Surveillance of Creutzfeldt-Jakob disease in Australia: 2008

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Abstract

Australia-wide surveillance of all human transmissible spongiform encephalopathies (TSEs) is performed by the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR), since establishment in October 1993. During the surveillance period 1 April 2007 to 31 March 2008, the ANCJDR received 78 new suspect case notifications of TSEs (67 in 2007, 13 in 2008). This level of suspect case notification aligns with the previous 2006/2007 surveillance period, which was elevated in comparison to the previous 5 years. Based on the total number of probable and definite Creutzfeldt-Jakob disease (CJD) cases, encompassing retrospective cases to 1970 and prospectively ascertained cases from 1993 to 31 March 2008, the average age-adjusted mortality rate is 1.16 deaths per million per year. In this short report, we provide updated Australian TSE figures and describe recent changes in surveillance mechanisms and review their impact on case notifications and eventual CJD classification. *Commun Dis Intell* 2008;32:232–236.

Keywords: Australian National Creutzfeldt-Jakob Disease Registry, Creutzfeldt-Jakob disease, disease surveillance, mortality, transmissible spongiform encephalopathies

Introduction

Globally, the incidence of the rare, transmissible group of neurodegenerative disorders, known as transmissible spongiform encephalopathies (TSEs) is reported to be 1 case per million population per year. This group of invariably fatal diseases includes the most common phenotype, Creutzfeldt-Jakob disease (CJD) and the rarer forms of Gerstmann Sträussler-Sheinker syndrome, fatal familial insomnia and variant CJD (vCJD). While the disease is transmissible, the majority of cases occur with no discernible aetiology, arising sporadically. For the remainder of cases, a genetic basis of disease or an iatrogenic association through medical intervention has been determined as an underlying cause. Confirmation of definite cases is based upon neuropathologic assessment of biopsied or post-mortem brain tissue whereas probable cases must fulfil internationally recognised and validated clinical criteria for classification.[1] Possible case classification is also based on defined criteria where there is a suspicion of CJD, however, there is not sufficient clinical evidence to support a probable classification and for this reason these cases are excluded from the following statistical analysis. The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in 1993 to provide nation-wide surveillance for all human TSE regardless of aetiology and offer specialised diagnostic services, including cerebrospinal fluid 14-3-3 protein analysis.

Australian National Creutzfeldt-Jakob Disease Registry surveillance

National TSE surveillance in Australia by the ANCJDR has involved the evaluation of 1,256 cases of suspect TSE of all aetiologies for the period 1 January 1970 to 31 March 2008. After detailed investigation, 531 cases were deemed non-CJD, 573 cases classified as definite (364) or probable (209) CJD and a further 12 cases fulfilling the possible case definition[1] (Table 1). For the 2007/08 period, 26 cases, consisting of 15 new suspect notifications

Table 1. Classification of cases by the ANCJDR, 1 January 1970 to 31 March 2008

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	323	36	5*	0	0	364
Probable	195	10	4	0	0	209
Possible	11	0	1	0	0	12
Incomplete	0	0	0	0	150†	150
Total	529	46	10	0	150	735

* Includes one 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 101 living cases.

and 11 previously notified cases, were confirmed as probable (n=6) and definite (n=20) CJD and 1 further case classified as possible CJD. One hundred and fifty cases are currently under review, with 101 of these cases still living as at 31 March 2008.

The aetiologic proportions of all Australian CJD cases are consistent with previous observations.[2] Cases classified as sporadic CJD comprise 90.6% of all Australian cases, while 8% of cases are genetic and the remaining 1.4% are iatrogenic. No further cases of familial or iatrogenic CJD have been classified during the 2007/08 surveillance period and no cases of vCJD have been identified in Australia as at 31 March 2008.

For sporadic cases, the median age at death is 66 years (males, 65 years; females, 67 years). Females account for 53.5% of sporadic cases and their median duration of disease is 4 months. A slightly shorter disease duration is observed in males (median, 3 months) and the combined median is 4 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.

Based on all definite and probable CJD cases, the average, age-adjusted mortality rate in Australia for the 1970/08 period is 0.87 deaths per million per year. By restricting the time frame to the more accurate, prospective surveillance period of 1993 to 2008, the mortality rate is 1.16 deaths per million per year. This figure and individual state and territory mortality rates (Table 2) align with reported global figures[3] with the exception of some of the smaller states and territories, where it is likely that there is some case under-ascertainment.

Table 2. Transmissible spongiform encephalopathies deaths and mortality rate, 1993 to 2008,* by state or territory

State or territory	Total TSE deaths	Mean age-adjusted mortality rate (deaths/million/year)
ACT	5	1.06
NSW	127	1.20
NT	3	0.74
Qld	55	0.98
SA	25	1.05
Tas.	6	0.71
Vic.	104	1.35
WA	35	1.21
Aust.	360	1.16

* Includes all deaths occurring between 1 January 1993 and 31 March 2008.

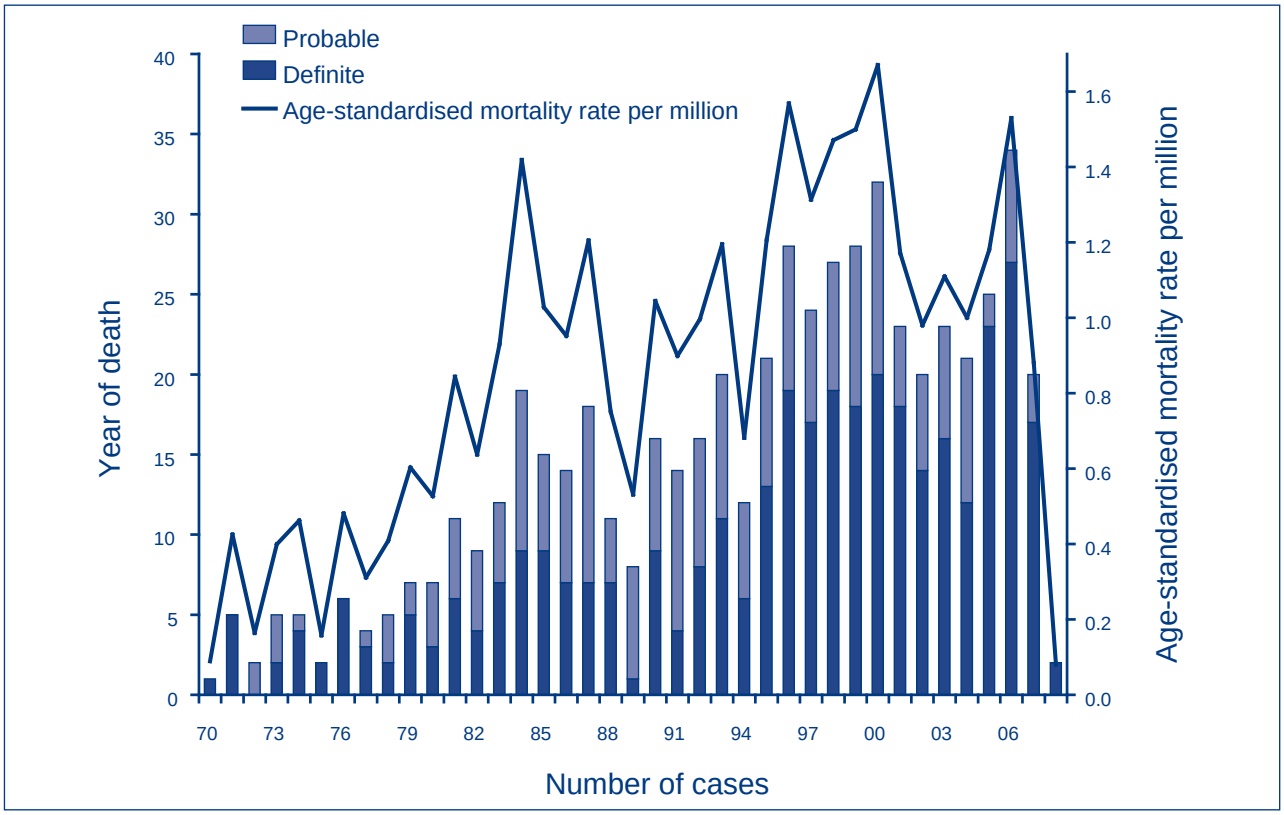
The temporal patterns of the annual mortality rates show distinct peak mortality rates in 2000 and 2006 (Figure 1). As described previously,[2] these peaks correlate with increased suspect case notifications in both 1999/00 and 2006 (Figure 2). In 2006, CJD was identified in every state and territory, which has not occurred in previous surveillance years and there was a marked increase in cases confirmed by neuropathologic examination, particularly in Queensland (Figure 1). A total of 6 cases (5 definite) were identified in Queensland in 2006 compared with 3 or fewer per year in the previous 5 years. This enhanced detection is attributable to the reorganisation and centralisation of Queensland CJD autopsy services in 2006, facilitating the timely neuropathological examination of cases. While temporal changes in annual CJD mortality rates are to be expected, the defined peaks in notifications and mortality need to be considered in relation to recent changes that have affected ANCJDR surveillance mechanisms.

Temporal changes in suspect Creutzfeldt-Jakob disease case notification

Since the ANCJDR began ascertaining both prospective and retrospective TSE cases in 1993, notification rates have fluctuated over time (Figure 2). By grouping all retrospective cases (where death is known to have occurred before 1993) and prospective cases, peaks in notification rates can be observed in 1993, 1995, 1996, and more recently in 1999–2000 and 2006. The earlier peaks largely comprise of retrospective cases identified by Australian Institute Health and Welfare death certificate searches, and national hospital and state morbidity searches. By excluding these cases, a clearer representation of the temporal trends in prospective ascertainment overall and in each of the states and territories can be observed (Figures 2 and 3).

In 1999/00, approximately 4.5 to 5.5 suspect cases per million population were notified per year in Australia. The peak during this period is attributable to 2 causes; firstly an increased awareness of CJD resulting from media coverage of vCJD and secondly, an increasing utilisation of the cerebrospinal fluid (CSF) 14-3-3 protein detection test by clinicians over this period. At that time all CSF referrals were treated as notifications and placed on the Register. As of March 2000, the ANCJDR increased screening of CSF 14-3-3 protein testing for the likelihood of clinical disease. From this time, only cases with positive 14-3-3 results or cases when clinicians had clinical information supporting notification, were entered on the Register for more detailed evalua-

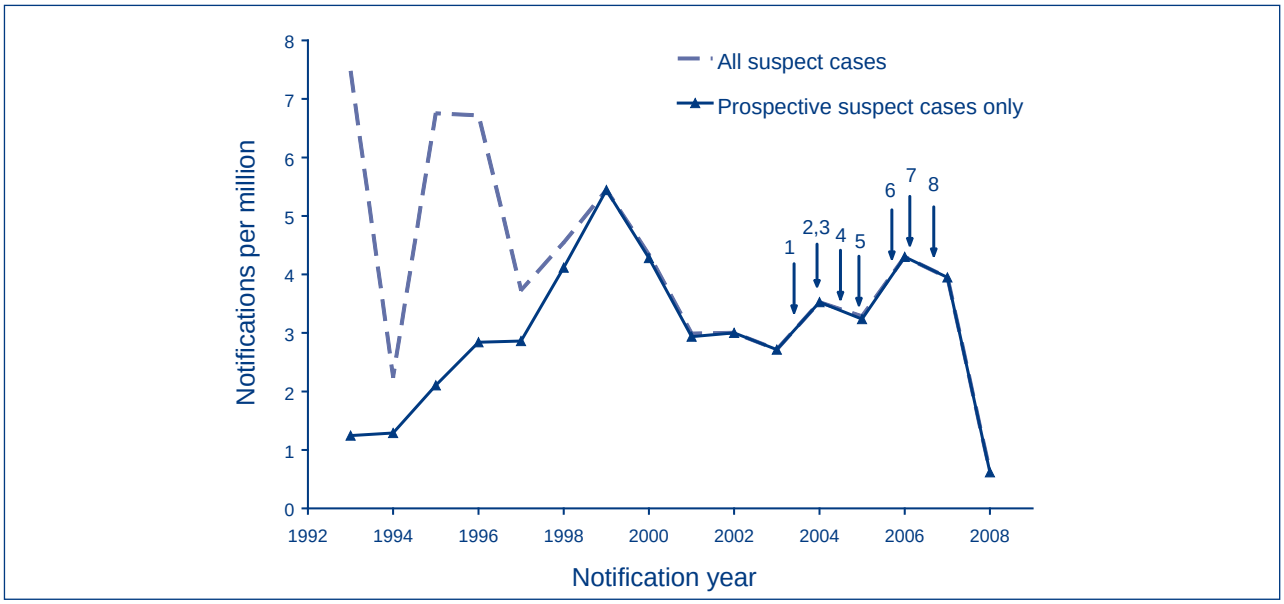
Figure 1. ANCJDR definite and probable cases, 1970 to 2008.* Number and age-standardised mortality rate



* To 31 March 2008.

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

Figure 2. Creutzfeldt-Jakob disease notification rates, 1993 to 2008,* all suspect cases and prospective cases only



* To 31 March 2008.

Numbers denote the point in time when Creutzfeldt-Jakob disease became notifiable in particular states and territories:
1 – Tasmania, 2 – Victoria, 3 – Western Australia, 4 – New South Wales, 5 – Northern Territory, 6 – Australian Capital Territory, 7 – Queensland, 8 – South Australia.

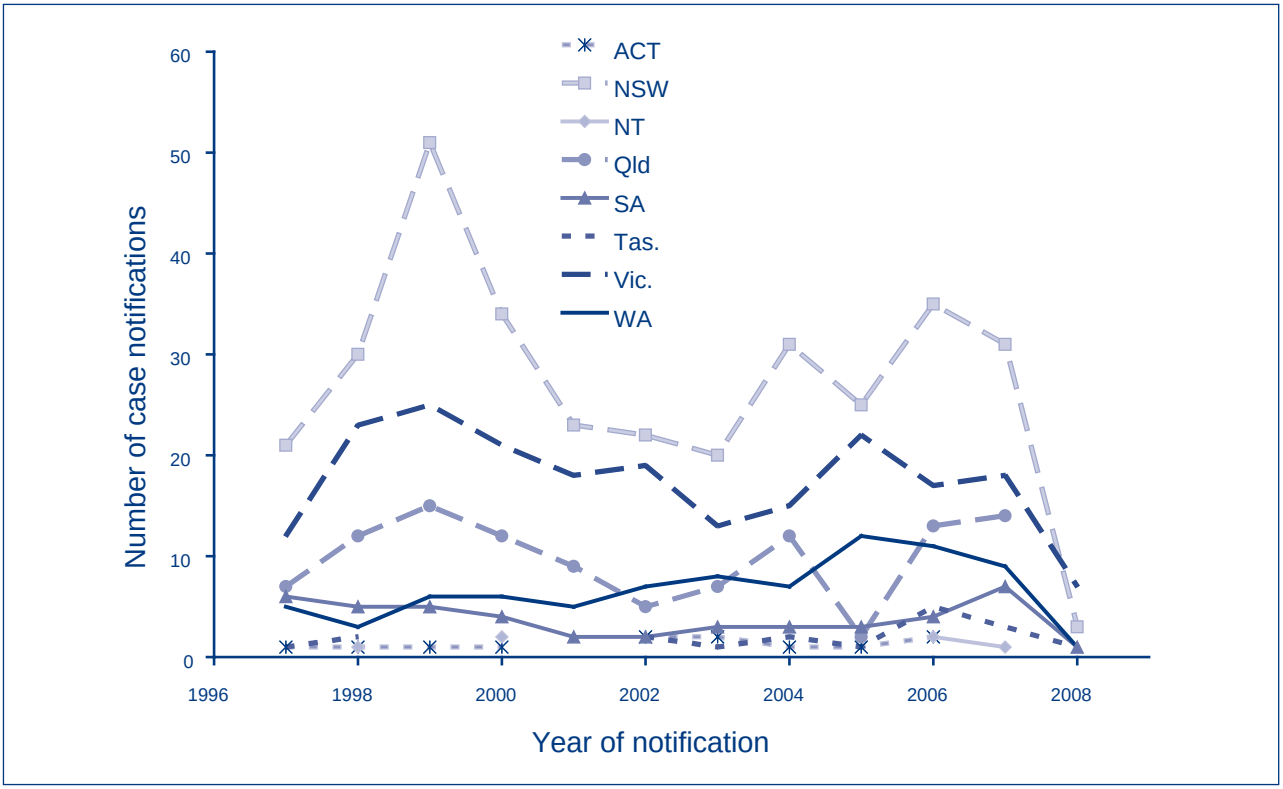
tion. All other referrals that were not entered on the Register but were found to have a negative, atypical or unsuitable result were followed up after 9 months and if found to be deceased, further evaluation was instigated. Consequently, formal suspect case notifications registered after this time declined in all states and territories (Figure 3) and we speculate that lower case ascertainment may have resulted from this new approach from 2000. Previous assessments have demonstrated that increased suspect CJD notifications to the ANCJDR appear to correlate with increased CJD case number confirmations.[2]

After the period of lower formal notifications registered during 2001 to 2003, the notification of suspect cases to the ANCJDR steadily increased (with the exception of Queensland in 2005), correlating with increased total CSF 14-3-3 protein testing referrals. By 2006 and 2007, the rate of suspect case notifications reached around 4 notifications per million per year (Figure 2). State notification rates generally reflect population distributions, particularly in 2006/07 (Figure 3). The increased notification rate of suspect cases for 2006/07 has occurred despite a change implemented by the ANCJDR from 1 January 2007. After careful consideration, the ANCJDR began charging a partial cost-recovery service fee of $75 for 14-3-3 protein CSF diagnostic testing.

There were concerns that charging may have negatively impacted on the single most important ascertainment method, the 14-3-3 protein CSF test. Referrals for this test is the source of the largest proportion of the initial suspect case notifications to the ANCJDR (42% of all notifications overall, 64% of all notifications since test was introduced in 1997). In contrast to expectation, total CSF referrals increased by 34% during 2007, suggesting that a fee for service had not deterred 14-3-3 test utilisation. It remains to be determined if there will be a negative impact over the longer term. There is no explanation at this time for the unexpected increase in CSF samples referred during 2007; however, it will be of interest to assess the 2008 CSF test referral rates in 2009.

An explanation for the increased suspect CJD notifications to the ANCJDR in 2006/07 may in part relate to the establishment of CJD as a notifiable disease in all states and territories of Australia. State by state scheduling of CJD as a notifiable disease occurred at different time points (Figure 2), but by June 2006, CJD was notifiable in all states and territories. The effect of this new notifiability status may have promoted disease awareness and facilitated increased notifications of suspect cases to the ANCJDR and respective health departments. In Victoria, the scheduling of CJD as a notifiable disease in 2004 was accompanied by the formalisation of a contrac-

Figure 3. Prospective, suspect Creutzfeldt-Jakob disease case notifications to the ANCJDR, 1997–2008,* by state or territory



* To 31 March 2008.

tual agreement between the Victorian Department of Human Services and the ANCJDR. While this agreement has not altered the number of suspect case notifications to the ANCJDR directly, it has improved communication between the ANCJDR and the DHS and led to the facilitation of a higher level of autopsy service in the State, resulting in an elevated autopsy rate and subsequently more timely classifications of Victorian suspect cases in recent years. Communication with health departments and organised autopsy services appear to be a key feature in effective CJD surveillance.

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