Surveillance of Creutzfeldt-Jakob disease in Australia: 2010 update

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Abstract

Surveillance of all human prion diseases in Australia has been the responsibility of the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) on behalf of the Australian Government Department of Health and Ageing since the Registry's inception in October 1993. The ANCJDR was established in response to the identification of 4 CJD deaths in recipients of human-derived pituitary hormone. The initial brief was to perform focused surveillance for any further iatrogenic cases of CJD; however the scope of surveillance was soon expanded to include all cases of CJD occurring in Australia both prospectively and retrospectively to 1970. The activities of the ANCJDR have evolved from: routine surveillance responsibilities to detailed epidemiological analysis at both national and international levels; expert advice in relation to, and management of, infection control issues; and the provision of a number of tests to aid the diagnosis and classification of CJD in suspect cases. In this brief report, surveillance outcomes are examined with the inclusion of figures from the reporting period of 1 April 2009 to 31 March 2010 and the diagnostic services offered by the ANCJDR are outlined to provide a greater insight into this aspect of the Registry. *Commun Dis Intell* 2010;34(2):96–101.

Keywords: Australian National Creutzfeldt-Jakob Disease Registry, CJD, human-derived pituitary hormone treatment, transmissible spongiform encephalopathies

Introduction

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), occur in both humans and animals. They include Creutzfeldt-Jakob disease (CJD), Gerstmann Sträussler-Sheinker syndrome, fatal familial insomnia and variant CJD (vCJD) in humans and bovine spongiform encephalopathy in cattle, scrapie in sheep and chronic wasting disease in deer and elk. The disease manifests itself as a rapid, neurodegenerative illness and is invariably fatal. In humans, the aetiology of disease is unknown in most cases and is described as sporadic CJD. In the remaining minority of cases, disease is related to an iatrogenic exposure through medical intervention or an underlying genetic cause. The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) investigates all cases of suspect human TSE in Australia and works actively to classify these cases according to the clinically validated criteria[1,2] as definite, probable and possible CJD cases. These classifications are based on neuropathological examination and clinical criteria.[1] A possible case classification is clinically suspected but diagnostically unsupported and therefore these cases are excluded from the following statistical analyses.

Australian National Creutzfeldt-Jakob Disease Registry surveillance update

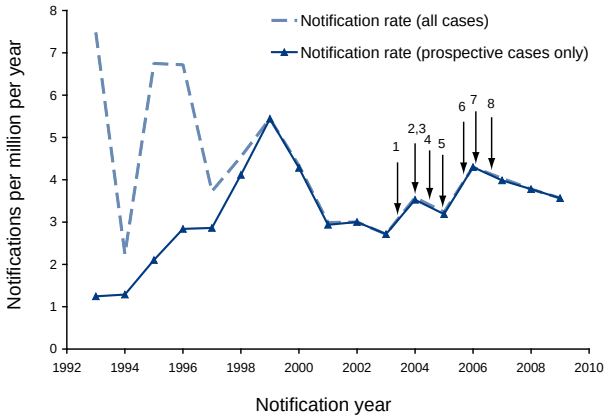
Notifications

From 1993 through to 31 March 2010, a total of 1,426 cases of suspect CJD have been notified to the ANCJDR, comprising of 309 notifications of case deaths prior to 1993 (retrospective cases) and 1,112 suspects notified prospectively. Since the last reporting period, a similar level of suspect case notification has been observed with 81 new cases referred for investigation (previous period – 90). Based on 1,090 prospective notifications for the complete calendar years between 1993 and 2009, the average annual number of notifications is 64 cases per year and the population-based referral rate is 3.2 suspect CJD cases per million per year. In the complete 2009 calendar year, the annual number of notifications has continued to be higher compared with pre-2006 levels (Figure 1). The reason for this is unclear although as speculated previously[3] it is likely to be related to increased referrals of cerebrospinal fluid (CSF) samples for 14-3-3 diagnostic testing. Of the 81 new notifications, 11 have been classified as definite CJD and nine have been removed from the registry, including seven excluded after neuropathological examination. For the remaining 61 incomplete cases, 22 are recorded as dead (11 with post-mortem examination pending) and 39 are still living. All incomplete cases are currently under investigation.

For all states and territories, the notification of prospective suspect cases has remained relatively stable compared with previous years (Figure 2), with the only exception being Tasmania where notifications have been in decline since 2006. A more recent trend is in New South Wales, where the lower number of notifications observed in 2008 has again been seen in 2009 with around 10 less

cases being notified for both years compared with the 2006–2007 period. The explanation for this does not rest with lower CSF referrals as the level of referrals for testing from New South Wales has remained consistently high over the last 3 years.

Figure 1: Annual notification rates of all suspect cases and prospective cases only, 1993 to 2009



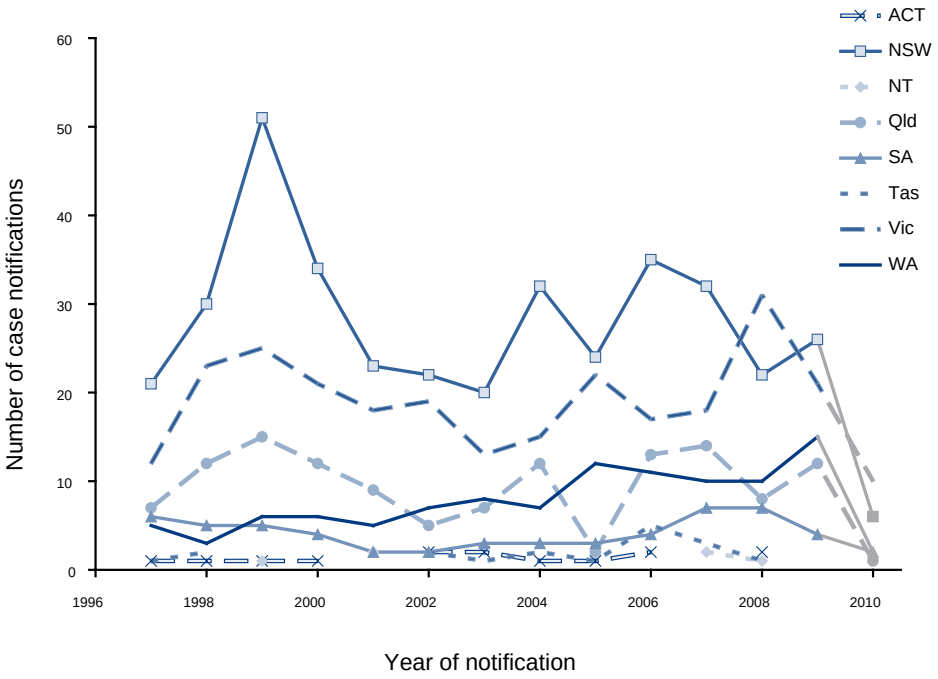
Numbers denote the point in time when Creutzfeldt-Jakob disease became notifiable in particular states and territories, 1 – Tasmania, 2 – Victoria, 3 – Western Australia, 4 – New South Wales, 5 – Northern Territory, 6 – Australian Capital Territory, 7 – Queensland, 8 – South Australia.

Case outcomes

Of the 1,426 notifications, a total of 560 suspect CJD cases have been excluded from the register with 46% of these having undergone neuropathological examination to provide an alternative diagnosis. The remaining 866 notifications are currently on the register and the large majority of these are definite and probable cases (629). A much smaller number (12) are possible cases (Table 1). Due to resource constraints, a concerning and ever-increasing number of incomplete cases grows annually and there are presently 224 incomplete cases that require investigation. This is an increase of 21% from the previous reporting period.

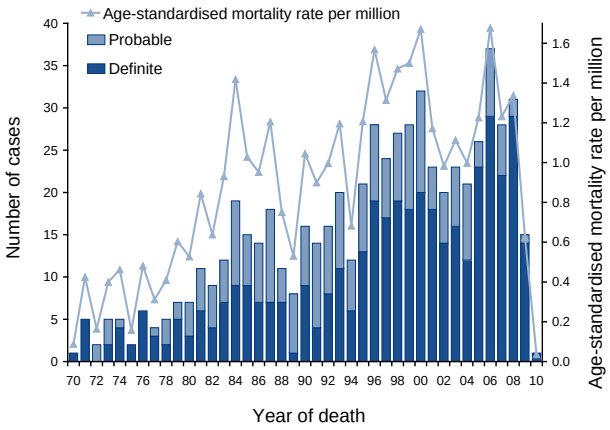
The number of definite and probable case deaths in 2009 is lower than expected; however, the current figure is provisional as several cases are awaiting case classification (Figure 3). The proportion of definite cases has increased since 2004 and this can perhaps be attributed to the ANCJDR's greater focus on assisting with autopsy planning and coordination. For the period 1993 to 2009, an average of 24.5 definite and probable CJD deaths per year has been recorded and the average age-adjusted mortality rate is 1.2 cases per million per year. These figures are consistent with previous long-term averages and with rates reported in other countries where similar surveillance systems are in

Figure 2: Prospective, suspect Creutzfeldt-Jakob disease case notifications to the Australian National Creutzfeldt-Jakob Disease Registry, 1997 to 2010, by state or territory



Grey lines denote findings for the incomplete 2010 surveillance year, which includes data to 31 March 2010 only.

Figure 3: Australian National Creutzfeldt-Jakob Disease Registry definite and probable cases 1970 to 2010,* number and age-standardised mortality rate



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

* To 31 March 2010.

place.[4] This outcome provides a level of confidence that the ANCJDR is achieving and maintaining a high level of CJD surveillance in Australia.

By state and territory, fluctuations in the annual number of CJD cases have been observed, but this has resulted in only minor changes in the long-term average of the annual age-adjusted mortality rates calculated with current figures for the complete calendar years 1993–2009 (Table 2). The average mortality rate for most states and territories ranges from 0.9 in Northern Territory to 1.5 in Western Australia, and this aligns with the other national CJD rates of disease.[4] The only outlying figure is in Tasmania, which continues to have the lowest mortality in Australia with 0.7 deaths per million per year (Table 2). While this trend is of concern, an examination of the results for the more recent period of 2000–2009, does indicate that Tasmanian CJD incidence may be more consistent with other Australian states and territories. Between 1993 and 1999, there was only 1 confirmed case of CJD in Tasmania and while this skews the incidence negatively for the entire 1993–2009 period, it suggests that potential under-ascertainment of cases in this state occurred prior to 2000.

For the 629 definite and probable cases, mortality is greatest amongst the 65–69 year age group (4.9 deaths per million per year). Slightly more CJD cases are female (54%), which has been a consistent finding in Australia. While this trend is true for both sporadic (53% female) and familial (56% female) CJD groups, the small number of iatrogenic cases occur with equal gender proportions. For all Australian CJD cases, female mortality peaks in the 65–69 year age group with 5.6 deaths per million per year while men in the 70–74 year age group have the highest rate of CJD mortality (4.6 deaths per million per year).

With restriction of the data to the 1993–2010 prospective period of case ascertainment, which is considered a more comprehensive, active and co-ordinated surveillance period providing the most accurate epidemiological data, mortality peaks at a much higher level than the surveillance period of 1970–2010 (Figure 4). Peak mortality occurs in the 65–69 year age group for both genders with 6.7 and 9.0 deaths per million per year for males and females respectively. Overall, the rate in this age group is 7.9 deaths per million per year for this period, which is a 6-fold increased rate of disease compared with CJD deaths in all age groups. More generally, the age-specific mortality rates clearly demonstrate that age is a risk factor for CJD with the greatest risk for both genders being those of 65 years or greater (Figure 4). It must be noted, however, that

Table 1: Classification of cases by the Australian National Creutzfeldt-Jakob Disease Registry, 1 January 1970 to 31 March 2010

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	366	42	5*	0	0	413
Probable	203	10	4	0	0	217
Possible	11	0	1	0	0	12
Incomplete	0	0	0	0	224†	224
Total	580	52	10	0	224	866

* 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 161 living cases.

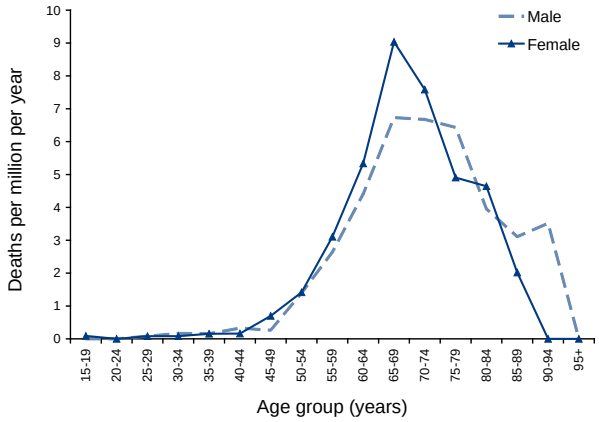
Table 2: Transmissible spongiform encephalopathy (TSE) deaths and mortality rate, by state or territory

State or territory	TSE cases by year of death											Total TSE deaths	Mean age-adjusted mortality rate (deaths/million/year)	
	00	01	02	03	04	05	06	07	08	09	10*		00–09†	93–09†
ACT			1		1		1		2			5	1.4	1.3
NSW	12	9	7	7	11	10	11	10	5	8		90	1.3	1.2
NT							2	1				3	1.0	0.9
Qld	7	3	3	3			7	2	4	2		31	0.8	1.0
SA	2			1	2		1	3	4	2		15	0.9	1.2
Tas			2			1	2					5	0.9	0.7
Vic	9	10	5	9	5	11	9	6	12	3	1	80	1.5	1.4
WA	2	1	2	3	2	4	4	6	4			28	1.3	1.5
Australia	32	23	20	23	21	26	37	28	31	15	1	257	1.2	1.2

* Provisional result for year to 31 March 2010.

† Includes all deaths occurring between the complete years 1 January 1993 or 1 January 2000 and 31 December 2009.

Figure 4: Age- and sex-specific mortality rates in all Creutzfeldt-Jakob disease cases 1993 to 2010



atypical cases do arise in both the younger and older age groups and the ANCJDR speculates that these groups have under-ascertainment, particularly those aged over 70 years.

The majority of Australian CJD cases have been classified as sporadic CJD (90.4%), whilst the remainder are familial (8.3%) and iatrogenic (1.3%) cases. Since the last reporting period, 20 new sporadic cases have been classified (16 definite, 4 probable) and 2 definite, familial cases. No cases of vCJD or further cases of iatrogenic cases have been identified. The inclusion of the 22 newly classified cases has not markedly altered the median illness duration or age at death of the 3 CJD aetiologies compared with previous reports. The median age at death occurs at 67 years in sporadic cases (males 66 years, females 67 years), 59 years in familial cases (males 51 years, females 62 years) and 42 years in iatrogenic cases (males 46.5 years, females 39 years). The median duration of illness is 4 months in sporadic cases (males 3 months, females 4 months), 6 months for familial cases (males 4.5 months, females 8 months) and 6.5 months for iatrogenic cases (males 2.5 months, females 9.5 months). Only 8% of all definite and probable CJD deaths occur under the age of 50 years and a third of these are attributable to iatrogenic or genetic CJD. The remaining cases have been investigated closely for the possibility of all forms of CJD including vCJD and after detailed follow-up, have been classified as sporadic cases.

Diagnostic functions of the Australian National Creutzfeldt-Jakob Disease Registry

One of the main operational functions of the ANCJDR is the provision of diagnostic tests to clinicians investigating a suspect case of CJD. Since 1997, the ANCJDR has offered a CSF test to detect 14-3-3 proteins in strongly clinically suspected cases in Australia and when requested, for cases in the Asia–Pacific region. The ANCJDR remains the only diagnostic laboratory offering this test in Australia. During the period from 1997 to 2010, 2,923 samples have been received and 2,570 (88%) of these have been tested. The remaining untested samples include those where testing is currently pending, unsuitable due to the sample, or where the ANCJDR has been advised by treating clinicians to not proceed with testing. An increasing number of annual referrals has been observed (Table 3) and currently the average number of CSF samples

Table 3: Referrals to the Australian National Creutzfeldt-Jakob Disease Registry for diagnostic testing 2000 to 31 March 2010*

Year	Brain tissue for immunohistochemical analysis†	Brain biopsy	Tonsil biopsy	Autopsy tissue‡ (Total annual CJD autopsies performed in Australia)	Genetic testing§	CSF testing	Total
2000	1	1		8 (34)	13	187	210
2001	4	3		19 (27)	27	209	262
2002	9			15 (26)	9	226	259
2003	2		1	14 (25)	6	237	260
2004	1			16 (22)	13	268	298
2005	1		1	21 (32)	22	276	321
2006	3	2	1	29 (36)	17	260	312
2007	1	1	2	28 (39)	13	349	394
2008		3	1	19 (39)	21	332	376
2009	1	1		28 (28)	14	335	379
2010	1	1	1	2 (8)	10	89	104
Total	24	12	7	199 (317)	165	2,768	3,175

* Referrals only. Numbers do not reflect the number of tested samples for the genetic and cerebrospinal fluid testing groups.

† Includes referrals of paraffin blocks and slide sets.

‡ Includes samples referred to the Australian National Creutzfeldt-Jakob Disease Registry annually.

§ Includes all referrals for PRNP testing and/or Codon 129 testing.

received per year is 218. The CSF test is a highly important surveillance mechanism as it is the most powerful notification tool for definite and probable CJD cases and more broadly, is the single most dominant initial notification source of all suspect cases to the Registry. Although the large majority of samples referred are not resolved as CJD, the greatest proportion of all prospective probable and definite cases have been initially referred through CSF referral. Since the test was offered in 1997, 66% of all definite and probable CJD cases have been initially notified to the ANCJDR via CSF referral. The benefit of ascertaining potential cases whilst clinical investigations are ongoing is that the Registry is able to effectively assist clinical teams in their investigations and further testing if required.

Other tests that are offered by the ANCJDR include genetic testing, to examine the prion protein gene (*PRNP*) for the presence of a mutation, tonsil biopsy testing for vCJD suspect cases and post-mortem brain-only examination. On rare occasions, brain biopsies are referred to the ANCJDR and these are tested as for tonsil biopsies with immunohistochemical and biochemical analytical techniques; however, it is to be emphasised that based on World Health Organization recommendations,[5] the ANCJDR advises against a brain biopsy examination due to the infection control implications involved with such a procedure and the possibility that biopsy testing is not as definitive as a whole brain examination. For these reasons, the ANCJDR advocates for whole brain examination after autopsy. The ANCJDR actively promotes the offered diagnostic tests to clinicians so that these options are available to all families should they wish to pursue these avenues of investigation. Table 3 outlines the number of cases referred to the ANCJDR for analysis of; brain specimens through biopsy or post-mortem; blood and DNA samples for genetic testing; and tonsil biopsies between 2000 and 2009. The Australian autopsy rate is notable with 63% of all suspect case deaths between 2000 and 2010 undergoing autopsy evaluation. This rate is also observed for the entire prospective period of 1993 to 2010.

In addition, the ANCJDR performs routine prion protein strain typing for molecular subtype classification in confirmed sporadic CJD cases, when frozen brain tissue is available for testing. Prion protein 'strains' correlate with phenotypic subtypes and thus these analyses provide a method to categorise the phenotypically heterogeneous group of sporadic CJD. Two sets of analyses are involved in this testing. Firstly, brain tissue is examined by Western blotting techniques to determine the glycoform profile of the protease-resistant prion protein, based on the size and abundance of the 2 glycosylated and 1 unglycosylated species of the protein. In addition, the Codon 129 genotype is determined by analysing DNA. A polymorphism at the Codon 129 site of the prion protein gene distinguishes cases into 3 different genotypes (MV, MM and VV). In conjunction, these tests provide a method by which sporadic

cases can be categorised into molecular subtypes that allow the ANCJDR to monitor potential geographical clustering of particular strains, and also provide a mechanism to assess sporadic cases for the possibility of vCJD and novel strain profiles.

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