Surveillance of Creutzfeldt-Jakob disease in Australia: update to December 2011

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Abstract

The Australian National Creutzfeldt-Jakob disease Registry (ANCJDR) is a Commonwealth Government-funded surveillance unit, responsible for the ascertainment of all cases of human transmissible spongiform encephalopathy (also known as prion diseases) in Australia. Having been in operation for 18 years, the activities of the ANCJDR have evolved and expanded over this timeframe, with the ANCJDR providing clinical, diagnostic and infection control advice and service. This update provides a review of the activities of the ANCJDR during 2011 and analysis of both prospective and retrospective (to 1970) data collected from 1993 to 31 December 2011. *Commun Dis Intell* 2012;36(2):E174–E179.

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Introduction

The surveillance of Creutzfeldt-Jakob disease (CJD) in Australia has been undertaken since 1993 by the Australian National CJD Registry (ANCJDR), located at The University of Melbourne. CJD is one form of the transmissible spongiform encephalopathy (TSE) family of rare neurological diseases. While the prime objective of the ANCJDR is to detect all cases of CJD and other TSE forms including Gerstmann Sträussler-Sheinker syndrome, fatal familial insomnia and variant CJD (vCJD) arising in the Australian population, the Registry also provides additional nation-wide infection control advice, diagnostic services, advice to family and clinicians and collaborates with both national and international surveillance counterparts. CJD may be acquired through medical intervention (iatrogenic CJD), inherited in an autosomal dominant pattern (familial CJD) or occur sporadically, as in the majority of cases (known as sporadic CJD). After evaluation by the ANCJDR, cases are classified in accordance with the European and Allied Countries Creutzfeldt-Jakob Disease Surveillance Consortium (EUROCJD) and World Health Organization (WHO) promulgated diagnostic criteria.[1,2] Definite cases are neuropathologically confirmed, whereas probable and possible cases are defined on the basis of clinical profile and diagnostic testing. Both definite and probable cases are considered to be confirmed CJD cases for the purposes of statistical analysis.

Methods

The ANCJDR is funded by the Australian Government Department of Health and Ageing to investigate all notified cases of suspected CJD in Australia. As of June 2006, CJD has been a notifiable disease in all Australian states and territories. Notification of suspect cases to the ANCJDR occurs through several mechanisms including referral for diagnostic testing, personal communications from clinicians, family members and hospitals, as well as searches of death certificates, hospital and health department records. These record searches were performed until 2004 and were integral in ascertaining retrospective cases of CJD in Australia between 1970 and 1993 and monitoring of prospective notifications.

After notification, the ANCJDR investigates all suspected cases for the clinical likelihood of CJD and where possible aims to classify all cases based on clinically validated criteria.[1,2] Definite cases are those that have been neuropathologically confirmed either by brain biopsy or post-mortem examination. Probable cases are classified on the basis of clinical profile, a typical electroencephalogram (EEG) and/or a positive 14-3-3 cerebrospinal fluid (CSF) test and/or characteristic MRI with high signal in the caudate/putamen. In addition to dementia, probable cases must display at least two of the following; myoclonus; visual or cerebellar signs; pyramidal or extrapyramidal features; and/or akinetic mutism with an illness duration of less than 2 years. Possible cases fulfill the same clinical profile in the absence of a typical EEG, characteristic MRI and either no 14-3-3 CSF test or a negative result. Based on data collected on definite and probable cases arising in Australia between 1970 and 2011, epidemiological analysis was performed, including age-adjusted annual mortality rates, calculated using direct standardisation and adjusted to the Australian Bureau of Statistics estimated resident population for Australia and each state and territory as at June 2000.

In this report, an update of Australian TSE surveillance will be presented for the reporting period from 1 January to 31 December 2011.

Results

Australian National Creutzfeldt-Jakob Disease Registry surveillance update to 31 December 2011

For the current reporting period of 1 January to 31 December 2011, 78 new suspect cases have been notified and evaluated by the Registry. Of these new suspect cases, nine were excluded (7 after neuropathological examination), 50 were incomplete, and 19 were classified as definite (17) or probable CJD (2). In total, 20 suspect cases were excluded from the register (13 after neuropathological confirmation) since 1 January 2011. For the same period, a total of 41 CJD cases were confirmed, with definite cases increasing from 432 to 457 and probable cases increasing from 221 to 237 cases.

As of 31 December 2011, 954 cases were included on the register with 694 of these being classified as probable or definite CJD cases; an additional 593 cases were excluded after detailed follow-up (Table 1). There are currently 14 cases of possible CJD of which 13 are sporadic and 1 iatrogenic. One of the possible sporadic cases was classified in 2011. Of the 245 incomplete cases, 167 are presently alive. The rapid annual increase in the number of incomplete cases on the register observed in recent years (20% increase per year) has been markedly reduced in 2011 (7% increase), due to the high level of cases confirmed by neuropathology coupled with a 4-fold increase in the number of probable cases classified. During 2011, the ANCJDR has made a concerted effort to focus staff on case review and classify outstanding cases.

During 2011, no further cases of iatrogenic CJD were identified. The most recent human-derived pituitary gonadotrophin-related CJD death occurred in 1991, while the most recent Lyodura-related CJD death occurred in 2000. As of 31 December 2011, no cases of vCJD have been identified in Australia.

Notifications

The level of notification of suspect CJD cases to the ANCJDR is an important factor influencing ascertainment adequacy of TSE cases in Australia. The ANCJDR currently relies on a surveillance program whereby suspect cases are notified directly to the ANCJDR through personal communication with clinicians and allied health professionals, families, health departments or through ANCJDR diagnostic services. A decline in notifications typically results in a decline in confirmed cases,[3] which underscores the importance of monitoring notification rates across Australia and by individual states and territories.

Since surveillance began in Australia, the notification of suspect cases to the ANCJDR has fluctuated, ranging from 40 to 131 cases per year. As described previously,[4] the fluctuation can be partly explained by changes in the criteria used to classify a suspect case and the inflation of notification numbers in the early years of the ANCJDR's operation when retrospective case deaths between 1970 and 1993 were actively ascertained through hospital, health department and death certificate searches. Since 2000, these factors no longer influence the annual number of cases notified, making this 12 year period a clearer representation of notifications. The average number of suspect cases notified to the ANCJDR for this period was 72 per year (range 54–89 cases).

In 2011, 78 new cases were added to the Registry as suspect cases for further investigation, which aligns with the 2000–2011 average. Over two-thirds of the 78 cases were ascertained through referral for 14-3-3 cerebrospinal fluid diagnostic testing, offered by the ANCJDR since 1997. The remainder were direct communications to the ANCJDR by clinicians, family or support services, and in a single case, notification occurred through a direct referral for genetic testing.

By state and territory, the notification of prospective suspect cases (those arising between 1993 and 2011)

Table 1: Classification of Creutzfeldt-Jakob Disease Registry cases, 1 January 1970 to 31 December 2011

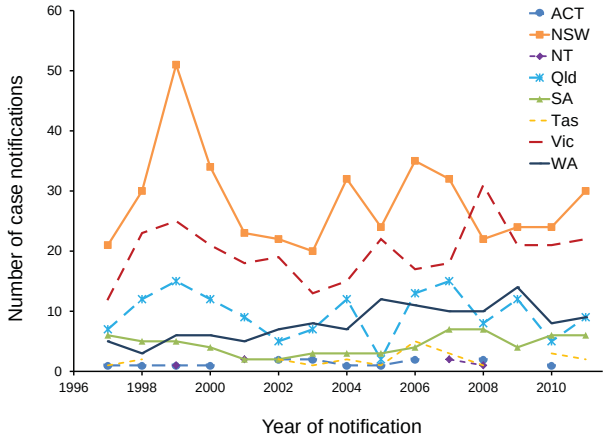
Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	410	43	5*	0	0	458
Probable	223	10	4	0	0	237
Possible	13	0	1	0	0	14
Incomplete	0	0	0	0	245†	245
Total	646	53	10	0	245	954

* 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 167 living cases.

to the ANCJDR has been relatively stable since 2006, compared with the previous years (Figure 1). Prior to this report, Tasmania was the only exception, with declining notifications since 2006, however, in 2010 and 2011, the number of notifications has returned to previously observed levels. Similarly, in 2011 notifications in New South Wales returned to pre-2008 levels of around 30 cases per year after 3 years of below average notifications.

Figure 1: Prospective, suspect Creutzfeldt-Jakob disease case notifications to the Australian National Creutzfeldt-Jakob Disease Registry, 1997 to 2011, by state or territory

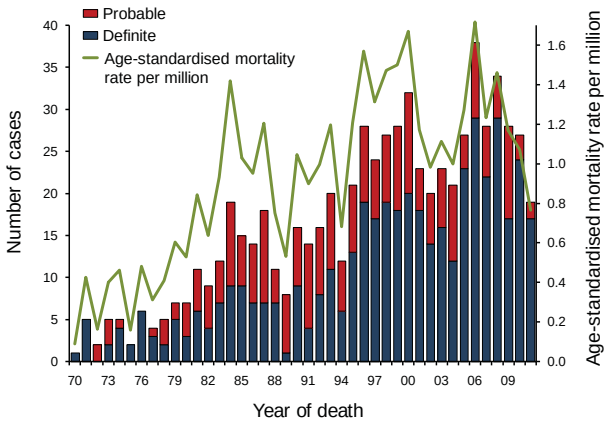


Based on the state and territory populations, Tasmania, New South Wales, Victoria and Western Australia had the highest average rates of suspect case notification with between 3.7–4.3 cases notified per million population per year for the 2000–2011 period. Western Australia had the greatest average rate of notifications at 4.3 cases per million population per year. Temporally, the annual rates in these States have remained relatively stable, with the exception of Western Australia where the rate has been increasing over the period to around 5 cases per million population per year. In the other states and territories, the average annual notification rates reside between 2.0 and 3.0 cases per million population per year with the Northern Territory having the lowest notification rate at 2.0 cases per million population per year. Minimal temporal change in notification rates was observed for the same period in Queensland, South Australia, the Northern Territory and the Australian Capital Territory.

Case outcomes

Since 1970, there has been an increasing positive trend in the annual number of TSE deaths in Australia rising from 10–15 in the mid-1980s to over 25 in the late 1990s, reaching an initial peak in 2000 (32 cases), a decline between 2001 and 2004 and then reaching over 25 cases since 2005 (Figure 2). The ANCJDR postulate that the 2001–2004 period of decline related to a reduction in overall notifications to the register and also fewer probable cases being classified during this time due to difficulties associated with case investigation. Since 2005, the annual number of confirmed definite and probable cases has been consistently between 25–35 cases with two further peaks in 2006 (38 cases) and 2008 (34 cases). It is believed that this sustained increase is a reflection of greater notifications and increased post-mortem examinations being performed on suspect CJD cases.

Figure 2: Number and age-standardised mortality rate of Australian National Creutzfeldt-Jakob Disease Registry definite and probable cases, Australia, 1970 to 2011*



Age-standardised mortality rates were calculated using the Australian Bureau of Statistics 2000 estimated resident population for Australia.

* To 31 December 2011

Although the ANCJDR retrospectively ascertained cases to 1970, it is the prospective ascertainment period from 1993 to 2011 that is considered a more meaningful period for analysis of Australian CJD incidence. For this timeframe, the average annual age-adjusted mortality rate was 1.2 deaths per million population; a slight increase from the previous reporting period and aligns closely with other EUROCJD countries where similar surveillance units are in operation.[5]

The ANCJDR has a large number of cases currently on the register that are incomplete (245) and remain under investigation. The ANCJDR aims to evaluate and classify all notified cases as definite, probable, possible or non-CJD, although obstacles such as a lack of available diagnostic information, next-

of-kin consent not being granted for investigation and staff resourcing for clinical assessment, can be encountered, which restrict the ANCJDR's ability to classify a case. During 2011, there was a concerted effort to clinically evaluate pending cases, made possible by the employment of an additional part-time neurologist to the unit. As a result, a large number of cases were classified as probable. This has affected the mortality rates for several years due to the time of death for some of these cases. Of the 41 cases confirmed as definite or probable in 2011, 17 died in 2011 and 2 were confirmed as living, definite cases by neuropathological examination of biopsy tissue. The remaining 22 cases died prior to 2011. Six died in 2010 and underwent post-mortem examination for case confirmation, while the remainder died in 2006, 2008, 2009 and 2010 and were classified as probable cases based on ANCJDR evaluation of the clinical and investigation profile. The confirmation of these previously known but unclassified cases on annual mortality rates has led to the age-adjusted mortality rate peaking at 1.7 cases per million population per year in 2006, while the rates in the other years reached 1.1–1.5 cases per million population per year. These figures provide the ANCJDR with an insight that the incidence of CJD in Australia may be closer to 2 cases per million population per year, rather than the presumed rate of 1 case per million population per year.[3] In several other countries where CJD surveillance is performed, mortality rates at this elevated level have been observed previously.[5] In some regions, this increase has been explained by increased awareness, and better case ascertainment and disease diagnosis.[6,7]

By state and territory, the 41 new cases confirmed in 2011 were identified in New South Wales (16), Victoria (11), Western Australia (8), Queensland (4) and South Australia (2). With the addition of these cases, the average age-adjusted mortality rates for the two periods of 1993–2011 and 2000–2011 shows that the majority of regions in Australia have rates above or close to 1 case per million population per year (Table 2). For the full prospective period (1993–2011), the highest mortality rates were observed in Victoria and Western Australia (1.4 and 1.6 deaths per million population per year, respectively). When analysing the incidence rates for sporadic cases, thereby excluding any influence of genetic and iatrogenic cases on incidence, Western Australia was associated with a 28% (95% CI, 2%–78%) greater rate than would be expected in the Australian general population. This greater risk could be due to optimal case ascertainment and notification to the ANCJDR and a more complete estimate of CJD incidence being achieved in this region.

Tasmania continues to have the lowest TSE mortality in Australia and it has been postulated that cases were being under-ascertained in this region. However, it should be noted that given the small population, the effect of 2 to 3 additional cases in Tasmania would result in the mortality increasing to 0.9–1.0 cases per million population per year. Furthermore, the restriction of the data to the recent 12 year period, where more uniform ascertainment, diagnostic capacity and case evaluation has been in place, the rate in Tasmania is closer to 1 case per million population per year, which is similar to the rates reported in other regions of lower population such as South Australia and the Northern Territory.

Case demographics

The 694 confirmed CJD cases comprise 8 iatrogenic cases, 53 familial cases and 633 sporadic cases. The 8 iatrogenic cases comprise 5 Lyodura-related cases and 3 pituitary-gonadotrophin associated cases.

Table 2: Transmissible spongiform encephalopathy deaths and mortality rates, by state and territory

State or territory	TSE cases by year of death													Total cases	Mean age-adjusted mortality rate (deaths/million/year)	
	00	01	02	03	04	05	06	07	08	09	10	11	Alive		00–11*	93–11*
ACT			1		1		1		2		1			6	1.4	1.3
NSW	12	9	7	7	11	10	12	10	6	10	5	10	1	110	1.3	1.2
NT							2	1						3	0.8	0.8
Qld	7	3	3	3			7	2	4	4	2	2		37	0.7	1.0
SA	2			1	2	1	1	3	5	2	4			21	1.0	1.3
Tas			2			1	2							5	0.8	0.7
Vic	9	10	5	9	5	11	9	6	13	7	11	4	1	100	1.5	1.4
WA	2	1	2	3	2	4	4	6	4	5	4	3		40	1.5	1.6
Aust	32	23	20	23	21	27	38	28	34	28	27	19	2	322	1.2	1.2

* Includes all deaths occurring between 1 January 1993 or 1 January 2000 and 31 December 2011.

A further definite pituitary-gonadotrophin associated case received pituitary hormone treatment in Australia but as disease onset and death occurred in the United Kingdom; this case was not included in the Australian statistical analysis.

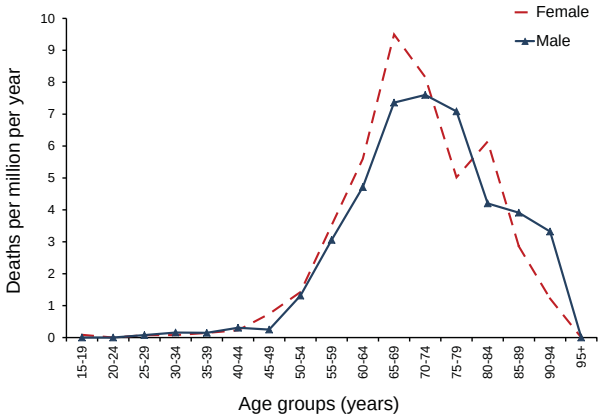
No new familial cases of CJD were identified since the last reporting period. Annually, between 1 and 4 familial cases are detected by the ANCJDR each year in Australia, although this number has been declining in the last 3 years. The ANCJDR offers genetic testing, however, as testing is dependent on consent by next-of-kin, the test is not systematically undertaken on all cases. The ANCJDR is also aware that genetic testing may be performed independently of the unit, and the results for some cases will be unknown to the ANCJDR. This raises the potential that some genetic cases may be misclassified as sporadic CJD.

All new cases confirmed during 2011 have been classified as sporadic CJD at this time. There has been no change to the median age at death or durations of all 3 CJD groups since the last reporting period, despite the inclusion of the new cases in the analysis. For all iatrogenic cases, median age at death is 39 years (range 26–62 years) and for all familial cases, 59 years (range 18–82 years). For all sporadic cases, the median remained at 66 years (range 25–90 years). Disease duration was 4.0 months for all cases, 3.7 months for sporadic cases (range 0.9–60 months) while longer in iatrogenic (6.5 months, range 2–25 months) and familial (6 months, range 1.25–192 months) cases. Within 6 months of disease onset, 73% of sporadic cases, 53% of familial cases and 56% of iatrogenic cases were deceased.

The gender breakdown of all Australian cases have remained the same as previously reported, with confirmed cases in females slightly higher for all cases (53%), sporadic cases (53%) and familial cases (55%). The iatrogenic group is divided into 3 female pituitary hormone-related cases, 1 female and 4 male Lyodura related cases. In men, incidence peaked in the 70–74 year age group with 7.6 cases per million per year; however, the incidence in both the 65–69 and 75–79 year age groups was also above 7 cases per million per year (Figure 3). In women, incidence appears to peak slightly at a younger age than men, peaking in the 65–69 year age group with almost 10 cases per million per year. It is important to note that these age groups have a 6 to 7 times greater incidence of CJD than that of the general Australian population (1.24 cases per million population per year).

As shown in Figure 2, the ascertainment of all Australian TSE cases has improved markedly since surveillance began in 1993. To investigate whether this increase correlates with an age-specific change

Figure 3: Age- and sex-specific mortality rates in all Creutzfeldt-Jakob disease cases, 1993 to 2011

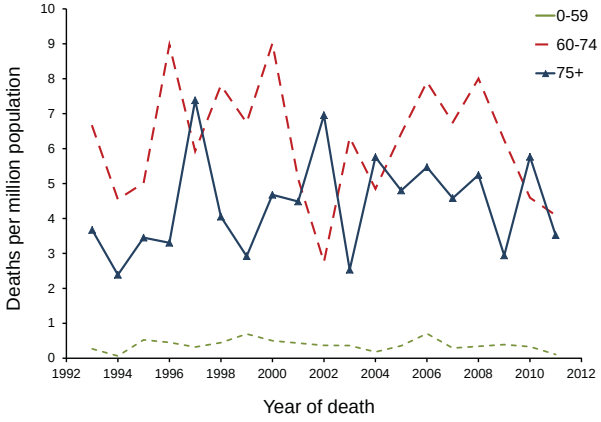


in ascertainment, the temporal changes in the annual mortality rate by specific age groups are shown in Figure 4. Since 1993, the annual rate of disease amongst the 60–74 year age group has remained relatively stable with an annual rate ranging from 3–9 case deaths per million persons. Although the 60–74 year age group constitutes the majority of cases, the rate in the older age group of 75 years or over shows a slight increasing positive trend over the 1993–2011 period and further supports the opinion that it is the detection of older age cases that has led to increased incidence over the active surveillance period.

Summary

In 2011, the ANCJDR continued surveillance activities to monitor the occurrence of all forms of TSE in Australia and also provide various services for the health sector and family members of suspect and confirmed cases, including expert advice, diagnostic tests and associated case investigation. Focused staff resources for case review and evaluation during 2011

Figure 4: Temporal change in age-specific mortality rates for Australian Creutzfeldt-Jakob disease cases, 1993 to 2011



has enabled an increased number of cases, especially probable cases, to be classified during the reporting period compared with previous years. This has increased the overall incidence rates in Australia and suggests that CJD incidence in some regions is closer to 2 cases per million population.

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