LETTERS

Variant Creutzfeldt-Jakob disease in older patients

Variant Creutzfeldt-Jakob disease (vCJD) is a zoonotic disease caused by cross-species transmission of bovine spongiform encephalopathy with a median age at onset of 27 years. In 1996, when the first cases were described, a clinicopathological phenotype distinct from sporadic CJD was defined and diagnostic criteria with a high sensitivity and specificity for vCJD have been validated.[1]

All definite and probable cases of vCJD (201/218) have been methionine homozygous (MM) at codon 129 of the prion protein gene (*PRNP*). If cases with the other *PRNP*-129 genotypes (MV, VV) have longer incubation periods, and are exposed at the same age, they will be older by the time they develop symptomatic disease. In addition, patients over 50 are more likely undergo surgical procedures and receive blood transfusions than younger patients and are, therefore, at greater risk of secondary vCJD. Future vCJD cases are likely to occur in older groups than in the primary epidemic. An important question is whether these patients have the same clinical phenotype and pattern of investigation findings as previously described.

A review of the 177 probable and definite vCJD cases referred to the UK surveillance system between 1995 and 2014 identified six cases aged over 55 years at the onset of symptoms.

All the cases developed progressive cognitive impairment and additional neurological features which are unusual in the more common forms of dementia in the middle-aged and elderly. Four had involuntary movements, three sensory symptoms and five ataxia, with the sixth case exhibiting an apraxic gait. Only three cases had early psychiatric symptoms, but withdrawal and behavioural disturbance were seen later in the clinical course in two cases (table 1). Only one of the five cases with MRI brain imaging showed typical pulvinar high signal,[2] with another showing less typical abnormalities. One case underwent a tonsil biopsy, which was positive for vCJD-related abnormal prion protein. Two of the older cases fulfilled the current WHO clinical criteria for a diagnosis in life of probable vCJD and two for possible vCJD. The final two cases did not fulfil criteria for either probable or possible vCJD but all the cases were confirmed neuropathologically with

Table 1 Clinical features in six older vCJD cases

Case Number	Onset year	Blood transmission	Age of onset	Duration of illness	Early psychiatric/ behavioral symptoms	Involuntary movements (myoclonus/ chorea/dystonia)	Sensory	Ataxia	Classification in life*	MRI	Other investigations	Working diagnosis at death
1	1999	No	74	7	Yes Agitated and paranoid	Yes	Yes	Yes	Possible vCJD	Not performed	14-3-3 and EEG not performed	Multi-infarct dementia
2	2002	No	62	8	Yes Depression, Withdrawal	Yes	Yes	Yes	Probable vCJD	Positive. Bilateral pulvinar sign	Negative 14-3-3. EEG non-specific slowing	vCJD
3	2002	Yes	68	13	Yes Depression, withdrawal, irritability	Yes	Yes	No (dyspraxic gait)	Possible vCJD	Negative	14-3-3 not performed. EEG non-specific slowing	FTD with parkinsonism/PSP (?CJD in late stages)
4	2006	Yes	74	11	No	No	No	Yes	Probable vCJD	Negative	Positive tonsil biopsy. 14-3-3 not performed. EEG non-specific slowing with occasional sharp transients	vCJD—but known to be at risk due to blood transfusion from affected case
5	2006	No	56	40	No. Withdrawal, Behavioural disturbance at 9 months	Yes	No	Yes	–	Negative	FDG PET showed severe right parietal hypometabolism. FPCIT normal. 14-3-3 and EEG not performed	FTD (?prion disease in late stages)
6	2010	No	59	33	No Behavioral disturbance, Delusions at 2 years	No	Yes	Yes	–	Suspicious, but not diagnostic. Subtle bilateral caudate and dorsomedial thalamic high signal	14-3-3 not performed. EEG non-specific slowing	Wernickes encephalopathy (?CJD at onset and in later stages)

*Retrospective classification.
?, possible; FDG PET, fluorodeoxyglucose-positron emission tomography; FPCIT, iodine-123 fluoropropylbeta-4-iodophenyltropane; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; vCJD, Variant Creutzfeldt-Jakob disease.

typical features of vCJD, including deposition of type 2B prion protein. DNA was extracted from postmortem tissue and all cases were MM at codon 129 of *PRNP*.

Two cases respectively were initially referred to neurology, general medicine and geriatrics and five out of the six cases were seen by a neurologist at some stage during the clinical illness. Two of the cases were diagnosed as probable vCJD in life: the second transfusion recipient who was clinically atypical of vCJD, but had a positive tonsil biopsy and a case with typical clinical features and a positive MRI brain. One case diagnosed as multi-infarct dementia fulfilled the clinical criteria for possible vCJD, but did not undergo an MRI brain or tonsil biopsy. In two cases, the final clinical diagnosis was frontotemporal dementia (FTD) and, in the final case, Wernicke's encephalopathy.

The data in this paper indicate that a small proportion of cases of vCJD have occurred in relatively older age groups. The National CJD Research & Surveillance Unit (NCJDRSU) has identified six cases of vCJD aged over 55 years, with a mean age at onset of 61 years, which contrasts with the overall mean age at onset in vCJD of 27 years (n=171). The older cases occurred relatively late in the vCJD outbreak overall, but there is no indication of a trend to an increase in the number of older cases with time.

There may be a diagnostic challenge in recognising these older vCJD cases among a population with a high overall incidence of dementia. All had a progressive history of cognitive impairment with four cases exhibiting a rapidly evolving dementia over 1 year. The rapidity of the final deterioration raised the suspicion of sporadic CJD in some of the cases. All had other neurological features suggestive of a dementia different from the common causes in their age group, such as involuntary movements, sensory symptoms or ataxia, but only two cases had sufficient clinical features to fulfil the criteria for probable vCJD. One of these cases had a typical MRI for vCJD and was diagnosed in life and one was recognised as vCJD in the context of being known to be at risk through a prior implicated blood transfusion.

The other four cases were not diagnosed in life with two being thought to have FTD, one multi-infarct dementia and one Wernicke's encephalopathy. In one of the cases initially diagnosed as FTD, the possibility of 'prion disease' was raised following a rapid decline and a repeat MRI was planned, but was not carried out. In three other cases the possibility of 'CJD' was mentioned in the case records after a rapid decline in the late stages of the illness. Thus, although vCJD was only diagnosed in life in two cases, the possibility of CJD or prion disease was raised in three other cases.

This report describes six pathologically confirmed cases of vCJD over the age of 55 years with a less consistent clinical phenotype than has been described in younger patients. The characteristic MRI pulvinar sign was seen in only one case. There a risk of the diagnosis being missed in older vCJD cases, particularly if patients are seen by specialties with less awareness of the clinical and investigative features of vCJD. Differentiating vCJD from other forms of subacute dementia in an older population with a higher background prevalence of dementia may be problematic and it is important to be aware that vCJD can occur in older age groups.[3 4] The diagnosis of vCJD should be considered in patients with atypical forms of dementia involving ataxia and/or involuntary movements and a rapid course or acute terminal deterioration. Repeat MRI or tonsil biopsy may be indicated if there is a suspicion of vCJD and postmortem in a regional neuropathology centres with expertise in CJD should be considered in such cases.[5]

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