Creutzfeldt-Jakob disease: Australian surveillance update to March 2007

Genevieve M Klug, Alison Boyd, Victoria Lewis, Samantha L. Douglass, Helene Roberts, Rebecca Argent, Colin L Masters, Steven J Collins

Abstract

From October 1993, prospective, national surveillance of the rare class of neurodegenerative diseases known as transmissible spongiform encephalopathies (TSEs) has been performed by the Australian National Creutzfeldt-Jakob Disease Registry. Surveillance of TSEs prior to October 1993, involved the retrospective ascertainment of TSE cases from 1970 to 1993. In this report, surveillance data for 2006 are presented in detail and compared to cumulative national TSE ascertainment as well as international experience. The higher incidence of TSEs in 2006 is not without precedent and can be attributed to higher referrals and consequent post-mortem rates. *Commun Dis Intell* 2007;31:194–197.

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Introduction

Transmissible spongiform encephalopathies (TSEs) comprise a unique group of transmissible neurodegenerative disorders, including Creutzfeldt-Jakob disease (CJD), Gerstmann Sträussler-Sheinker syndrome, fatal familial insomnia and variant CJD (vCJD). Pathogenesis centres on a conformational change of the endogenous normal prion protein (PrPc) to a disease-associated conformer (PrPres), with subsequent accumulation in the brain, associated with neuronal damage, spongiform change and ultimately death. Precise mechanistic details concerning the molecular conversion of PrPc and

the subsequent pathogenetic pathways remain to be elucidated. Most human TSE cases arise sporadically with no plausible explanation (approximately 85%). Less commonly, TSEs are linked to a mutation in the prion protein gene (*PRNP*) (approximately 13%–15%) or arise through horizontal transmission (most commonly an iatrogenic event). Iatrogenic CJD has been associated with several different transmission routes, including neurosurgical procedures, parenteral hormone therapy and more recently for vCJD, through the transfusion of blood products in the United Kingdom (UK).[1,2]

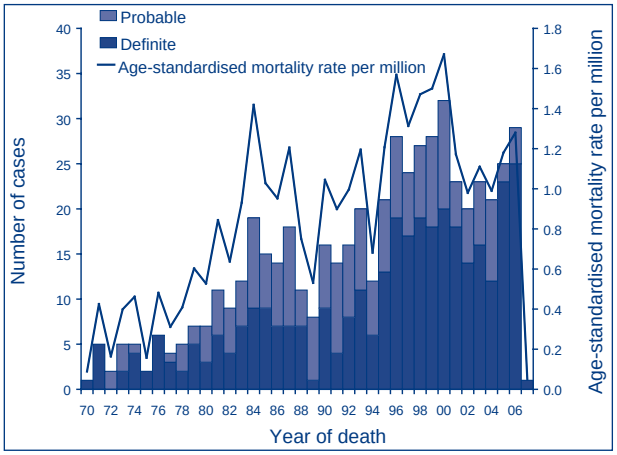
Australian National Creutzfeldt-Jakob disease Registry surveillance

After 13.5 years of Australian national surveillance, the Australian National Creutzfeldt-Jakob disease Registry (ANCJDR) has ascertained 1,178 cases of suspect TSE. Of these, 489 have been evaluated and classified as non-TSE on the basis of detailed follow-up of clinical histories and/or neuropathological examination. The remaining 689 cases have been classified as TSE according to internationally recognised case definitions[3] or are still under investigation (Table 1). As of 31 March 2007, the Registry has classified 344 cases as definite CJD, 203 cases as probable CJD and there are 11 possible cases. Definite cases are classified after confirmation of disease by neuropathological examination (usually post-mortem), whereas a probable case classification is determined by the clinical features and diagnostic investigation results that typify CJD. Investigation of the 131 incomplete cases is ongoing, with 86 of these patients still alive. The average, age-adjusted, CJD mortality rate for the entire 1970–2007 cohort is 0.86 deaths per million per year. For the prospective ascertainment period (1993– 2007), which provides a more accurate rate of CJD deaths in Australia, the mortality rate is 1.16 deaths per million per year.

TSE surveillance summary to 31 March 2007 with an emphasis on 2006

In 2006, increases in both notifications of suspect CJD cases (30% increase) and the number of confirmed CJD cases (21% increase) were observed compared with the previous year (Figure, Table 2). This annual number of referrals and CJD cases has been observed previously by the ANCJDR during 1999–2000 (Figure), a period that correlated with intense media attention regarding vCJD both domestically and internationally. Part of the explanation for the 2006 increase relates to increased referrals of suspect cases for cerebrospinal fluid 14-3-3 protein diagnostic testing offered through the ANCJDR and to a lesser extent through personal communications from family members and clinicians. These increased ante-mortem notifications enabled a greater number of autopsies to be conducted in this patient group, leading to the confirmation of a greater number of cases than usual, underscoring the importance of ongoing facilitation of post-mortem examinations.

Number and age-standardised mortality rate for ANCJDR definite and probable cases, 1970 to 31 March 2007



Mortality rates were calculated using the Australian Bureau of Statistics 2000 resident population estimates for Australia.

Table 1. Classification of cases on the Australian National Creutzfeldt-Jakob disease Registry, 1 January 1970 to 31 March 2007

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	303	36	5*	0	0	344
Probable	189	10	4	0	0	203
Possible	10	0	1	0	0	11
Incomplete	0	0	0	0	131†	131
Total	502	46	10	0	131	689

* Includes 1 definite iatrogenic case who received pituitary hormone treatment in Australia but disease onset and death occurred while a resident of the United Kingdom. This case is not included in statistical analysis since morbidity and mortality did not occur within Australia.

† Includes 86 living cases.

Table 2. Number of suspect cases notified and Creutzfeldt-Jakob disease outcomes, 1997 to 2007

Referral year	Suspect cases	CJD	% CJD
1997	69	29	42.0
1998	85	29	33.7
1999	102	33	32.0
2000	83	28	33.7
2001	58	26	44.8
2002	59	22	37.3
2003	54	22	40.7
2004	71	24	33.8
2005	66	23	34.8
2006	88	28	31.8
2007	21	1	4.7
Total	756	265	35.0

Fluctuating annual peaks in total CJD numbers is anticipated as a natural temporal variation in such a rare disease.

Three quarters of the cases notified in 2006 were ascertained via referrals for the cerebrospinal fluid 14-3-3 protein testing. The ANCJDR began offering 14-3-3 testing in September 1997, and since then the diagnostic test has been the initial referral source of 476 suspect CJD cases. Based on the total 1,178 referrals, since October 1993, the 14-3-3 testing has accounted for 40% of all referred suspect cases and establishes the diagnostic test as the most effective notification source of suspect CJD in Australia. The ANCJDR continues to provide this national diagnostic service.

The Australian CJD surveillance findings are congruous with those reported by international CJD surveillance units (notwithstanding the absence of a case of vCJD in Australia). In accordance with global experience, as reported previously, the large majority of definite and probable Australian cases (for the period 1970–2007) occurred sporadically (approximately 90%) with no obvious familial or iatrogenic association.[4] Familial cases (due to *PRNP* mutations) accounted for 8.4% of all Australian CJD cases and the remaining 1.5% of cases, were iatrogenic cases. For sporadic cases, the median age at death was 67 years (males, 66 years; females, 67 years). Fifty-four per cent of sporadic cases were female and their median duration of disease was 4 months. In men, slightly shorter disease duration was observed (median, 3 months). In comparison to sporadic CJD, genetically determined TSEs typically have a younger age at death (median, overall 59 years; males, 51 years; females, 62 years) and longer illness duration (median, overall 6 months; males, 4 months; females, 7.5 months) but equal sex ratio, identical to the sporadic CJD cohort. If compared to the total sporadic CJD cohort, the 2006 CJD cases had a similar age at death (overall, 64 years, males, 64 years, females 65.5 years), and duration (overall, 3 months, males, 2 months, females, 3 months) and the sex ratio was also consistent.

Due to the difficulty in differentiating sporadic CJD from some genetically determined forms of CJD, testing to detect mutations in *PRNP* is offered to the majority of patients with definite and probable CJD, but particularly when a family history of CJD exists, or when families are particularly interested in testing. Genetic testing is not systematically performed in Australia, in contrast to several European Union (EU) countries, where typically more than 50% of all CJD cases have undergone genetic testing.[5] Despite the non-routine genetic testing approach within Australia, the proportion of Australian TSE with an underlying *PRNP* mutation ascertained during the prospective surveillance period (1993–2007) was 10.2%, and is comparable with other EU countries consistently undertaking higher rates of genetic testing of CJD cases.[5] Over the last 12 months, at the time of publication, no cases of vCJD or further cases of iatrogenic CJD have been identified.

ANCJDR surveillance for vCJD

One of the primary ANCJDR activities is the surveillance of potential vCJD cases in Australia. The first identified case of vCJD was in the United Kingdom in 1995[6] and since this time the worldwide total of primary vCJD cases has reached 199, with 11 of these cases still alive (Table 3).[5] In the UK, three further symptomatic cases have been classified as secondary vCJD, with disease transmission almost certainly arising via the transfusion of blood products (non-leucodepleted red blood cells) from donors who developed the disease subsequent to donation. It is now evident that the primary disease epidemic has lessened in the UK,[7] yet in France the number of cases has increased and plateaued in 2005/2006. Despite the decline in the UK, there is still cause for concern regarding the potential for a prolonged 'tail' to the primary transmission epidemic based on differential genetic susceptibilities in the population leading to longer incubation periods, and the potential for secondary transmissions from sub-clinical carriers who may never develop disease but may transmit CJD in the health care setting.

To date, vCJD has not been identified in Australia. With the recognition of vCJD in Canada, the Republic of Ireland, Japan and the United States of America (USA), and given similarities in the reciprocal migration patterns and travel profiles of residents of Australia, Canada and the USA with

the UK, questions persist as to why this is the case. The number of Australians potentially exposed to contaminated UK meat products during the high risk period of 1980–1996 is large, and thus the likelihood of identification of at least 1 to 2 cases of vCJD in Australia is anticipated (personal communication, S Collins). Upon suspicion of this type of CJD, diagnostic testing on tonsil or brain biopsies to detect PrPres is offered by the ANCJDR and since 2000, on average, 1 Australian suspect vCJD case has been investigated every 2 years.

One possible explanation for the lack of identification of vCJD so far in Australia is clinical misdiagnosis or non-identification, but this is considered unlikely. Of all suspect TSE referrals between 1993 and 2006 where death is known to have occurred, 58% have undergone neuropathological examination. This large proportion of autopsied cases, accompanied by thorough ANCJDR screening of medico-demographic data and a comprehensive review of the available molecular-clinical profiles of Australian sporadic cases (where death occurred between 1992–2003 and appropriate tissue samples were available),[8] provides an underlying confidence that a case of vCJD has not been missed in Australia. The ANCJDR surveillance for vCJD continues to rely heavily on notifications and access to comprehensive clinical information. Variant CJD has a distinctly different clinical profile to classical CJD. Patients are typically younger at age of onset (12–74 years; median 26 years),[7] present with psychiatric and/or limb sensory symptoms, and have longer illness durations with later onset of dementia. Investigation findings also vary from classic CJD: the electroencephalograph is typically negative for periodic complexes; the MRI shows a characteristic high T2 signal in the pulvinar region of the thalamus; and the PrPres molecular pattern is distinctive. On brain biopsy or autopsy examination, neuropathological findings in the brain also distinguish vCJD and classical CJD.

Table 3. Worldwide number of variant Creutzfeldt-Jakob disease, to April 2007

Country	Total number of primary cases	Number alive
United Kingdom	162	6
France	22	2
Republic of Ireland	4	1
USA	3	0
Netherlands	2	0
Canada	1	0
Italy	1	0
Japan	1	0
Portugal	1	1
Saudi Arabia	1	1
Spain	1	0
Total	199	11

Adapted from: http://www.eurocjd.ed.ac.uk/results.htm

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Author details

Miss Genevieve M Klug, Research Assistant
Ms Alison Boyd, Registry Co-ordinator
Miss Victoria Lewis, Research Assistant
Ms Samantha L Douglass, Administrative Assistant
Ms Rebecca Argent, Research Assistant
Dr Helene Roberts, Neurology Fellow
Professor Colin L Masters, Director
Assoc. Prof. Steven J Collins, Director
Australian National Creutzfeldt-Jakob Disease Registry

Corresponding author: Miss Genevieve Klug, Australian National Creutzfeldt-Jakob Disease Registry, Department of Pathology, The University of Melbourne, Victoria, 3010. Telephone: +61 3 8344 1949. Facsimile: +61 3 9349 5105. Email: gmjak@unimelb.edu.au

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