Advisory Committee on Dangerous Pathogens TSE Subgroup

Updated position statement on occurrence of vCJD and prevalence of infection in the UK

Introduction

Variant Creutzfeldt-Jakob Disease (vCJD) is one of a small number of neurological diseases known as Transmissible Spongiform Encephalopathies (TSEs). Disease is associated with toxic build-up of an abnormal (misfolded) form of the prion protein (PrP). First identified in the late 1980s, vCJD is considered to be the human form of Bovine Spongiform Encephalopathy (BSE): there is strong experimental evidence that these diseases were caused by the same infective agent. Despite efforts to develop effective treatments, vCJD has always proven to be fatal once symptoms have developed.

Although most of the UK population was exposed to BSE, symptomatic cases of vCJD have remained rare to date. There have been 178 cases in the UK (classified as definite or probable according to accepted criteria). With one exception, all of those tested have a genetic characteristic shared by about 40% of the UK population: they are methionine homozygotes at the polymorphic codon 129 of the prion protein gene. However the most recent case in the UK (whose diagnosis was recently established post mortem) is of a different genotype, heterozygote at codon 129.

With CJD, there are particular concerns about potential spread from central nervous system (CNS) and lymphatic tissue, including blood. The UK has taken steps to reduce the risks of vCJD transmission through the blood supply and through re-use of surgical instruments. No evidence of vCJD transmission by surgery has been found to date, but transmission via donated blood has occurred. The necessity and cost-effectiveness of these measures depends to a large extent on how many people are "silent", asymptomatic carriers of the vCJD/BSE prion, who may possibly pose a risk of transmission to others. Prions are very difficult to inactivate, as demonstrated by another TSE, "sporadic" CJD (sCJD), which has on rare occasions in particular circumstances been transmitted by a range of medical and surgical procedures involving material that is either from or is believed to have been in contact with CNS tissue.

Appendix Tissue surveys

To investigate the potential number of sub-clinical carriers in the UK population, various studies have tested for the presence of abnormal prion protein in tissue samples stored after routine surgery. Until very recently these concentrated largely on the population born between 1961 and 1985; this cohort is known to have been exposed to BSE. The largest of those previous studies (known as the Appendix-II survey) tested 32,441 appendix samples by Immunohistochemical (IHC) staining, of which 16 tested positive. This was interpreted as meaning that around 1 in 2,000 of the UK population exposed to BSE may be carrying the vCJD/BSE prion.

To test this interpretation, a further study ("Appendix-III") has been carried out with results that have now been reported (https://www.gov.uk/government/publications/creutzfeldt-jakob-disease-cjd-surveillance-biannual-updates). This survey used exactly the same methods and criteria to test appendices taken from individuals *not* previously thought to have had significant exposure to BSE, i.e.:

- stored appendices removed during operations carried out prior to 1980 (i.e. well before any large-scale incidence of BSE became apparent),
- appendices taken from patients born after 1st January 1996 (the year by which measures to remove BSE from the food chain were fully in place).

Following extensive examination, appendices in both groups have been confirmed as staining positively immunohistochemically. There are 2 positive samples from 14,692 appendices removed during 1970-79 (*i.e.* about 1 in 7,000) and 5 out of 14,824 removed from patients born in 1996 or later (*i.e.* about 1 in 3,000). However, none of these positive samples are from appendices *removed before 1978* or from patients born *after 2000*. Thus they come from amongst the "latest" of the pre-1980 appendices, and the "earliest" of the post-1996 patients – i.e. relatively close to the population previously considered to be at highest risk.

If the two groups (before 1980 and after 1996) in the Appendix-III study are combined, the central prevalence estimate for these groups is roughly 1 in 4,200 (240 per million), compared with the 1 in 2,000 (500 per million) from Appendix-II. However, this difference is not statistically significant: in fact the figures in all the populations tested are consistent with a constant underlying rate. The latest results are also very similar to the previous "Appendix I" study of the 1961-85 cohort, which found 3 positive samples in roughly 12,000 tested, a rate of positivity of 1 in 4,000 (250 per million).

Interpretation

This finding must be considered in the context of existing evidence, regarding the relationships between prevalence of abnormal prion protein, dietary exposure to BSE and the appearance of clinical vCJD cases (key elements of this evidence are summarised in the background notes below.) It is challenging to provide a single narrative consistent with all known evidence.

The Appendix-III study was designed to examine the presumed absence of abnormally-staining appendices outside the population considered most at-risk of acquiring vCJD from BSE in the food chain. Its presence in these other groups has now been established. As noted, comparing the Appendix-II and -III studies provides some limited evidence for the most highly BSE-exposed cohort having a higher prevalence of abnormally staining appendices, but this is far from conclusive. More than one interpretation of the evidence can be defended at present, though all leave some questions unresolved. One could question whether IHC staining found in these studies is necessarily related to vCJD. However, the nature of the staining appears highly distinctive: it is similar to that typically found in vCJD cases (both before and after onset of clinical symptoms) and is not found in other conditions such as sCJD. We therefore consider that where samples are deemed to have tested positive

by the IHC technique, this is highly indicative of the abnormal prion protein that has only been seen in cases of vCJD. Given that assumption, two potential interpretations are as follows:

- There is no significant difference in the prevalence of this abnormal prion protein staining between any of the appendix survey populations. There is a low background prevalence of vCJD-related abnormal prion protein staining in human lymphoid tissues that may not progress to vCJD. This background prevalence is unrelated to the intensity and extent of dietary exposure to BSE.
- Alternatively, while there is no statistical difference in prevalence of vCJD -related abnormal prion protein across birth and exposure cohorts, the central estimates vary in a direction consistent with the changing intensity over time of the observed BSE epidemic in cattle. All may therefore be attributable to BSE exposure. However, this conclusion suggests that human exposure began in the late 1970s and continued through the late 1990s, albeit at a lower rate than in the mid-1980s.

Neither interpretation, on its own, provides an entirely satisfactory explanation. In principle, it is possible to combine elements of both. There could be some "background" prevalence in all groups, plus some additional prevalence associated with BSE in the most highly-exposed population. However, detailed examination has revealed no consistent qualitative distinctions between the staining of the positive samples that might suggest two different sources. Whichever interpretation is adopted, the contrast between the prevalence of abnormal prion protein and the number of clinical vCJD cases seen to date suggests that only a few of those with this protein abnormality will develop any symptoms of prion disease.

Implications

A variety of risk management measures are currently in place to limit the risks of person-to-person transmission by blood transfusion or by re-use of surgical instruments. However the latest study is interpreted, the possible prevalence of asymptomatic vCJD that can be transmitted to others remains of concern, and maintenance of a precautionary approach is required. More specifically, it remains a reasonable working assumption that the highest prevalence of asymptomatic infection is likely to be in the cohort known to have had high exposure to BSE and which currently contains all the known clinical cases of vCJD. However, some interpretations of the Appendix-III results complicate the use of any specific cut-off date to define a low-risk population cohort (e.g. "born after 1996"). Differences in interpretation therefore have some practical implications for risk management. These questions are likely to be better understood by study of the natural course of vCJD infection and development (or otherwise) of clinical disease, including variations in host /agent interactions. Although there is research currently focussed in that direction, realistically, answering these questions may take time. It is meanwhile essential to maintain a high level of both human and animal TSE surveillance, and it will remain so for some decades to come.

Background

Key existing pieces of evidence include the following.

Clinical vCJD cases

- There have been 178 confirmed or probable[1] clinical vCJD cases in the UK, 175 presumed to be associated with dietary BSE exposure and 3 with blood transfusion. The individuals' ages, dates of symptom onset, diagnosis and death are known, as is the geographical distribution of cases. None has a date of birth after 1989.
- Outside the UK, over 50 cases have been diagnosed to date, 27 of them in France. (source: http://www.cjd.ed.ac.uk/documents/worldfigs.pdf). Worldwide there is currently only one living patient (in Italy) with diagnosis of vCJD.
- There is potential for under-reporting of vCJD amongst elderly patients, though its extent is not known: this question is currently under investigation as part of a DH-funded research study.
- Until very recently, all the definite and probable cases tested had a genetic characteristic shared by about 40% of the UK population: they are methionine homozygotes at polymorphic codon 129 of the prion protein gene. The most recent of these patients in the UK suffered onset of symptoms in 2012 and died in 2013.
- However, the most recent UK case (confirmed in April 2016) occurred in a different genetic group: this patient was a methionine-valine heterozygote at codon 129 (http://www.cjd.ed.ac.uk/documents/worldfigs.pdf). This finding has confirmed the expectation of further waves of cases amongst other genotypes. Another heterozygote patient had previously been classified as a *possible* clinical case (Kaski, Mead, Hyare *et al*, 2009), but the diagnosis of vCJD could not be designated as "probable" or "definite" due to insufficient evidence.
- The age profile at onset of symptoms has remained static throughout the epidemic, with a median of 28 years in the UK. (The French cases also show a static age profile, but with a median of 36 years at onset.)
- There is strong experimental evidence that the known vCJD cases were caused by the same infective agent as BSE.

Potential for secondary (person-to person) transmission

- sCJD was demonstrated to be transmissible by neurosurgery in case studies published as long ago as 1974 (Bernoilli *et al*, 1977). Transmission can also occur by injection or implantation of CJD-infected central nervous system (CNS) material as seen in the epidemic of iatrogenic CJD in recipients of human growth hormone derived from cadaveric pituitaries (Rudge, Jaumuktane, Adlard *et al*, 2015).

[1] Definite, probable and possible cases are classified according to specific criteria developed for epidemiological studies of prion disease agreed by the World Health Organisation. Details can be found on National CJD Research & Surveillance Unit website at http://www.cjd.ed.ac.uk/criteria.htm

- In vCJD (unlike sCJD), immunohistochemical (IHC) staining studies demonstrate the presence of disease-related PrP in lymphoreticular and other tissues, while animal transmission studies demonstrate presence of the infective agent (Bruce, McConnell, Will and Ironside (2001); Ritchie *et al*, (2009); Notari *et al* (2010).
- No evidence of transmission of vCJD by surgery has been found to date, in contrast to sCJD.
- Transmission of vCJD by blood components and fractionated plasma products has occurred. vCJD developed in three recipients of red cells (prior to the introduction of leucodepletion) from donors who also developed vCJD (Llewelyn *et al*, 2004), and there is evidence of preclinical vCJD in a recipient of red cells from another blood donor who also developed vCJD (Peden, Head *et al*, 2004). This latter recipient was an individual who was heterozygote at codon-129 in the prion protein gene. This case had positive staining for prion protein in lymphoid tissue, but not in the brain, and the presence of vCJD infectivity was confirmed by experimental transmission (Bishop *et al*, 2013).
- Probable transmission of vCJD by fractionated plasma products was detected in an asymptomatic patient with a coagulation disorder who had been exposed to multiple potential sources of infection, including transfused blood components, endoscopy, and multiple batches of Factor VIII, including two batches prepared from pools of plasma which contained plasma from a donor who later developed vCJD (Peden, McCardle *et al*, 2010) . One of multiple spleen samples tested, but no other tissue, had positive staining for prion protein. A risk assessment concluded that the patient was likely to have been infected through the fractionated plasma products rather than any other source. This patient was also an MV heterozygote.

Population prevalence of abnormally-staining Prion Protein

- Results of three major appendix surveys carried out to date all show prevalence of abnormal prion protein in the UK population to be around 1 in 2,000 – 1 in 5,000, using Immunohistochemical (IHC) testing. These include the two studies discussed above and the first survey now known as "Appendix – I" (Hilton *et al*, 2004). This found 3 positive samples in roughly 12,000 tested from the 1961-85 birth cohort, a rate of positivity of 1 in 4000 (250 per million).
- A large-scale study of stored tonsils (de Marco *et al*, 2010) found no evidence of abnormal prion protein in 80,000 samples using ELISA testing. However there was a single positive sample in 10,000 samples re-tested using IHC. This latter result is also statistically consistent with the appendix data.
- Samples classed as positive by IHC testing in all the Appendix Surveys show similar patterns of staining to those found in clinical and pre-clinical vCJD cases.
- These "positive" samples are distributed across all Codon-129 genotypes.

- It should be noted that the use of tissue surveys as indicators of population prevalence depends on the assumption that the tissues come from a representative sample of the general population – in particular, that the risk of prion infection is unrelated to the chance of having one's appendix removed. Whilst there seem no specific reason to think otherwise, this remains an important caveat.

UK Exposure to BSE:

- A very large increase in *symptomatic* BSE cases in UK cattle became apparent through the late 1980s. The epidemic peaked in 1992, with over 36,000 known cases in that year, and the total number of infections is likely to have been much higher, possibly in the region of 3 million (Smith and Bradley, 2003). The exact pattern of human exposure to cattle with undiagnosed infections is unknown, but is likely to have been widespread (i.e. the majority of people were exposed).
- Arnold and colleagues at the Animal and Plant Health Agency have developed a model of the BSE epidemic in Great Britain which inputs a case of BSE into the UK rendering system in the early 1970's and their output can be fitted to the observed number of cases first seen in the 1980's. This model provides estimates of the number of subclinical and clinical cattle in the 1970s and 1980s in Great Britain, and hence the potential number of infected cattle entering the food chain. This has been translated into infectious units entering the food chain each year, taking into account the impact of control measures on BSE infectivity in the food chain. The model can be found at: https://app.box.com/s/hhhhg857fjpu2bnxhv6e.
- Key steps to limit the BSE outbreak were taken from 1988 onward, including a succession of ruminant feeding bans, and the UK epidemic declined markedly after 1992. However, it has not disappeared entirely: two cases were detected in 2015.
- In addition, steps to remove potentially-infective material from the human food chain were implemented from 1988, including compulsory slaughter and destruction of suspect cattle, and the November 1989 bans on specified bovine offals (SBO) for human consumption.
- Though the efficacy of some early interventions has been questioned, human exposure to BSE is thought to have largely ceased by 1996, given the ban on use of MRM from bovine vertebral column in late 1995 and the 1996 exclusion of all cattle over 30 months and head meat from all over 6 months.

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