Variant Creutzfeldt–Jakob disease: an update

There cannot have been many medical publications this decade that have had an impact to equal that of the paper by Robert Will and colleagues on a 'new variant' of Creutzfeldt–Jakob disease (CJD), published in the *Lancet* in April 1996 (Will et al, 1996). This did not simply affect the scientific community, but also farming, economics, politics and diplomacy.

The authors, who were monitoring the human spongiform encephalopathies (*Table 1*) in the UK, at the National CJD Surveillance Unit in Edinburgh, first became aware of an unusual form of CJD in the autumn of 1995. These cases were characterized by an atypical clinical phenotype (particularly at the start of their illnesses), a relatively youthful age of onset, a longer disease duration when compared with sporadic CJD and hitherto unrecognized neuropathological appearances of the CNS.

Ten of the 11 cases published by the summer of 1996 originated from the UK, a country in which bovine spongiform encephalopathy (BSE) had reached epidemic proportions in the early 1990s, and an aetiological link was queried. To date 48 cases of what is now called variant CJD (vCJD) have been identified on neuropathological or strong clinical grounds, and apart from the single case from France all others have been in the UK.

TABLE 1. Human spongiform encephalopathies

Sporadic Creutzfeldt–Jakob disease
Inherited Creutzfeldt–Jakob disease, including Gerstmann–Sträussler syndrome and fatal familial insomnia
Iatrogenic Creutzfeldt–Jakob disease
Kuru
Variant Creutzfeldt–Jakob disease

CLINICAL PHENOTYPE

Comprehensive descriptions of the clinical phenotype of vCJD have been published (Zeidler et al, 1997). The first 14 cases (8 of whom were female) had a mean age of onset of 29 years (range 16–48 years), and a median disease duration of 14 months. These figures can be contrasted with those in sporadic CJD, where the mean age of onset is around 65 years and the median disease duration is around 4 months.

Two striking and unusual (for CJD) presenting features are sensory disturbance and psychiatric illness. Indeed, the early stage of the illness can be devoid of 'hard' neurological signs, and in one case it took about 24 months for cerebellar ataxia to develop after having presented with personality change and sensory symptoms. As the disease evolves, more 'typical' features are seen, including ataxia, global cognitive impairment and involuntary movements (including chorea and myoclonus).

Cortical blindness, a relatively common finding in sporadic CJD, was seen in only 3 out of the first 14 patients, whereas upgaze paresis (an unusual feature in sporadic CJD) was seen in half. Terminally, patients are rigid, myoclonic and akinetic mute, features that are common to most forms of human spongiform encephalopathy.

INVESTIGATIONS

The characteristic electroencephalographic appearances of sporadic CJD, of periodic sharp wave complexes in all leads throughout the recording, are not encountered in vCJD. High T2 signal emanating from the pulvinar region of the thalamus may be a relatively specific magnetic resonance imaging (MRI) finding. Western blot analysis for the 14-3-3 protein in CSF, which when tested appropriately in sporadic CJD cases has a sensitivity in excess of 90%, has a lower sensitivity for the diagnosis of vCJD.

One of the many fascinating (and unexplained) observations in vCJD has been the fact that, to date, all of the confirmed cases have been methionine homozygous at the polymorphic codon 129 of the prion protein (PrP) gene open reading frame (a finding in approximately 70% of sporadic CJD cases). Mutations of the same gene, which are encountered in all cases of inherited CJD, are not identified in vCJD.

MANAGEMENT

The management of vCJD is currently purely supportive. All suspected cases in the UK should be referred to the National Surveillance Unit in Edinburgh (as should all cases of human spongiform encephalopathy). Relatives and friends may find contact with the support groups informative and comforting (see *Useful addresses*). Guidelines on minimizing the potential for person-to-person transmission of vCJD have been put forward (NHS Executive, 1999), and particularly when investigating suspected cases (by brain biopsy, for example), should be scrupulously adhered to. However, it is also worth emphasizing that there is no epidemiological evidence that person-to-person spread of any form of CJD occurs via routine clinical or social contact.

NEUROPATHOLOGY AND EXPERIMENTAL TRANSMISSION STUDIES

The hallmark of vCJD is the presence, on histological examination of the

brain, of dense eosinophilic amyloid plaques (staining positively with anti-PrP antibody) with a pale periphery surrounded by a zone of spongiform change: the so-called 'florid' plaques. Similar lesions were identified in brains of macaques which had been inoculated intracerebrally with BSE cattle brain homogenate (Lasmézas et al, 1996).

Molecular analysis of PrP glycoforms in different types of CJD revealed that vCJD had a distinctive profile, one which was shared by naturally transmitted BSE in the domestic cat and experimental BSE in the macaque (Collinge et al, 1996). The final and most compelling evidence that vCJD was caused by the BSE agent came from transmission experiments in which the characteristic 'signature' of BSE was reproduced when vCJD was experimentally transmitted to a panel of inbred mouse strains (Bruce et al, 1997).

Recently attempts have been made to establish the diagnosis of vCJD antemortem by tonsil biopsy. In a small series, in which unequivocal final diagnoses were available in three neuropathologically confirmed cases of vCJD, two cases of definite/probable sporadic CJD, two cases of inherited CJD and one patient who recovered clinically, protease-resistant PrP of a distinctive glycosylation pattern (different to that in brain) was demonstrated in the vCJD cases alone (Hill et al, 1999).

It is unlikely, however, that this technique will obviate the need for brain biopsy in subjects being investigated with suspected vCJD. In this, as in all other forms of spongiform encephalopathy, the main reason for performing a biopsy should be in case evidence of an alternative and treatable form of CNS disease emerges, such as a vasculitis or Whipple's disease. These disorders are unlikely to be identified by tonsil biopsy, while the risk and expense of biopsy of potentially infectious material will not be spared.

THE FUTURE

Almost 4 years after its identification, this rare and tragic disease continues to attract worldwide attention. At this time all but the most sceptical believe that the condition is aetiologically related to BSE, although the route by which 'inoculation' has taken place is not fully resolved.

Other questions also remain. Why does vCJD affect a particularly young population? Is the observation that all affected subjects up to now are methionine homozygous at codon 129 of the PrP gene significant? And, most importantly, how many more people are going to die of it? Continued vigilance and cooperation with surveillance and research exercises are likely to be the crucial first steps in attempting to answer these questions. **HM**

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KEY POINTS

- Variant Creutzfeldt–Jakob disease (vCJD) is a novel human spongiform encephalopathy, aetiologically related to bovine spongiform encephalopathy (BSE).
- By November 1999 (4 years after its first recognition), 47 cases had been identified in the UK and a single case in France.
- The clinical phenotype of vCJD is well characterized.
- Although there are no diagnostic tests, short of biopsy, results of investigations may support the suspicion of vCJD.
- Suspected cases should be referred to the National Surveillance Unit in Edinburgh, where vCJD was first identified, as should all cases of human spongiform encephalopathy in the UK.
- There are many unanswered questions about vCJD, the most important of which is how many individuals are eventually likely to succumb to it.

Useful addresses

CJD Support Network
Birchwood, Heath Top
Ashley Heath, Market Drayton
Salop TF9 4QR
Tel: 01630 673973
Email cjdnet@alzheimers.org.uk

Human BSE Foundation
Greenfields
Bath Road
Devizes SN10 1QG
01380 720033
humanbse.foundation@virgin.net

Bruce ME, Will RG, Ironside JW et al (1997) Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* **389:** 498–501

Collinge J, Sidle KCL, Meads J, Ironside J, Hill AF (1996) Molecular analysis of prion protein strain variation and the aetiology of 'new variant' CJD. *Nature* **383:** 685–90

Hill AF, Butterworth RJ, Joiner S et al (1999) Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet* **353:** 183–9

Lasmézas CI, Deslys J-P, Demaimay R et al (1996) BSE transmission to macaques. *Nature* **381:** 743–4

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