studies.

3 Exposure to BSE from beef and beef products has already been substantially reduced by the measures taken in the UK. Exposure to BSE

has always been lower in other countries. The group considered that implementation of their recommendations will ensure that any continuing risk of exposure to BSE in beef and beef products will be reduced to a minimum.

As surveillance worldwide is increased for both BSE and V-CJD, more information will become available in the coming months. WHO will keep these developments under review and update the recommendations as appropriate.

In 1997, the experts have made the following statements for the reduction of possible transmission of TSE through medicinal products (43)

The consultation has made the following recommendations:

Medical Products and sources of animal origin:

Whenever possible, cattle (bovine) sources should be avoided for the preparation of medicinal products and devices; other animal species naturally affected by a TSE should likewise be avoided as an alternative source.

If unable to avoid bovine sources, source countries should be those which have low or no BSE confirmed by an effective surveillance system among cattle, and where the possibility of contamination during the collection of material is maintained at a minimum. In addition, inactivation and or removal procedures should be used where possible.

The consultation further recommended these guidelines should also be applied to medical products from other animal species with naturally-acquired TSE.

Medical Products and devices of human origin:

Although there has been no proven or even probable instance of CJD transmission from human to human by blood transfusion or blood products, observation must continue. The experts concluded that blood transfusions continue to be safe. Routine internationally recognized donor selection criteria should exclude individuals who are at risk of CJD and other familial TSE.

Persons who have undergone treatment using extracts of human pituitary gland (growth hormone and gonadotropin), have received

human dura mater grafts and have a family history of CJD or other familial TSE should be excluded from giving blood.

In addition, as over 50 cases of CJD have resulted from cadaveric dura mater grafts, the consultation recommended that dura mater should no longer be used.

The main conclusion of this consultation is that despite the new information available since May 1996, which has been carefully examined, the recommendations developed at the time regarding products entering the food chain still stand. Those regarding medicinal products have been updated. At the same time, additional recommendations concerning blood and blood products have been made as outlined above. WHO will continue to follow the situation, taking into consideration any new element that could modify or change its conclusions and recommendations in the area of human and animal spongiform encephalopathies.

Finally, there is no doubt that a surveillance of new cases of nvCJD and the development of tests to assess patients with CJD and its variant forms and importantly tests to evaluate persons and animals carrying the disease will be essential to estimate the risk and to control the spread of the disease.

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