Variant Creutzfeldt-Jakob disease

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Current evidence indicates that variant Creutzfeldt-Jakob disease is caused by the transmission of bovine spongiform encephalopathy to humans. The clinical and investigative features of variant CJD are relatively distinct from sporadic CJD and the neuropathological appearances are novel. The number of cases of vCJD in the UK may have peaked, but the total future number of cases of vCJD is uncertain and the possibility of secondary iatrogenic transmission via blood transfusion has recently been identified.

key words: variant Creutzfeldt-Jakob disease, clinical features, investigations, epidemiology

INTRODUCTION

Human prion diseases are rare, uniformly fatal, disorders of the central nervous system that occur in distinct aetiological forms: sporadic, hereditary and transmissible. Scientific and public interest in prion diseases has increased following the identification of bovine spongiform encephalopathy (BSE) and evidence that this condition is the cause of variant Creutzfeldt-Jakob disease (vCJD), representing the first known zoonotic spread of prion diseases from animals to humans.

Prion diseases are characterised by prolonged incubation period from the time of infection to the onset of neurological symptoms, followed by rapid deterioration and death. In the incubation period there is no clinical evidence for the disease, but infectivity may be present in extra-neural tissues, in particular the lymphoreticular system. Identification of infected humans or animals is not currently possible before the onset of clinical symptoms and signs. These features of prion diseases, together with the relative resistance of prions to decontamination, pose a major challenge to public and veterinary health.

The transmission of BSE to the human population was considered initially to be unlikely by many scientists and official bodies in the UK and elsewhere. It was, however, recognised that there was a potential for prion strains to change their characteristics, including species specificity, after cross-species transmission. Legislative measures to minimise human exposure to the BSE agent were introduced and one recommendation in the UK was that Creutzfeldt-Jakob disease (CJD) should be studied nationally in order to identify any change in the characteristics of this condition following the appearance of BSE in cattle. In 1990 The National CJD Surveillance Unit (NCJDSU) was set up with the aim of identifying all suspect cases of CJD and obtaining detailed clinical, epidemiological, pathological and genetic information on cases. A project to harmonise national surveillance systems for CJD was funded by the European Union in 1993 and included France, Germany, Italy, the Netherlands, Slovakia and the UK (Will et al. 1998).

A small number of cases of CJD with a remarkably early age at death were referred to the NCJDSU in 1995 and early 1996 and by March 1996 ten cases had been identified. The average age of those that died was only 29 years. Critically these cases shared an unusual clinical and pathological phenotype for CJD, which was thought to be novel. An article entitled ‘A new variant of Creutzfeldt-Jakob disease in the UK’ was published in April 1996 (Will et al. 1996) suggesting that these cases might be causally linked to the epidemic of BSE in...
UK cattle. This article reviews current information on variant CJD (vCJD) and sporadic CJD (sCJD).

**CLINICAL FEATURES OF vCJD AND sCJD**

The age at onset and death from vCJD and sCJD are relatively distinct. Figure 1 shows the numbers of deaths from vCJD and sCJD identified in the UK since 1990 by 5-year age groups and shows a bimodal distribution. This pattern has not previously been identified during previous periods of CJD surveillance either in the UK (going back to 1970), or in other countries in which systematic surveillance for CJD has been carried out. Identification of suspect cases of CJD depends on referral by adult neurologists in the UK and a separate system for identification of cases of vCJD in the paediatric age group (Verity et al. 2000) has led to the identification of six cases of vCJD aged less than 16 years at onset. There is an overlap between vCJD and sCJD in the age of death, but even in the UK there is a higher incidence of sCJD in the age group 40–44 years at death. A relatively young age at death cannot in itself be regarded as a diagnostic of vCJD.

Survival, defined as the interval between first symptom and death, is more prolonged in vCJD in comparison to vCJD (Fig. 2). Increasing age is associated with a decrease in relative survival in sCJD but, even taking this into account, the duration of illness in vCJD is more prolonged with a median survival of 13 months in vCJD in comparison to 4 months in sCJD. There is an overlap of clinical characteristics, but the vCJD cases as a group are clinically relatively distinct from sCJD and are also remarkably homogeneous in comparison to the variation in the clinical presentations in sCJD. In vCJD the early clinical course is characterised by psychiatric symptoms, although a minority have neurological symptoms from the onset, usually in the form of persistent pain or memory impairment (Spencer et al. 2002). Neurological signs develop after about 6 months and include ataxia, cognitive impairment and involuntary movements, which may be dystonic, choreiform or myoclonic. There is progressive neurological deterioration and patients become mute, incontinent and bed-bound (Zeidler et al. 1997) with death usually due to intercurrent infection. The early stages of sCJD are typified by rapidly progressive dementia and myoclonus, associated with multifocal neurological deficits such as dysphasia and ataxia (Will et al. 1984). The terminal stages of sCJD are similar to vCJD. The clinical features of younger patients with sCJD may be atypical, often with a protracted duration of illness and the distinction of vCJD and sCJD may be impossible on clinical grounds alone in individual cases. However, as a group there is a striking difference between vCJD and sCJD.

In parallel to the clinical differences between vCJD and sCJD, there are distinct findings on specialist investigations. The electroencephalogram (EEG) in sCJD shows ‘characteristic’ periodic triphasic complexes in 60–70% of cases, but these EEG appearances have

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**Figure 1.** At death of variant and sporadic CJD since 1990 in the UK by 5-year age groups. *to May 2004
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not been found in any case of vCJD. The cerebrospinal fluid (CSF) 14-3-3 immunoassay is positive in over 90% of cases of sCJD but is positive in only about 50% of cases of vCJD (Green et al. 2001). The MRI brain scan shows high signal in the caudate and putamen in about 70% of cases of sCJD, but the high signal changes in vCJD are in a different part of the brain, the posterior thalamus, and are found in 80–90% of cases (Collie et al. 2001). Assessment of MRI brain scan changes in all forms of CJD depends on the relative signal intensity in different brain areas, i.e., in vCJD the signal intensity in the pulvinar region of the thalamus is higher than in the caudate and putamen or cerebral cortex. Table 1 summarises the differences between sCJD and vCJD.

Table 1. Differences between sporadic and variant CJD

<table>
<thead>
<tr>
<th></th>
<th>sCJD</th>
<th>vCJD</th>
</tr>
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<tbody>
<tr>
<td>Mean age at death</td>
<td>66 years</td>
<td>29 years</td>
</tr>
<tr>
<td>Median duration of illness</td>
<td>4 months</td>
<td>14 months</td>
</tr>
<tr>
<td>Thalamic MRI high signal</td>
<td>Caudate/putamen</td>
<td>Pulvinar</td>
</tr>
<tr>
<td>EEG</td>
<td>“Typical” 70%</td>
<td>“Typical” 0%</td>
</tr>
</tbody>
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NEUROPATHOLOGY OF sCJD AND vCJD

The recognition of the neuropathological phenotype of vCJD as novel, with extensive florid plaque deposition, was critical to the identification of vCJD and the hypothesis of its causal link with BSE. The neuropathological aspects of human prion diseases are described in a separate chapter in this volume.

EVIDENCE FOR A CAUSAL LINK BETWEEN BSE AND vCJD

There was a possibility when vCJD was first identified in 1996 that the appearance of an apparently novel clinico-pathological phenotype of CJD in the UK might be explained by improved ascertainment of atypical...
Table 2. Diagnostic criteria for sporadic, accidental transmission and familial TSEs

1 SPORADIC

1.1 DEFINITE:
Neuropathologically/immunocytochemically confirmed

1.2 PROBABLE:
1.2.1 I + 2 of II +III
1.2.2 Possible + positive 14-3-3

1.3 POSSIBLE:
I + 2 of II + duration < 2 years

2 ACCIDENTALLY TRANSMITTED TSE

2.1 DEFINITE
Definite CJD with a recognised iatrogenic risk factor (see box)

2.2 PROBABLE
2.2.1 Progressive predominant cerebellar syndrome in human pituitary hormone recipients
2.2.2 Probable CJD with recognised, iatrogenic risk factor (see box)

3 GENETIC TSE

3.1 DEFINITE
3.1.1 Definite TSE + definite or probable TSE in 1st degree relative
3.1.2 Definite TSE with a pathogenic PRNP mutation (see box)

3.2 PROBABLE
3.2.1 Progressive neuropsychiatric disorder + definite or probable TSE in 1st degree relative
3.2.2 Progressive neuropsychiatric disorder + pathogenic PRNP mutation (see box)

RELEVANT EXPOSURE RISKS FOR THE CLASSIFICATION AS IATROGENIC CJD
The relevance of any exposure to disease causation must take into account the timing of the exposure in relation to disease onset

— Treatment with human pituitary growth hormone, human pituitary-gonadotrophin or human dura mater graft.
— Corneal graft in which the corneal donor has been classified as definite or probable human prion disease.
— Exposure to neurosurgical instruments previously used in a case of definite or probable human prion disease.

This list is provisional as previously unrecognised mechanisms of human prion disease may occur.

— PRNP MUTATIONS ASSOCIATED WITH GSS NEUROPATHOLOGICAL PHENOTYPE

— PRNP MUTATIONS ASSOCIATED WITH CJD NEUROPATHOLOGICAL PHENOTYPE

— PRNP MUTATIONS ASSOCIATED WITH FF1 NEUROPATHOLOGICAL PHENOTYPE
  D178N-129M

— PRNP MUTATION ASSOCIATED WITH VASCULAR PRP AMYLOID
  Y145s

— PRNP MUTATIONS ASSOCIATED WITH PROVEN BUT UNCLASSIFIED PRION DISEASE
  H187R, 216 bpi

— MUTATIONS ASSOCIATED WITH NEURO-Psychiatric DISORDER BUT NOT PROVEN PRION DISEASE
  I138M, G142S, Q160S, T188K, M232R, 24 bp, 48 bp, 48 bp + nucleotide substitution in other octapeptides

(additional list of mutations appended)

cases of CJD. The incidence of sCJD had approximately doubled in the UK between surveillance periods for CJD in the early 1980s and the early 1990s. The increase was attributed to improved case ascertainment, particularly in the elderly, and probably linked to increased awareness of CJD. Other European countries were subject to similar potential ascertainment bias and in March 1996 it was established that cases with a similar clinicopathological profile had not, at that time, been identified in France, Germany, Italy or the Netherlands, through the European surveillance system for CJD. A new form of CJD had been identified in the UK, which is the country with the greatest potential human exposure to BSE, a novel potential risk factor for human prion disease, and not in other countries.

Current evidence indicates that vCJD is indeed a new disease. No case with a similar neuropathological appearance has been identified despite review of archival material, including a systematic study in Europe (Budka et al. 2002). Laboratory studies have shown that the isotype of prion protein (PrP) deposited in the brain in vCJD is similar to experimentally transmitted BSE (Collinge et al. 1996) and that florid plaques are present in the brains of macaque monkeys inoculated with BSE (Lasmezas et al. 1996). Transmission experiments in wild type and both human and bovine transgenic mice
have demonstrated that the transmission characteristics of vCJD, including incubation period and distribution of neuropathological changes, are very similar in BSE and vCJD and distinct from sCJD (Bruce et al. 1997, Hill et al. 1997, Scott et al. 1999). Most cases of vCJD have been identified in the UK, consistent with a link with BSE, and the single cases of vCJD identified in Canada and the USA, in which human exposure to BSE was probably minimal, had a history of extended residence in the UK. There is now compelling evidence for a causal link between BSE and vCJD.

### RISK FACTORS FOR vCJD

Risk factors for vCJD included a young age, methionine homozygosity at codon 129 of the prion protein gene (PRNP) and residence in the UK. The reason for the young age distribution of cases is not known, but may relate to an increased age-related exposure to BSE through consumption of particular foodstuffs or an increased susceptibility to infection in the young because of biological factors, yet to be identified.

In sCJD methionine homozygosity at codon 129 of PRNP is a risk factor for the development of disease (Table 4). Only about 38% of the normal Caucasian population have this genotype. In vCJD all 124 tested cases to date are methionine homozygotes and this genotype may represent a true susceptibility factor. However, there is also the possibility that variations at this locus may influence incubation period, by analogy with other forms of human prion disease, and cases of human BSE infection with a valine homozygous or heterozygous codon 129 genotype may yet be identified. Variations at codon 129 of PRNP can also affect disease phenotype, but, to date, there is no good evidence for another new form of human prion disease in the UK.

National attribution of vCJD is defined as the country of normal residence at the time of disease onset. Numbers of cases of vCJD by country are listed in Table 5. Residence in the UK is a relative, but not a necessary, risk factor for the development of vCJD. All the cases of vCJD in the UK and the Canadian, Irish and US cases, were potentially exposed to BSE in the UK after examination of lifetime residential history. However, the

### Table 3. Diagnostic criteria for variant Creutzfeldt-Jakob disease

<table>
<thead>
<tr>
<th>4. vCJD</th>
<th>I and 4/5 of II and IIIA</th>
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<tbody>
<tr>
<td>4.1 DEFINITE</td>
<td>I A Progressive neuropsychiatric disorder</td>
</tr>
<tr>
<td></td>
<td>B Duration of illness &gt; 6 months</td>
</tr>
<tr>
<td></td>
<td>C Routine investigations do not suggest an alternative diagnosis</td>
</tr>
<tr>
<td></td>
<td>D No history of potential iatrogenic exposure E No evidence of a familial form of TSE</td>
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<tr>
<td>4.2 PROBABLE</td>
<td>II A Early psychiatric symptomsa</td>
</tr>
<tr>
<td></td>
<td>B Persistent painful sensory symptomsb</td>
</tr>
<tr>
<td></td>
<td>C Ataxia</td>
</tr>
<tr>
<td></td>
<td>D Myoclonus or chorea or dystonia</td>
</tr>
<tr>
<td></td>
<td>E Dementia</td>
</tr>
<tr>
<td>4.3 POSSIBLE</td>
<td>III A EEG does not show the typical appearance of sporadic CJDc</td>
</tr>
<tr>
<td></td>
<td>(or no EEG performed) B Bilateral pulvinar high signal on MRI scan</td>
</tr>
<tr>
<td></td>
<td>IV A Positive tonsil biopsyd</td>
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<tr>
<td>a depression, anxiety, apathy, withdrawal, delusions.</td>
<td></td>
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<tr>
<td>b this includes both frank pain and/or dysesthesia.</td>
<td></td>
</tr>
<tr>
<td>c generalised diphasic periodic complexes at approximately one per second.</td>
<td></td>
</tr>
<tr>
<td>d tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.</td>
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<td>e spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum</td>
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### Table 4. PRNP codon 129 genotype in normal population, sporadic and variant

<table>
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<tr>
<th></th>
<th>% MM</th>
<th>% MV</th>
<th>% VV</th>
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<tbody>
<tr>
<td>Normal population</td>
<td>39</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>sCJD (UK 1990–2003)</td>
<td>66</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>vCJD</td>
<td>100</td>
<td>0</td>
<td>0</td>
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### Table 5. Number of cases of vCJD by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
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<tbody>
<tr>
<td>UK</td>
<td>146</td>
</tr>
<tr>
<td>France</td>
<td>6</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
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</table>
French cases and the Italian case had not been resident in the UK and must have been exposed to BSE outside the UK and probably in their own country through indigenous BSE or imports from a BSE affected country. Transmission of BSE to the human population is thought to have been through dietary exposure, probably to high titre (CNS) bovine tissues, probably in the 1980s (Will 1999). There is currently only limited evidence in support of this hypothesis, for example there are major methodological difficulties in establishing an increased risk for vCJD through past consumption of commonly consumed food products. However, there is no reasonable alternative hypothesis for the cause of vCJD.

Concern about BSE has increased following identification of cases in an increasing number of countries, but the absolute numbers of cases of BSE are very much lower than in the UK. Data from UK Customs and Excise suggest that there was extensive export of bovines, cattle feed and food products from the UK to European and other countries in the 1980s and early 1990s. One study suggests that the relative exposure of the human population in France to BSE, taking account of exports from the UK and the epidemic of BSE in French cattle, is about a tenth of that in the UK (Alperovitch and Will 2002).

PUBLIC HEALTH

The likely future number of cases of vCJD is a crucial question for public health in the UK and for the first few years after the identification of vCJD analyses of the numbers of deaths or clinical onsets of vCJD per quarter showed an increasing trend with time. However, the numbers of deaths and clinical onsets per annum have declined over the past 2–3 years (Fig. 3), and statistical analyses are now consistent with an epidemic that may have peaked (Andrews et al. 2003). There is, however, the possibility of further waves of cases related to infections in individuals with different genetic backgrounds at codon 129 of PRNP or in relation to variations with time in the pattern of human dietary exposure to BSE (Bruce et al. 2001).

Mathematical models estimating the total future number of cases have indicated a wide range of future scenarios. One early calculation estimated the total numbers of cases of vCJD in the UK to range from 80–130,000 (Cousens et al. 1997) and, although more recent models provide more conservative estimates, there is uncertainty about the likely size of the total vCJD epidemic. All these calculations necessarily depend on a range of assumptions and critical determinants such as the mean incubation period of BSE in humans or the infectious dose of BSE for humans are unknown.

The possibility of secondary transmission of vCJD from person to person has led to a range of measures to minimise this risk in the UK and many other countries. The pathogenesis of vCJD is distinct from other forms of human prion disease in that there is detectable immunostaining in lymphoreticular tissues and, in one study (Cooper, Bird, 2002), higher levels of peripheral infectivity. The possibility of a risk of transmitting vCJD through blood transfusion led to a study in the UK aimed at identifying all recipients of labile blood products donated by vCJD cases. A single case has been identified in which vCJD was confirmed in a recipient of a blood transfusion donated by an individual who themselves developed vCJD (Houston et al. 2000). This raises the possibility of transmission of vCJD through blood transfusion, consistent with similar findings in an experimental model of BSE in sheep (Llewelyn et al. 2004). There is currently no evidence for transmission of vCJD through other potential iatrogenic routes such as contaminated surgical instruments, but this does not preclude such a possibility because the incubation period could be long and the period of current observation is relatively short.

CONCLUSION

There is now convincing evidence that the BSE agent is a human pathogen, but vCJD remains an exceedingly rare disease, even in the UK. There is, however, uncertainty about the future course of the vCJD epidemic in the UK and this poses a challenge to public health, not least because of the possibility of secondary transmission.

REFERENCES


