Surveillance for Creutzfeldt-Jakob disease in Australia: update to December 2012

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Abstract

Nation-wide surveillance for transmissible spongiform encephalopathies including Creutzfeldt-Jakob disease (CJD) is undertaken by the Australian National Creutzfeldt-Jakob disease Registry (ANCJDR), based at the University of Melbourne. Surveillance has been undertaken since 1993. During this period the unit has evolved and adapted to changes in surveillance practices and requirements, the emergence of new disease subtypes, improvements in diagnostic capabilities and the overall heightened awareness and understanding of CJD and other transmissible spongiform encephalopathies in the health care setting. In 2012, routine surveillance continued. This brief report provides an update on the surveillance data collected by the ANCJDR prospectively from 1993 to December 2012, and retrospectively to 1970. It also highlights the recent release of the revised Australian CJD Infection Control Guidelines.

Keywords: Creutzfeldt-Jakob disease, prion disease, transmissible spongiform encephalopathy, disease surveillance

Introduction

In 1993 the Allar's inquiry into the use of cadaver-derived pituitary hormones under The Australian Human Pituitary Hormone Program and the association with four medically acquired (iatrogenic) Creutzfeldt-Jakob disease (CJD) deaths recommended the formation of an Australian surveillance unit to monitor further cases of iatrogenic CJD in Australia.[1] The Australian National Creutzfeldt-Jakob disease Registry (ANCJDR) was established in October 1993 at the Department of Pathology at the University of Melbourne. The monitoring of further Australian iatrogenic CJD cases related to pituitary hormone treatment for infertility or short stature and contaminated dura mater grafts remains one of the core objectives of the ANCJDR. However, the ANCJDR's activities have changed to encompass the surveillance of all types of CJD including sporadic, genetic and variant CJD and other transmissible spongiform encephalopathies (TSEs) such as Gerstmann Sträussler-Sheinker Syndrome (GSS) and fatal familial insomnia (FFI).

Sporadic CJD currently accounts for between 85% and 90% of all CJD cases internationally.[2] Cases are defined as sporadic when there is no discernible transmission event and when there is no family history and/or negative prion protein gene (*PRNP*) testing. Familial TSEs include genetic CJD, GSS and FFI. These cases are classified as such if there is a disease-specific mutation in *PRNP* or a TSE is confirmed in a 1st degree relative. *PRNP* mutations include single nucleotide substitutions and poly-nucleotide insertions and deletions. Polymorphisms in *PRNP* such as at codon 129 are thought to influence the disease phenotype (including in relation to particular mutations), as well as susceptibility to sporadic and some forms of iatrogenic CJD. Classification of iatrogenic CJD cases is dependent on a typical clinical profile and recognition of a transmission risk.

Since 1993 there has been considerable change in the understanding of surveillance for TSEs. This is due to the appearance of new disease subtypes, greater clinical awareness, improved and varied diagnostic capabilities, continued scientific research and the world wide focus on CJD through the emergence of variant CJD (vCJD) in 1996. In response to these changes, the ANCJDR has adapted with available resources to meet the increasing demands for diagnostic testing, clinical and expert infection control advice, and the steadily growing number of suspected case notifications directed to the ANCJDR for evaluation.

Methods

Various mechanisms have been established by the ANCJDR in order to ascertain all cases of TSE in Australia since 1970. During 2012 cases were referred through several mechanisms including diagnostic test referral, personal communication by clinicians, families, health departments and hospitals and the CJD counselling service. As of June 2006, CJD was listed as a notifiable disease in all states and territories.

Since September 1997 the ANCJDR has offered national diagnostic testing for the presence of a family of low molecular weight proteins called 14-3-3 proteins in cerebrospinal fluid (CSF). This single test has provided an increasingly larger proportion of the annual suspected case notifications. It is currently the predominant (49.9%) and continually increasing source of notifications. The CSF 14-3-3 protein test is now the most broadly utilized diagnostic tool for CJD. As of 2012, all CSF samples tested by the ANCJDR were followed-up at three months and, if necessary, again at nine months after initial referral to determine the outcome for the patient.

This is performed to assist in the determination of the sensitivity and specificity of the diagnostic test. The follow-up at three months was introduced to enable a more timely prompt for clinicians and has led to more case outcomes being determined than follow up at nine months only. If death has occurred within three months of the original referral and CJD is considered a possible diagnosis, further case evaluation is performed.

After notification of a suspected case and a detailed evaluation, the ANCJDR utilises internationally recognised case definitions for the classification of definite, probable and possible cases.[3-5] Suspected CJD cases retain an incomplete status until evaluation is complete. 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 and a typical electroencephalogram (EEG) and/or a positive 14-3-3 CSF test and/or a characteristic magnetic resonance imaging (MRI) with high T2 weighted image 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 two years. Possible cases fulfil the same clinical profile in the absence of a typical EEG, characteristic MRI and either no or a negative 14-3-3 CSF test result. The method of classification of possible cases is in accordance with the European Creutzfeldt Jakob Disease (EUROCJD) and World Health Organization (WHO) promulgated diagnostic criteria and has been in use since 1 January 2001.[5]

Annual TSE incidence rates were calculated using direct age-standardisation, based on the Australian Bureau of Statistics 2000 estimated resident population for Australia and each state and territory.[6]

Results

In 2012, 53 new suspected TSE cases were added to the ANCJDR for evaluation. The source of notification for these new cases included requests for a CSF 14-3-3 protein test (62%), personal communication from a neurologist, neuropathologist, clinician or hospital (23%), health department notification (7%), communication from a family (6%) or from the CJD counselling service (2%). The proportion reported from each source is consistent with those in 2011. CSF referral has accounted for 74% of all referrals since 2000, with 21% by direct personal communication (comprising medical practitioners, 16%, families, 4% and hospitals, 1%).

In 2012 notification numbers declined nationally by 37% compared to the previous year (Figure 1). Contributing to this decrease were fewer notifications in several states including Victoria (32%), New South Wales (45%), Western Australia (60%) and Tasmania (100%). The remaining states and territories remained unchanged from the previous year. This decline in notifications is unexplained and these rates will be closely monitored in 2013.

In 2012, 38 of the 53 notified cases were still under investigation. The annual proportion of suspected cases notified between 1993 and 2011 that were subsequently classified as definite or probable TSE cases ranges from 32% to 78%, with a mean of 46%.

Figure 1: Prospective notifications of suspected TSE cases notified to the ANCJDR, 1993 to 2012, by state or territory and year

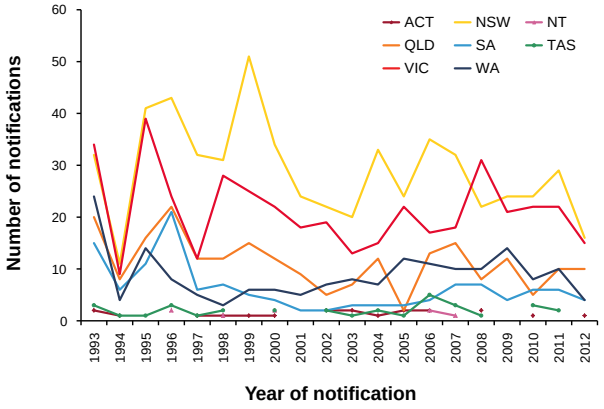
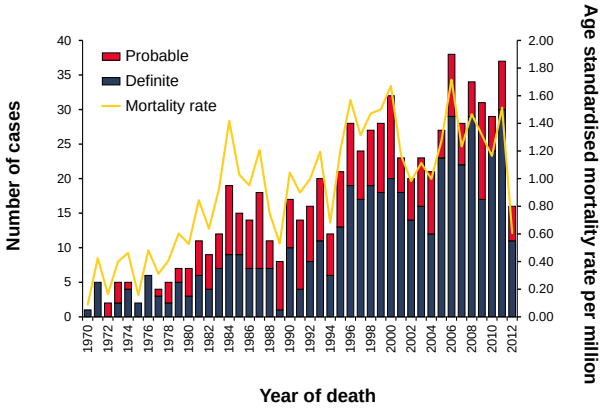


Figure 2: Number of definite and probable TSE cases and age-standardised mortality rate in Australia, 1970 to 2012, by classification and year



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

Figure 3: Definite and probable TSE cases, 1970 to 2012, by aetiology and year

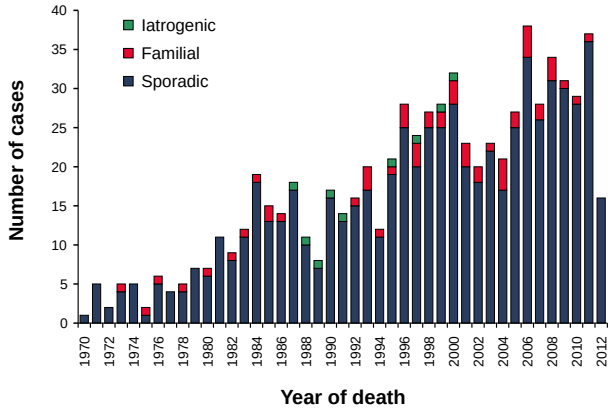
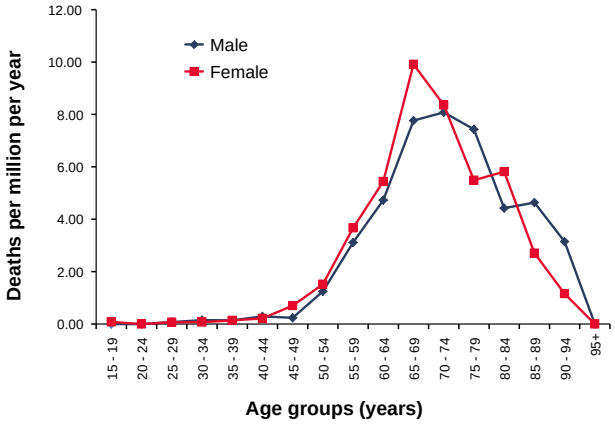


Figure 4: Mortality rates for all TSE cases 1993 to 2012, by sex and age group



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

As of 31 December 2012, 962 suspected TSE cases were on the register with 733 of these being classified as Australian probable or definite TSE cases (Table 1).

An additional 638 cases were excluded after detailed follow-up. Of the 53 new suspected cases added to the register in 2012, 3 were excluded (2 following neuropathological examination), 38 are incomplete, 8 were classified as definite CJD and 4 as probable CJD. During 2012, 45 suspected cases were excluded from the register (10 after neuropathological examination) and 38 cases were classified as sporadic CJD and 1 as familial TSE. There are currently 14 cases of possible CJD of which 13 are sporadic and 1 iatrogenic. Of the 214 incomplete cases, 135 are presently alive. In comparison to the rapid increase in the number of incomplete cases on the register observed between 2003 and 2010 (average 22% increase per year), an overall reduction in the size of this group was recorded in 2012 (12% decrease).

Between 1 January 2012 and 31 December 2012, there were no new cases of iatrogenic CJD. 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 2012, there had been no known cases of vCJD in Australia.

Between 1970 and 2000, the annual incidence of TSEs in Australia steadily increased (Figure 2).

As for other international CJD surveillance programs, the increase probably reflects case ascertainment bias stemming from improved recognition, investigation, case confirmation and reporting. The incidence of TSE in Australia declined and stabilized at around 1.0 case per million per year during 2001-2004, but increased to 1.72 cases per million per year in 2006. Incidence remained at around 1.3 to 1.4 cases per million per year between 2007 and 2012.

The majority of the confirmed Australian TSE cases have been of sporadic aetiology (92%) and this has been a consistent observation from 1970 to 2012. Familial and iatrogenic cases constitute 7% and 1%

Table 1: Classification of ANCJDR cases 1970 to 2012

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	433	44	5*	0	0	482
Probable	238	10	4	0	0	252
Possible	13	0	1	0	0	14
Incomplete	0	0	0	0	214**	4
Total	684	54	10	0	214	962

* 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 135 living cases

Table 2: TSE deaths and age-adjusted mortality rates, 2000 to 2012, by year and state or territory

	TSE cases by year of death															Mean age-adjusted mortality rate (deaths/ million/year)
	00	01	02	03	04	05	06	07	08	09	10	11	12	Alive	Total	
ACT			1		1		1		2		1				6	1.25
NSW	12	9	7	7	11	10	12	10	6	11	5	14	2	1	117	1.24
NT							2	1							3	0.74
QLD	7	3	3	3			7	2	4	4	2	5	5		45	0.78
SA	2			1	2	1	1	3	5	2	4	4			25	1.13
TAS			2			1	2						1		6	0.85
VIC	9	10	5	9	5	11	9	6	13	9	13	9	6	1	115	1.62
WA	2	1	2	3	2	4	4	6	4	5	4	5	2		44	1.49
AUS	32	23	20	23	21	27	38	28	34	31	29	37	16	2	361	1.25

Age-standardised mortality rates were calculated using the Australian Bureau of Statistics 2000 estimated resident population for Australian states and territories

respectively of all definite and probable cases. Between 1993 and 2012 the average number of familial cases classified in Australia was 2 cases per year. Since 2009 only one familial case has been classified per year. The overall proportion of cases classified as familial TSE has declined (Figure 3).

Between 2002 and 2012 the majority of states and territories had age-adjusted mortality rates above or close to 1.0 case per million per year (Table 2). The highest mean mortality rates were observed in Victoria and Western Australia (1.62 and 1.49 deaths per million per year, respectively).

From 1970 to 2012 there were more female TSE cases (54%) than male for all forms of TSE combined. This was also true for sporadic (54%) and genetic (55%) forms. A comparison of age and sex-specific mortality shows the similarity of rates between males and females with some exceptions in the older age groups (Figure 4).

The median age of death from all forms of TSE between 1970 and 2012 was 67 years with little difference between the sexes (men, 66 years, women, 67 years). For familial cases, a difference did exist between the sexes, as the median age at death was 52 years in males and 62 years in females. The range in age at death from TSE was broad for both the sporadic (25-90 years) and familial (18-82 years) group with median age at death being 67 and 59 years respectively. For the eight iatrogenic cases, death occurred between the ages of 26 and 62 years and disease duration from onset to death was between 2 and 25 months (median, 6.25 months). For all TSE cases, 92.9% of deaths occured over the age of 50. This demonstrates that older age groups are at risk of developing TSEs and this is consistent for all TSE aetiologies. Of the 39 cases confirmed with a TSE in 2012, all deaths occurred in those over the age of 50 years.

Between 1970 and 2012, disease duration from onset varied between the three aetiologies. Sporadic TSE cases had much shorter disease duration than both iatrogenic and familial cases with 50% of deaths occurring within 3.5 months of onset (range, 0.9 – 60 months). From 1970 to 2012 familial cases were associated with a significantly greater survival time in comparison to sporadic TSE with the median illness duration of 6 months (range, 1.5 – 192 months). Within 6 months of disease onset, 72% of sporadic cases, 53% of familial cases and 56% of iatrogenic cases had died.

Discussion

There are several possible explanations regarding the range in the annual number of notifications and the proportion of suspected cases that were subsequently confirmed as TSE cases. These include the prospective surveillance approach employed, diagnostic capacity changes such as the CSF 14-3-3 protein test and MRI, enhanced clinician awareness, a greater public health profile for CJD through the focus on variant CJD. In addition, the notifiable status of CJD was established in all states and territories by June 2006. Specifically, Tasmania (May 2003), Victoria (Jan 2004), Western Australia (Jan 2004), New South Wales (April 2004), Northern Territory (Dec 2004), Australian Capital Territory (Sept 2005), Queensland (Dec 2005), South Australia (June 2006).

In 2012 there was a high number of cases confirmed or excluded by neuropathology. There was also a 4-fold increase in the number of probable cases and a two-fold increase in the number of cases excluded

from the ANCJDR after detailed evaluation. These changes led to a 12% decrease in the number of incomplete or unresolved cases on the register. As in 2011, the ANCJDR made a concerted effort during 2012 to focus staff resources on performing case reviews and classifying outstanding, incomplete cases.

Fluctuating peaks in the incidence of TSE might be expected in such a rare disease. The ANCJDR believes that there are a number of factors responsible for the 2000-04 decline. These include a reduction in the number of probable cases classified due to broadened surveillance responsibilities, difficulties experienced following changes to the privacy legislation, and changes to the registration of cases referred for CSF 14-3-3 protein testing. The subsequent peak incidence in 2006 aligns with a increasing trend in notifications in 2005–06. This can be attributed predominantly to increased ante-mortem notifications through the CSF 14-3-3 protein test, which has enabled a greater number of post-mortem examinations to be actively investigated for suspected TSE. Ultimately, with more post-mortem examinations being performed, a greater number of suspected TSE cases have been confirmed. Currently, the proportion of all suspected cases notified to the ANCJDR between 1993 and 2011, (including those cases excluded from the register after evaluation and where death is known to have occurred) who have undergone a post-mortem examination is 62%. The ANCJDR also believes that the peak incidence rates of 1.67 and 1.72 cases per million per year observed in 2000 and 2006 respectively provide a more accurate estimation of the true incidence of TSEs in Australia, underscoring the importance for post-mortem examinations to be actively promoted in all suspect cases. The mean annual age-adjusted TSE mortality rate for the 1993 to 2012 period was 1.26 deaths per million per year. This rate aligns with the reported figures for other countries with similar surveillance mechanisms to those in Australia.[7]

The ANCJDR has maintained a non-systematic approach to the prion protein genotyping of confirmed TSE cases. This may have contributed to our lower percentage of familial cases (7%) compared with European CJD surveillance programmes, which report that between 12% and 14% of cases are familial.[8] In recent years the free *PRNP* genetic testing service provided by the ANCJDR to CJD patients and families has been decentralised due to their preference for an "on-demand" service. Although the ANCJDR still performs routine genetic testing three times annually, testing is now also undertaken by external, independent laboratories and genetic services. The separation of *PRNP* testing from the ANCJDR may have inadvertently contributed to the reduced proportion of genetic TSE cases observed over the last few years (Figure 3).

In 2012 the Australian CJD Infection Control Guidelines were revised by the Communicable Diseases Network Australia and published in January 2013.[9] These guidelines provide updated information for health care and funeral industry professionals and families of CJD patients. They aim to provide greater clarity for infection control and ensure ease of use and the avoidance of unnecessary discrimination or disadvantage for families affected by CJD.[10]

During 2012, the ANCJDR continued nation-wide surveillance for all forms of TSE and has identified a decrease in the number of suspected cases notified for evaluation. Overall disease incidence has not been affected by this decline; however, it remains to be determined how this will influence incidence rates in 2013. Notifications will be closely monitored during 2013.

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