

Advisory Committee on Dangerous Pathogens (ACDP) TSE Risk Assessment Subgroup

Position Statement on occurrence of vCJD and prevalence of infection in the UK population

Preface

Variant Creutzfeldt-Jakob Disease (vCJD) is a fatal human Transmissible Spongiform Encephalopathy (TSE). This is a type of neurological disorder associated with the presence of an abnormal, 'misfolded' form of prion protein, making vCJD one of a small number of 'prion diseases'. It almost certainly first spread to humans via cattle infected with Bovine Spongiform Encephalopathy (BSE), or 'Mad Cow' disease. To date, 176 patients in the UK have died from vCJD. They have typically been young, with a median age of about 28 years at onset of symptoms.

Earlier fears of large numbers of vCJD deaths have fortunately not been realised, and the number of new cases each year has been in decline for several years. However, there is evidence that many more people might be infected, while not showing any symptoms. If these people are *infective*, the risk of 'secondary' (person-to-person) transmission could be greater than implied by the small number of cases seen so far. In particular, there have been concerns about the risks of vCJD being spread via blood transfusion, and possibly through the re-use of surgical instruments. A number of precautionary steps are in place to reduce these risks¹, though it appears impossible to eliminate them entirely.

Meanwhile, there remain great scientific uncertainties around the disease and its behaviour. A key question is how the evidence on prevalence of infection in the population is to be reconciled with the small number of symptomatic, clinical cases diagnosed. Scientific advice to the Department of Health on risk assessment is provided by the Advisory Committee on Dangerous Pathogens (ACDP) TSE Risk Assessment Subgroup. Prompted in part by the emergence of new evidence on the prevalence of infection, the Department requested the Subgroup to set out a brief, high-level summary of what is known – and not known – about the incidence and prevalence of vCJD within the UK population. The result is the following Position Statement, discussed at the Subgroup's meeting on July 13th 2012 and finalised through subsequent

¹ For an overview of risk reduction measures related to blood see <http://www.transfusionguidelines.org.uk/index.aspx?Publication=DL&Section=12&pageid=794>, and for surgical risk reduction measures see <http://www.dh.gov.uk/ab/ACDP/TSEguidance/index.htm>

correspondence. Its aim is to make available a summary of current thinking on some key scientific issues, aimed primarily at professional audiences. The intention is that this statement should be revisited and updated as appropriate as new evidence becomes available. The Subgroup will continue to provide scientific advice on the effectiveness of further precautions.

ACDP Position Statement

Occurrence of vCJD

As of July 2012, 176 patients in the UK have been found to have definite or probable² clinical vCJD, and over 220 cases have been reported world-wide. As with other prion diseases, development of disease is influenced by genetic factors, in particular at position (“codon”)129 of the prion protein gene. At this position, healthy individuals have the amino-acid methionine (termed methionine homozygous, or MM), valine (valine homozygous, or VV) or both amino-acids (methionine-valine heterozygous, or MV). These groups comprise approximately 40%, 10% and 50% of the UK population respectively. All those probable and definite vCJD patients who have been genetically tested, have been MM homozygous at codon 129.

The UK vCJD patients comprise a single wave of clinical cases: numbers of known onsets peaked in 1999 and deaths and diagnoses both peaked in 2000. The most recent onset of symptoms in a UK patient was in September 2010, and there are currently no living vCJD patients in the UK³.

There is strong evidence that three of the 176 UK patients were infected through red cell transfusions from donors who themselves went on to develop vCJD. No other secondary cases have been identified to date, but the possibility of some of the other 173 patients having been infected through person-to-person transmission cannot be ruled out. In addition, abnormal prion protein was found in spleen samples from two further patients who died of unrelated causes, one having had a red cell transfusion from a donor who developed vCJD, and another having received fractionated plasma products partly sourced from such a donor. Though neither patient showed any symptoms of vCJD, these may well represent further transmission of infection.

There is evidence of disease amongst the other codon 129 genotypes, making it plausible that further clinical cases may appear in the remaining 60% of the population. One MV heterozygote patient has been classified

² In this context, the terms “probable” and “definite” refer to specific criteria developed for epidemiological studies of prion disease agreed by WHO. Details can be found on National CJD Research & Surveillance Unit website at <http://www.cjd.ed.ac.uk/criteria.htm>

³ Two remain alive in France: see <http://www.cjd.ed.ac.uk/vcjdworld.htm>

as a *possible* clinical case, though the diagnosis of vCJD could not be designated as “probable” or “definite” due to insufficient evidence.

Case ascertainment can never be regarded as perfect, and some clinical cases may have been missed or misdiagnosed (perhaps amongst elderly patients). However, there is no indication of large-scale under-reporting of clinical vCJD.

Prevalence of infection

The most recent study of prevalence of abnormal prion protein tested 32,441 appendix samples, collected during surgery on patients born between 1941 and 1985. Of these, 16 samples were judged to be “positive”⁴. This indicates a central prevalence estimate very close to 1 in 2,000 in the age cohort covered, with a 95% Confidence Interval running from approximately 1 in 3,500 to 1 in 1,250.

The previous *Hilton et al* study published in 2004 tested appendix samples from a narrower cohort of patients, almost all born between 1961 and 1985. This found three positive samples from 11,247 tested, suggesting a central prevalence estimate of approximately 1 in 4,000 with 95% Confidence Interval running from roughly 1 in 1,400 to 1 in 20,000. Although the confidence intervals of the two studies overlap, the new study thus narrows the range considerably, as well as providing a higher central estimate.

Abnormal prion protein has previously been found in tissue samples taken from all codon 129 genotypes, rather than being confined to MM homozygotes. Two of the “positive” appendices from the *Hilton et al* survey were from VV homozygotes, while the two asymptomatic recipients of blood products referred to earlier were both MV heterozygotes. The new findings confirm that all genotypes are susceptible to vCJD infection.

Interpretation

The “positive” samples found in these prevalence surveys have been compared with samples taken from vCJD patients and from individuals with known exposure to vCJD. Unless and until there is any evidence to the contrary, positivity in these tests should be seen as indicative of vCJD

⁴ Of these 12 showed indicative patterns of staining with more than one antibody. For summary of results <http://www.hpa.org.uk/hpr/archives/2012/news3212.htm>.

infection. **The recent appendix survey therefore provides the most reliable available indication of the prevalence of asymptomatic vCJD infection within the UK population⁵.**

There is thus an increasingly marked divergence between the estimated prevalence of vCJD infection and the observed number of clinical cases. This divergence would be even greater, were the test procedure used in the survey considered to have a sensitivity significantly below 100%.

The observation that clinical cases have so far been confined to MM homozygotes is insufficient to explain this divergence. For example, if exposure to BSE had infected 1 person in 2,000 in the 1941-85 birth cohort, and if all infected MMs had had incubation periods similar to those seen so far, some thousands of MM cases would already have appeared⁶.

The working assumption is that the bulk of the infections identified by the appendix survey would have been caused by dietary exposure to BSE in cattle⁷. The fundamental linkage to BSE can be tested by examining samples collected prior to the BSE outbreak.

Given the assumed significance of exposure to BSE, prevalence of vCJD infection should be much lower amongst those born from 1996 onward, given the measures by then in place to protect the food chain. This proposition can also be tested directly, by studying tissue samples from this post-1996 birth cohort.

⁵ Like the Hilton *et al* study, the new appendix survey used Immunohistochemistry (IHC) to screen samples. A large scale prospective survey of tonsil samples found no positives in 95,672 tested using a high throughput enzyme immunoassay technique (Frosh *et al*, 2004; Clewley *et al*, 2009). However re-testing of 9,672 samples using IHC revealed one specimen with a strongly positive follicle (de Marco *et al*, 2010). It is therefore considered that IHC provides the more reliable method of detection.

⁶ This can be illustrated by a rough calculation considering infections solely in the 1941-85 cohort. At the height of exposure to BSE, circa 1990, this cohort comprised about 30m people, 40% (12m) of them MM homozygotes. A prevalence of 1 in 2,000 (if due to primary infection) implies that 6,000 of these individuals would have been infected through BSE exposure. Collectively, they would have had life-expectancy normal for their age, so there would have been only a small number of deaths due to other causes. Had the incubation periods seen in the actual MM cases been typical of this larger MM group, most of these 6,000 infections would already have appeared as clinical cases. This takes no account of additional infections in other genotypes or in other age cohorts.

⁷ The possibility of some of the “positive” appendix samples having arisen from secondary, person-to-person transmission cannot be excluded, but this appears relatively unlikely. These samples were typically taken from fairly young patients, less likely to have received blood transfusions or to have undergone prior neurosurgery.

Taken together, the evidence on prevalence of infection and clinical case numbers implies that even amongst MMs, only a minority of those infected develop clinical symptoms within about 20 years of primary infection. The remainder go into a long-term, asymptomatic state.

There may be many reasons for differences in individual response to vCJD infection, and these have yet to be fully understood. One suggestion is that cross-species transmission (as when vCJD originated from BSE), generates multiple strains of the infectious agent with different characteristics. In any case, the development of disease following infection is likely to depend on a complex interaction between the infective agent and the individual. Key factors may include the dose and route of infection, while individual characteristics affecting susceptibility to clinical disease include codon 129 genotype and possibly other genetic factors. Onset of prion disease may also be triggered, or inhibited, by other conditions. The understanding needed to disentangle the possible causal factors does not yet exist.

Whatever the reasons for infected individuals entering a long term asymptomatic state, much depends on whether this could be expected to last indefinitely, or eventually lead to clinical symptoms. This is presently an open question, given the single wave of MM cases observed. The precautionary assumption is that **further clinical cases may appear after much longer incubation periods than those seen so far**⁸, though their number could be significantly reduced by intervening deaths from other causes.

Secondary transmission

Moving onto the risks of secondary (person-to-person) transmission, the precautionary assumption is that **presence of abnormal prion protein is indicative of vCJD infectivity** - that positivity of an appendix sample implies that blood and other peripheral tissues would be infective. Those with long-term asymptomatic vCJD infection would thus be potential sources of secondary infection – in particular though donation of blood or tissues and via the re-use of surgical instruments.

It is also reasonable to assume that all those exposed to the vCJD agent by such routes would be susceptible to infection, given the detection of abnormal prion protein in all codon 129 genotypes (though the degree of

⁸ Incubation Periods of over 40 years have been observed for Kuru, though these appear to be extreme.

susceptibility to infection, and to the onset of clinical disease, may well vary markedly between individuals).

Given the available evidence on key factors such as the infectivity of blood and tissues, and on the efficacy of instrument decontamination and measures such as leucodepletion of blood, one would expect some hundreds of secondary infections to have occurred every year, from the mid-1990s onward. As already noted, three of the 176 known vCJD patients are believed to have arisen from blood-borne infection (all through transfusion of non-leucodepleted red cells prior to 1999), whilst no clinical cases have been linked to surgery.

It remains possible that a few further vCJD patients could have been infected by secondary transmission, whilst the expected numbers of secondary clinical cases would be significantly reduced by the limited survival and life expectancy of patients undergoing blood transfusion or neurosurgery.

Nevertheless, the contrast between predicted numbers of infections and the appearance of clinical cases that might be attributed to secondary transmission is again striking. A number of explanations are possible, perhaps in combination. For example, infectivity in tissues may be lower than currently assumed, or appear at these levels only close to the onset of clinical symptoms. Surgery may turn out to be a relatively inefficient route of infection. Leucodepletion may have had a substantial impact on blood-borne transmission risks. Nevertheless, it remains plausible that secondary infections are occurring in significant numbers and that (as with primary infection) many infected individuals enter a long-term asymptomatic state.

As before, it is an open question as to whether or not these individuals would eventually develop symptoms, or are non-susceptible to development of clinical vCJD. In either case, the precautionary assumption is that while asymptomatic, they would represent possible sources of further onward infection.

Conclusions

Clearly, many scientific uncertainties remain, and it is challenging to interpret case numbers and prevalence estimates when so much remains to be known about the course of the disease and the factors that affect it.

While fundamental research into prion diseases continues, it is essential to ensure that consistent, long-term surveillance of the population continues. This should include development of methods to characterise the disease and if appropriate differentiate between strains.

Despite the welcome fall in vCJD diagnoses, the indication of relatively widespread, albeit “silent”, vCJD infection necessitates continued attention to the risks of secondary, person-to-person transmission, and for applied research to support the development and implementation of risk management strategies.

Gaining further information on prevalence of infection also remains a key area, especially through the investigation of tissues from groups unexposed to BSE and of the feasibility of surveying the prevalence of abnormal prion protein in blood.

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