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Variant Creutzfeldt-Jakob disease

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Abstract. 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. The number of cases of vCJD are increasing with time in the UK, but the total future number of cases of vCJD is uncertain.

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INTRODUCTION

Human prion diseases are rare disorders of the central nervous system that are uniformly fatal. Scientific interest in these diseases has been stimulated by their occurrence in distinct aetiological forms, sporadic, hereditary and transmissible and by the explanation of this diversity through the prion hypothesis. Public awareness and concern about prion diseases has increased following the identification of bovine spongiform encephalopathy (BSE) and the accumulating evidence that this condition is the cause of variant Creutzfeldt-Jakob disease (vCJD), thereby representing the first known zoonotic spread of prion diseases from animals to humans.

One of the characteristic features of all prion diseases are prolonged incubation period from the time of infection to the onset of neurological symptoms, followed by rapid deterioration and death. During the incubation period there is no clinical evidence of disease, but infectivity may be present in extra neural tissue, and the lymphoreticular system in particular. There is currently no practicable test that allows the identification of humans or animals that are infected before the onset of clinical symptoms and signs. Together with the relative resistance of prions to decontamination, these features of prion diseases pose a major challenge to public and veterinary health.

In the late 1980s, the possibility that BSE might be transmissible to the human population was considered by many scientists and official bodies in the UK and elsewhere to be unlikely. However, it was recognised that there was a potential for prion strains to change their pathogenicity after cross-species transmission. As a result, legislative measures to minimise human exposure to the BSE agent were introduced and it was recommended 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 UK cattle. The national CJD Surveillance Unit (NCJDSU) started work in 1990 with the aim of identifying all suspect cases of CJD in the UK and obtaining detected clinical, epidemiological, pathological and genetic information on cases. In 1993 a project to harmonise national surveillance systems for CJD was funded by the European Union and included France, Germany, Italy, the Netherlands, Slovakia and the UK (Will et al. 1998).

In 1995 and early 1996, a small number of cases of CJD with a remarkably early age at death were referred to the NCJDSU. By March 1996 10 cases had been identified with an average at death of 29 years and with an unusual clinical and pathological phenotype for CJD. An article entitled "A new variant of Creutzfeldt-Jakob

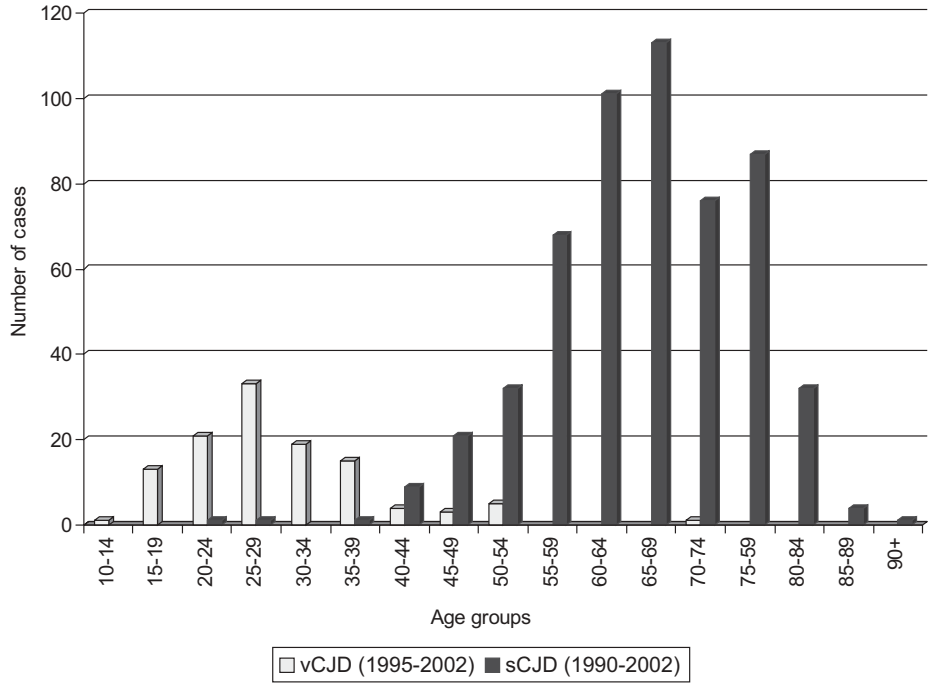

Fig. 1. Age at death of variant and sporadic CJD since 1990 in the UK by 5 year age groups.

disease in the UK" was published in April 1996 (Will et al. 1996) and suggested that these cases might be causally linked to the epidemic of BSE in UK cattle. This article reviews current data comparing variant CJD (vCJD) and sporadic CJD (sCJD), discusses the aetiological hypothesis and considers the possible public health implications.

CLINICAL FEATURES OF vCJD AND sCJD

vCJD and sCJD have a different age distribution. Figure 1 shows the numbers of deaths from vCJD and sCJD identified in the UK since 1990 by 5 year age groups. There is a bimodal distribution which is distinct from previous experience in the UK (going back to 1970) or from any other country which has carried out systematic surveillance for CJD. Because identification of suspect cases of CJD depends in the UK on referral by adult neurologists, there is a separate system for identification of cases of vCJD in the paediatric age group (Verity et al. 2000) and 6 cases aged less than 16 years at onset have been identified to date. It is of note that there is an overlap between vCJD and sCJD in the age of death, but that even in the UK there is a higher incidence of sCJD in the age group 40-44 years at death.

The duration of illness, defined as the interval between first symptom and death, is shown in Fig. 2, which shows that survival is more prolonged in vCJD in comparison to sCJD. The median duration of illness in vCJD is 13 months in comparison to 4 months in sCJD. There is an inverse relationship between age and survival in sCJD but, even taking this into account, the duration of illness in vCJD is prolonged. Although there is an overlap of clinical characteristics, the vCJD cases as a group are clinically relatively distinct from sCJD and are also remarkably homogeneous in comparison to the disparate clinical presentations in sCJD. In vCJD the early clinical course is dominated 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). After about 6 months there are frank neurological signs, including 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). Death is often due to intercurrent infection. Although the terminal stages of vCJD are similar to sCJD, the early stages of sCJD are typified by rapidly progressive dementia and myoclonus, associated with multifocal neurological deficits such as dysphasia and ataxia (Will

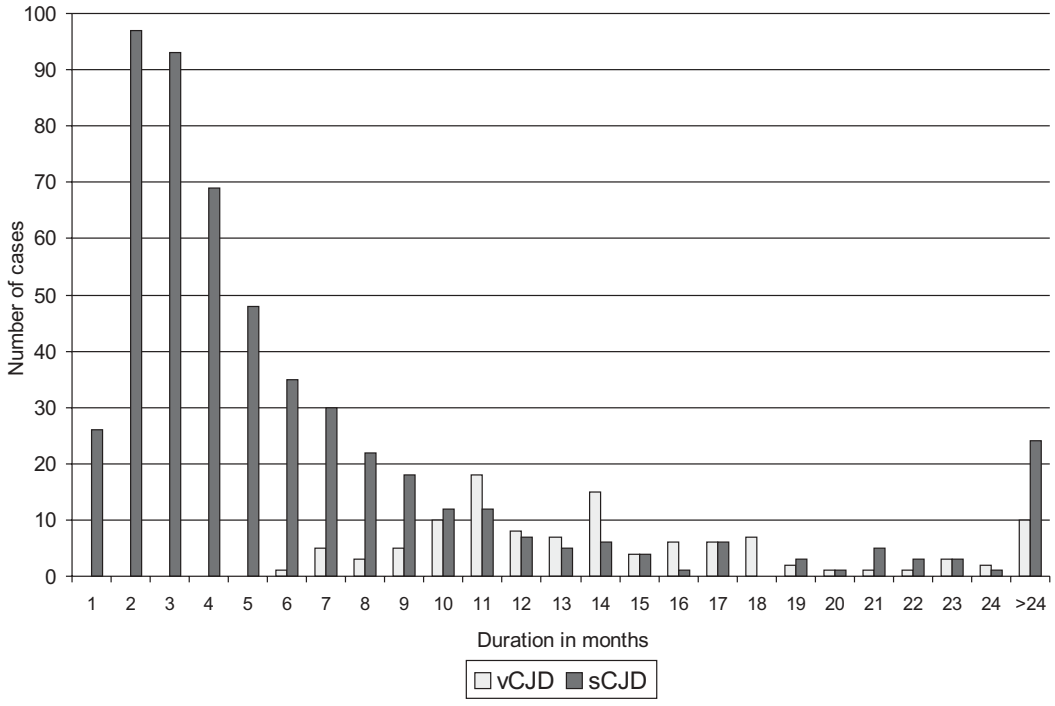

Fig. 2. Duration of illness in variant and sporadic CJD in months.

and Matthew 1984). It is of note, however, that the clinical features of younger patients with sCJD may be atypical, often with a protracted duration of illness. The distinction of vCJD and sCJD may be impossible on clinical grounds alone in individual cases, but as a group there is a striking difference between vCJD and sCJD.

The clinical differences between vCJD and sCJD are underpinned by contrasting findings on specialist investigation. The electroencephalogram (EEG) in sCJD shows "characteristic" periodic triphasic complexes in 60-70% of cases. These EEG appearances have not been found in any case of vCJD. The cerebrospinal fluid (CSF) 14-3-3 protein 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 and high signal in a different part of the brain, the posterior thalamus, in about 90% of cases of vCJD (Collie et al. 2001). It is important to stress that an 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 I summarises the differences between sCJD and vCJD.

NEUROPATHOLOGY OF sCJD AND vCJD

This is discussed in a separate chapter of this volume, but 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 a causal link with BSE.

EVIDENCE FOR A CAUSAL LINK BETWEEN BSE AND vCJD

At the time of the initial characterisation of vCJD in 1996 there was concern that improved ascertainment of atypical cases of CJD might explain the appearance of an apparently novel clinico-pathological phenotype of CJD in the UK. There had been a doubling of the incidence of sCJD in the UK between periods of systematic surveillance of CJD in the early 1980s and the early 1990s, which was attributed to improved case ascertainment, particularly in the elderly, and probably linked to increased awareness of CJD because of extensive media coverage. There was similar potential ascertainment bias in other European countries and in March 1996 it was established through the European surveillance system for CJD that cases with a similar clinico-pathologi- cal profile had not, at that time, been identified in France, Germany, Italy or the Netherlands. A new form of CJD had been identified in the country, the UK, with the greatest potential human exposure to a new potential risk factor for human prion disease, BSE, and not in other countries.

There is now convincing evidence 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). Additional evidence comes from laboratory studies, which have demonstrated 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). Laboratory transmission studies in wild type human transgenic and bovine transgenic mice demonstrate that the transmission characteristics of

Table I

Differences between sporadic and variant CJD

	sCJD	vCJD
Mean age at death	66 years	29 years
Median duration of illness	4 months	13 months
Thalamic MRI high signal	caudate/putamen 60%	pulvinar 90%
EEG	"typical" 70%	"typical" 0%

Table II

PRNP codon 129 genotype in normal population, sporadic and variant

	% MM	% MV	% VV
Normal population	39	50	11
sCJD (UK 1990-2002)	68	16	16
vCJD	100	0	0

vCJD, including incubation period and distribution of neuro- pathological changes, are very similar in BSE and vCJD and distinct from sCJD (Bruce et al. 1997, Hill et al. 1997, Scott et al. 1999). The evidence of a causal link between BSE and vCJD is now compelling.

RISK FACTORS FOR VCJD

Established 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 could 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 yet to be identified biological factors.

All tested cases of vCJD to date (>100 cases) are methionine homozygotes at codon 129 of *PRNP* compared to about 38% of the general Caucasian population. Methionine homozygosity is also a risk factor for the development of sCJD (Table II). In vCJD methionine homozygosity could be a true susceptibility factor but there is also the possibility, by analogy with other forms of human prion disease, that variations at this locus may influence incubation period. Cases of human BSE infection with a valine homozygous or heterozygous codon 129 genotype may yet occur. Variations at this locus can also affect disease phenotype, but, to date, there is no good evidence of another new form of CJD in the UK.

Residence in the UK is a relative, but not a necessary, risk factor for the development of vCJD. The numbers of cases of vCJD by country are listed in Table III.

National attribution of vCJD is defined as the country of normal residence at the time of disease onset. All the cases of vCJD in the UK, together with the Irish and US cases, were potentially exposed to BSE in the UK after examination of lifetime residential history. However the

Table III

Number of cases of vCJD by country	
UK	123
France	6
Republic of Ireland	1
Italy	1
USA	1

French cases and the Italian case had not been resident in the UK and must have been exposed to BSE outside the UK. The favoured hypothesis is that transmission of BSE to the human population was through dietary exposure, probably to high titre (CNS) bovine tissues, probably in the 1980s (Will 1999). The evidence supporting this hypothesis is currently weak but there is no reasonable alternative hypothesis and there are major methodological difficulties in establishing an increased risk for vCJD through past composition of commonly consumed food products. On the assumption that the dietary hypothesis is correct, the cases of vCJD in France and Italy must have been exposed to BSE in their own country.

Exposure to BSE outside the UK may be linked to indigenous cases of BSE or export from the UK of infected cattle, cattle feed or food products in the 1980s. 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

A critical question for public health in the UK is how many cases of vCJD will occur in the future. Analyses of the numbers of deaths or clinical onsets in vCJD per quarter indicates an increasing trend with time, with an estimated doubling of cases every 3 years (Andrews et al. 2000). 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 remains great uncertainty about the likely size of the 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.

An additional problem for public health is the theoretical possibility of secondary transmission of vCJD from person to person. The pathogenesis of vCJD is different from other forms of human prion disease with detectable immunostaining in lymphoreticular tissues and, presumably, higher levels of peripheral infectivity. There is a possibility that there may be a risk of transmitting vCJD through contaminated surgical instruments or through labile or fractionated blood products donated by individuals who later develop vCJD. There is currently no evidence of transmission of vCJD through these routes but this does not preclude such a possibility because the incubation period could be long and the period of current observation is short. A range of measures to minimise the risk of secondary transmission of vCJD have been taken in the UK and other countries.

CONCLUSION

VCJD remains an exceedingly rare disease, even in the UK. However there is now strong evidence that the BSE agent is a human pathogen and there remains great uncertainty about the future course of the vCJD epidemic in the UK and other countries. This poses a challenge to public health because of the extended incubation period in these diseases, because of the evidence of peripheral pathogenesis in vCJD and because the agents of prion diseases are relatively resistant to sterilisation. Policy decisions often have to be made on the basis of judgement rather than scientific fact. One lesson from the history of BSE and vCJD is that legislative measures aimed at reducing risk should be enforced.

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