Variant Creutzfeldt-Jakob disease in older patients

Citation for published version:

Digital Object Identifier (DOI):
10.1136/jnnp-2014-309397

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Journal of Neurology, Neurosurgery & Psychiatry

Publisher Rights Statement:
Available under Open Access

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
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

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Onset year</th>
<th>Blood transmission</th>
<th>Duration of onset (months)</th>
<th>Blood transmission</th>
<th>Early psychiatric/behavioural symptoms</th>
<th>Early gait disorder</th>
<th>MRI</th>
<th>Other investigations</th>
<th>Working diagnosis at death</th>
<th>Working diagnosis at death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1999</td>
<td>No</td>
<td>7</td>
<td>Yes</td>
<td>Agitated and paranoid</td>
<td>Yes</td>
<td>MRN</td>
<td>Negative</td>
<td>Possible vCJD</td>
<td>vCJD, Multi-intract dementia</td>
</tr>
<tr>
<td>2</td>
<td>2002</td>
<td>No</td>
<td>8</td>
<td>Yes</td>
<td>Depression, withdrawal, irritability</td>
<td>Yes</td>
<td>MRN</td>
<td>Negative</td>
<td>Probable vCJD</td>
<td>FTD with parkinsonoid (CJD in late stages)</td>
</tr>
<tr>
<td>3</td>
<td>2002</td>
<td>Yes</td>
<td>13</td>
<td>Yes</td>
<td>Depression, withdrawal, irritability</td>
<td>No</td>
<td>MRN</td>
<td>Negative</td>
<td>Probable vCJD</td>
<td>FTD (prion disease in late stages)</td>
</tr>
<tr>
<td>4</td>
<td>2006</td>
<td>Yes</td>
<td>11</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>MRN</td>
<td>Positive tonsil biopsy</td>
<td>Probable vCJD</td>
<td>vCJD, but known to be at risk due to blood transfusion from affected case</td>
</tr>
<tr>
<td>5</td>
<td>2006</td>
<td>No</td>
<td>40</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>MRN</td>
<td>Negative</td>
<td>Probable vCJD</td>
<td>FTD (prion disease in late stages)</td>
</tr>
<tr>
<td>6</td>
<td>2010</td>
<td>No</td>
<td>33</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>MRN</td>
<td>Negative</td>
<td>Probable vCJD</td>
<td>FTD (prion disease in late stages)</td>
</tr>
</tbody>
</table>

---

1 Retrospective classification.
2 Possible; FTD, frontotemporal dementia; PD, 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 is 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 5 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

Salwa el Tawil,1 Graham Mackay,1 Louise Davidson,2 David Summers,2 Richard Knight,1 Robert Will1

1National CJD Research & Surveillance Unit, University of Edinburgh, Western General Hospital, Edinburgh, UK
2Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK

Correspondence to Professor Robert Will, National CJD Research & Surveillance Unit, University of Edinburgh, Bryan Matthews Building, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; r.g.will@ed.ac.uk

Contributors The study was conceived by RW, RK, SeT and GM. Clinical data was produced and analysed by SeT, GM and LD. MRI’s were reviewed by DS. SeT and GM produced the first draft of the paper which was reviewed and revised by all other authors.

Competing interests None.

Ethics approval Lothain Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCE
Variant Creutzfeldt-Jakob disease in older patients

Salwa el Tawil, Graham Mackay, Louise Davidson, David Summers, Richard Knight and Robert Will

J Neurol Neurosurg Psychiatry 2015 86: 1279-1280 originally published online January 21, 2015
doi: 10.1136/jnnp-2014-309397

Updated information and services can be found at:
http://jnnp.bmj.com/content/86/11/1279

These include:

References
This article cites 5 articles, 1 of which you can access for free at:
http://jnnp.bmj.com/content/86/11/1279#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Open access (203)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/