Variant Creutzfeldt-Jakob disease

Update, MV case, Appendix III, blood tests, EID article

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# VARIANT CREUTZFELDT-JAKOB DISEASE: CURRENT DATA (MAY 2017)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)</th>
<th>TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)</th>
<th>RESIDENCE IN UK &gt; 6 MONTHS DURING PERIOD 1980-1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>175 (0)</td>
<td>3 (0)</td>
<td>178¹</td>
</tr>
<tr>
<td>France</td>
<td>27 (0)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>4 (0)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>3 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>USA</td>
<td>4² (0)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2 (0)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Japan</td>
<td>1³ (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>3 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Portugal</td>
<td>2 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>5 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1 (0)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

¹case 178 from the UK was heterozygous at codon 129 of the PRNP gene
²the 3rd US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the USA since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. In the 4th US patient, the history indicated that exposure to infection most likely occurred prior to moving to the USA.
³the case from Japan had resided in the UK for 24 days in the period 1980-1996.
vCJD CASES BY YEAR AND COUNTRY
1994-2016 (n=230)

*MV at codon129 of the PRNP gene
vCJD DEATHS PER ANNUM IN THE UK

![Bar chart showing the number of vCJD deaths per annum in the UK from 1995 to 2017. The chart is labeled and shows two categories: MM and MV.]
Case report

Male, aged 36 years

No significant past medical or family history

2015: apathy, depression, altered behaviour and difficulty managing at work for the preceding year
Developed ataxia, myoclonus and progressive cognitive impairment

Died 2016

Duration of illness: 20 months

MRI: high signal in caudate and putamen
Codon 129 genotype: MV

Post mortem: variant CJD
Codon 129 genotype in vCJD

- 160/161 tested cases in UK: MM
- 1/161 tested cases in UK: MV
- 52/52 cases outside UK: MM
- Normal UK population: MM 44% MV 45% VV 11%
Median and posterior distributions of projected time series

Cases:
A: Total number
B: Transfusion associated
C: Unidentifiable transfusion associated

Genotypes:
D: MM
E: MV
F: VV
Variant CJD in an individual heterozygous for PRNP codon 129

Diego Kaski, Simon Mead, Harpreet Hyare, Sarah Cooper, Ravi Jampala, James Overell, Richard Knight, John Collinge, Peter Rudge

www.thelancet.com Vol 374 December 19/26, 2009

Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow).
(B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).
A high index of suspicion of vCJD in individuals with:

- a vCJD phenotype
- an MV genotype
- an MRI with high signal in caudate and putamen
- a negative RT QuIC

- particularly in younger patients

A firm diagnosis requires neuropathology (or possibly tonsil biopsy)
This study provides definitive evidence that spleen tissue from an asymptomatic individual contains variant Creutzfeldt-Jakob disease infectivity and that the variant Creutzfeldt-Jakob disease agent retains infectivity following passage through an MV genotype host.
Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

O Noel Gill head of department, Yvonne Spencer head of pathology, Angela Richard-Loendt senior research histologist, Carole Kelly senior CJD scientist, Reza Dabaghian senior scientific and technical manager, Lynnette Boyes histologist, Jacqueline Linehan senior research histologist, Marion Simmons veterinary research pathologist, head of EU Reference Laboratory for TSE, Paul Webb pathology research scientist, Peter Bellerby pathology research scientist, Nick Andrews senior statistician, David A Hilton consultant neuropathologist, James W Ironside professor of clinical neuropathology, Jon Beck research scientist, Mark Poulter research scientist, Simon Mead reader in neurology, consultant neurologist, Sebastian Brandner professor of neuropathology, honorary consultant neuropathologist

- 16/32,441 samples positive
- 493 per million (95%CI: 282-801)
- 1 in 2,000
- Codon 129: MM 8, MV 4, VV 4
Infection report
Volume 10 Number 26   Published on: 12 August 2016

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens
The Appendix-III survey examined by immunohistochemistry (IHC) appendices removed at operation and collected from 44 hospitals throughout England. Abnormal prion accumulation was detected within the follicular dendritic cells of seven appendices out of 29,516 suitable samples examined.
Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens
The other five positive samples were found in the 14,824 appendices from subjects born in 1996 or later and removed at operation in 2000 through 2014: all five were in the sub-group of 10,074 born in 1996 through 2000.

[i.e. aged 4-18 years]
UK CASES OF vCJD BY YEAR OF BIRTH AND NON-UK CASES BORN AFTER 1989
Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease

Luis Concha-Marambio,¹,² Sandra Pritzkow,¹ Fabio Moda,¹,³ Fabrizio Tagliavini,³
James W. Ironside,⁴ Paul E. Schulz,¹ Claudio Soto¹,²,*

We used the protein misfolding cyclic amplification (PMCA) technique to analyze blood samples from 14 cases of vCJD and 153 controls, including patients affected by sCJD and other neurodegenerative or neurological disorders as well as healthy subjects. Our results showed that PrP$^\text{Sc}$ could be detected with 100% sensitivity and specificity in blood samples from vCJD patients. Detection was possible in any of the blood fractions analyzed and could be done with as little as a few microliters of sample volume.
PRION DISEASES

Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Daisy Bougard, Jean-Philippe Brandel, Maxime Bélondrade, Vincent Béringue, Christiane Segarra, Hervé Fleury, Jean-Louis Laplanche, Charly Mayran, Simon Nicot, Alison Green, Arlette Welaratne, David Narbey, Chantal Fournier-Wirth, Richard Knight, Robert Will, Pierre Tiberghien, Stéphane Haïk, Joliette Coste

This assay allowed the blinded identification of 18 patients with clinical vCJD among 256 plasma samples from the two most affected countries, with 100% sensitivity [95% confidence interval (CI), 81.5 to 100%], 99.2% analytical specificity (95% CI, 95.9 to 100%), and 100% diagnostic specificity (95% CI, 96.5 to 100%). This assay also allowed the detection of silent carriage of prions 1.3 and 2.6 years before the clinical onset in two blood donors who later developed vCJD.
2. Human TSEs current status

2.1. Sporadic, genetic and iatrogenic forms of human TSEs

There is no evidence that sporadic, genetic or iatrogenic forms of human TSEs have been transmitted from person to person through exposure to plasma products or urinary derived medicinal products. Systematic surveillance for CJD of all types has been undertaken in a number of countries, including a collaborative study in the EU since 1993, and no case of sporadic, genetic or iatrogenic CJD has been causally linked to prior treatment with plasma products.
Sporadic Creutzfeldt-Jakob Disease in 2 Plasma Product Recipients in the United Kingdom

Patrick Urwin, Kumar Thanigaikumar, James W. Ironside, Anna Molesworth, Richard S Knight, Patricia E. Hewitt, Charlotte Llewelyn, Jan Mackenzie, Robert G. Will

Emerging infectious diseases, In press 2017
Sporadic Creutzfeldt-Jakob disease (sCJD) has not been previously reported in patients with clotting disorders treated with fractionated plasma products. We report 2 cases of sCJD identified in the United Kingdom in patients with a history of extended treatment for clotting disorders; 1 patient had hemophilia B and the other von Willebrand disease. Both patients had been informed previously that they were at increased risk for variant CJD because of past treatment with fractionated plasma products sourced in the United Kingdom.
<table>
<thead>
<tr>
<th><strong>Case 1</strong></th>
<th><strong>Case 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Willebrand’s Disease</td>
<td>Haemophilia B</td>
</tr>
<tr>
<td>Rx:</td>
<td>Rx:</td>
</tr>
<tr>
<td>Since aged 9</td>
<td>Since early 40s</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>6 units FFP</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>Factor IX (UK sourced and</td>
</tr>
<tr>
<td>Factor VIII (UK sourced and</td>
<td>recombinant)</td>
</tr>
<tr>
<td>recombinant)</td>
<td></td>
</tr>
<tr>
<td>Notified to be at risk of vCJD</td>
<td>Notified to be at risk of vCJD</td>
</tr>
<tr>
<td>No history of iatrogenic exposure</td>
<td>No history of iatrogenic exposure</td>
</tr>
<tr>
<td>No family history of dementia/CJD</td>
<td>Vascular dementia</td>
</tr>
</tbody>
</table>
However, both cases had clinical and investigative features suggestive of sCJD. This diagnosis was confirmed in both cases on neuropathologic and biochemical analysis of the brain. A causal link between the treatment with plasma products and the development of sCJD has not been established, and the occurrence of these cases may simply reflect a chance event in the context of systematic surveillance for CJD in large populations.
Patients with inherited bleeding disorders registered in the National Haemophilia Database on 1st March 2011 by diagnosis and sub-groups at risk of vCJD for public health purposes.

<table>
<thead>
<tr>
<th>Patient group and subgroups</th>
<th>Number of patients with bleeding disorders by diagnostic subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemophilia A</td>
</tr>
<tr>
<td>a. Total registered in the National Haemophilia Database (NHD)</td>
<td>5337</td>
</tr>
<tr>
<td>b. Registered patients designated ‘at risk’ of vCJD: (treated with UK-sourced coagulation factor concentrates between 1980 and 2001)</td>
<td>2246</td>
</tr>
<tr>
<td>c. Registered patients at risk of vCJD known to have received implicated FVIII and FIX batches</td>
<td>556</td>
</tr>
</tbody>
</table>
KEY NUMBERS FROM THE 2015 REPORT ON THE ANNUAL GLOBAL SURVEY

111 COUNTRIES REPRESENTED

304,362 People with bleeding disorders identified

187,183 People with Hemophilia
74,819 People with von Willebrand disease (VWD)
42,360 People with Other Bleeding Disorders

5.6% (17,296) Increase in number of people with bleeding disorders identified

Factor VIII Usage per capita
0.53 IU (0.05 – 3.52) Median (IQR)

(81 countries, 63% of world population)

WFH
WORLD FEDERATION OF HEMOPHILIA
FEDEURACION MUNDIAL DE HEMOFILO
RESULTS: To date, 65 CJD donors have been enrolled along with 826 of their blood recipients. These recipients have contributed 3934 person-years of follow-up and no transfusion-transmitted cases of CJD have been recognized.

CONCLUSION: From this study, as well as other epidemiologic studies, there is no evidence of CJD transfusion transmission; this risk remains theoretical.
Staff at the NCJDRSU

- Jan Mackenzie
- James Ironside
- Richard Knight
- Alison Green
- Mark Head
- Matthew Bishop
- Patrick Urwin
- Michelle Gillies
- Gurjit Chohan
- Louise Davidson

Transfusion Medicine Epidemiology Review

- Patricia Hewitt
- Charlotte Llewelyn
- National Blood Services
- Health and Social Care Information Centre

Clinicians throughout the UK

Patients and their families

The Roslin Institute

- Jean Manson
- Abigail Diack

Public Health England

- Katy Sinka