Transmissible spongiform encephalopathies in Australia

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Abstract

The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) commenced surveillance in September 1993 as part of the Commonwealth's response to 4 cases of pituitary hormone (gonadotrophin)-associated Creutzfeldt-Jakob disease (CJD). With the passage of time, the Registry has become responsible for ascertaining all human transmissible spongiform encephalopathies (TSE; also known as prion diseases) within Australia since 1970. Included in the spectrum of diseases monitored are classical (sporadic, genetic, and health care acquired) CJD, and variant CJD (vCJD), first reported in 1996 in the United Kingdom. Variant CJD has not yet been diagnosed in Australia. Final classification of persons with suspected human prion disease is based upon all available clinical, investigational and pathological information. Ascertainment methods are diverse and include prompted, half-yearly personal communications from neurologists and neuropathologists, death certificate searches, and morbidity separation coding searches of major hospital, and State and Territory databases. More recently, referral for diagnostic CSF 14-3-3 protein testing (performed by the ANCJDR) has considerably increased prospective notifications of suspect cases. As at September 2001 there were 460 cases on the register; 237 definite cases, 168 probable and 55 incomplete cases awaiting final classification. *Commun Dis Intell* 2001;25:248-253.

Keywords: Transmissible spongiform encephalopathies; TSE; Creutzfeldt-Jakob disease; CJD; vCJD

Introduction

Transmissible spongiform encephalopathies (TSE) constitute a group of invariably fatal neurodegenerative diseases which affect both animals and humans. In 1998 Prusiner reviewed TSE[1] summarising developments since the 1950s, emphasising events over the last 2 decades. Bovine spongiform encephalopathy (BSE; 'mad cow' disease) and scrapie are the most common animal forms while Creutzfeldt-Jakob disease (CJD) is the most common human phenotype. Variant CJD (vCJD) is believed to be linked to the consumption of BSE prion protein-contaminated beef or beef products. This association was first positively identified in United Kingdom (UK) cattle in 1986. Variant CJD is characterised clinically by a younger age at death (mean 29 years), prominent psychiatric presenting symptoms, and longer illness duration. Classical CJD typically presents as a rapidly progressive dementia in older persons, often associated with myoclonus and ataxia. Other forms of human TSE include Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI) and Kuru, with the first two almost invariably associated with mutations in the prion protein gene (PRNP) on chromosome 20. Kuru occurs exclusively in a restricted geographical region in the Eastern Highlands of Papua New Guinea (PNG) and is related to the practice of ritualistic endo-cannibalism as a mourning rite of deceased relatives. The disease has almost disappeared since the cessation of cannibalism in the 1950s.

Neuropathologically, varying combinations of microvacuolation of the gray matter, astrocytic gliosis, neuronal loss and immunodetectable deposits of prion protein are characteristic changes of TSE. Disease pathogenesis appears intimately linked to expression of an abnormal protease-resistant conformation of the prion protein (PrP^{res}), although precise mechanistic details of how this isoform arises from the normal mammalian prion protein (PrP^{c}) and consequent pathophysiological steps remain to be elucidated. The infectious unit or particle (termed prion) carries no nucleic acid and appears predominantly, if not exclusively, composed of PrP^{res}. Expression of PrP^{c} is obligatory for disease development and successful transmission, with PrP^{res} thought to serve as a template facilitating further conversion of the wild type prion protein, PrP^{c}, into the disease causing isoform. Early transmission studies in the 1960s established transmissibility, however TSE are not considered classical infectious diseases.

The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in September 1993 in response to the recognition of 4 probable human pituitary hormone (hPG) related CJD deaths. The original Registry's objective was detailed scrutiny for further health care acquired CJD cases over the restricted period 1 January 1988 to 31 December 1997. This 10-year epoch was intended to encompass the highest likely period surrounding the 4 index cases. However, following the commissioned inquiry into the use of human pituitary hormones under the Australian Human Pituitary Hormone Program (AHPHP), reporting in 1994,[2] recommendations were adopted to expand ANCJDR activities, including retrospective case ascertainment to 1 January 1970. Prospective monitoring to ensure complete ascertainment of any further occurrences of health care acquired CJD has required the Registry to continue to

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evaluate all persons suspected to be manifesting a TSE. CJD is not a notifiable disease in Australia.

The most common form of human prion disease is sporadic CJD which by definition is without apparent cause. This form constitutes between 85 to 90 per cent of all human TSEs, and typically death occurs after a median illness duration of 4 months. Less commonly, the CJD phenotype can occur as a result of a mutation in the PRNP gene (genetic form), or as a consequence of horizontal transmission, which in Western societies to date is invariably from inadvertent contamination through health care provision (health care acquired CJD). Sources of health care acquired CJD transmission[3] have included cornea[4] and dura mater transplants,[5] as well as treatment with cadaveric pituitary hormones.[6,7] Genetic forms of human TSE account for approximately 12–14 per cent of all cases when systematic PRNP genotyping is undertaken,[8] while health care acquired CJD is very rare with only 10 cases so far recognised in Australia. Variant CJD represents a new strain of human prion disease and based on a range of data, most likely occurred as a consequence of BSE crossing the species barrier from cattle to man via the consumption of contaminated meat products. Australia remains free of BSE which is now recognised in a number of European countries, and most recently Japan.

As of September 2001, the ANCJDR had classified 405 persons who had died from clinically likely (probable) or definite prion disease, with a further 55 incomplete (suspect) cases requiring further investigation before final classification is possible. These incomplete cases are either awaiting postmortem neuropathological examination or additional clinical details.

Classification methods and case ascertainment

Classification of human prion diseases is based on internationally accepted criteria (Table 1),[9,10] with minor modifications. In brief, definite cases are those neuropathologically confirmed, preferably with the presence of PrP^{res} demonstrated in the brain, by immunochemical methods. Probable or clinically likely patients with CJD manifest a combination of rapidly progressive dementia with any two of the following features: myoclonus; visual or cerebellar dysfunction; pyramidal or extrapyramidal dysfunction; or akinetic mutism. Variant CJD is distinguishable from classical CJD clinically and neuropathologically. Since 1997, a positive 14-3-3 result has been the most useful premortem investigation whereas prior to 1997 an EEG showing typical periodic discharges was used as an aid in

Table 1. Classification criteria for classical and variant CJD

	Definite	Probable
Classical CJD	• Neuropathologically confirmed *supplemented by* • Immunochemical confirmation of PrP^{res}	• Progressive dementia <2 years *Investigations* • Typical EEG *and/or* • Positive CSF 14-3-3 protein test At least 2 out of 4 of the clinical features: • Myoclonus • Visual or cerebellar dysfunction • Pyramidal/extrapyramidal dysfunction • Akinetic mutism
Variant CJD	• Progressive neuropsychiatric disorder *and* • Neuropathological confirmation of diagnosis of vCJD	• Progressive neuropsychiatric disorder without family history of prion disease • Duration of illness >six months *and* 4 out of 5 of the clinical features: • Early psychiatric symptoms • Persistent paraesthesia or dysaesthesia • Ataxia • Myoclonus or chorea • Dementia *Investigations* • Abnormal but non-typical EEG for CJD *and* • Bilateral pulvinar high signal on MRI *or* • A positive tonsil biopsy

diagnosis.[11] The ANCJDR does not utilise the possible classification. Cases unable to fulfill the above criteria are excluded with one exception: a single health care acquired case due to cadaveric pituitary growth hormone was classified as a possible case because of concomitant medical problems militating against the probable classification.

The various mechanisms by which the ANCJDR ascertains cases of suspected prion disease are summarised in Table 2. The most frequent method of primary case ascertainment has been personal communications by medical practitioners, usually by telephone or correspondence, particularly neurologists and pathologists. At the inception of the Registry, all neurologists and neuropathologists within Australia were asked to inform the ANCJDR of any cases encountered during their entire professional practice. As a safeguard, reply-paid mail-outs are posted to these two important specialist groups semi-annually, prompting reporting of recently deceased or prospective cases.

Table 2. First sources of case ascertainment

Method	Per cent
Personal communications, including	66.5
Neurologists (includes mail-out reply cards)	(40.1)
Neuropathologists (includes mail-out reply cards)	(17.5)
Pituitary Hormones Task Force	(3.7)
Family	(4.7)
CJD Counselling Service	0.5
Death certificates	23.3
Hospital and health department searches	10.2
Hospital medical records	(8.2)
Health department search	(2.0)
Total	100

Death certificate searches through the Australian Health Index have proven to be of benefit in the retrospective ascertainment of cases. A search for death certificates in 1995 revealed 188 cases specifically coded to CJD. Unfortunately, death certificate searches for the epoch 1970 to 1979 have been impracticable due to the Australian Bureau of Statistics previously discarding identifying information and the lack of a standardised disease coding system across Australia. The ANCJDR routinely performs annual searches for CJD-coded death certificates through the Australian Institute of Health and Welfare (AIHW). The prospective notification mechanisms of the ANCJDR usually facilitate detection of patients approximately 18 months prior to death certificate notification.

The most time-consuming method of case ascertainment has been a nation-wide search of the health information departments of all university-affiliated teaching hospitals seeking all separations specifically coded to CJD and pre-senile dementia according to the ICD-8 and 9, and more recently the CJD specific ICD-9 CM code. In addition, searches have been performed within each State and Territory health information coding system using the CJD specific codes, providing similar but not identical information to that obtained from the hospitals. The reasons for search discrepancies vary but have included coding or data entry errors. Specific searches of private hospital data were not undertaken.

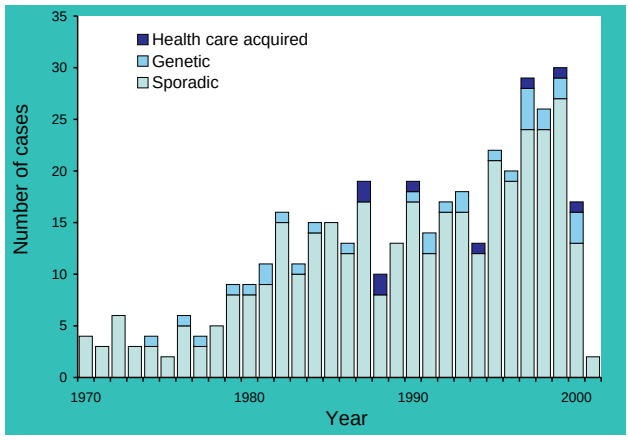
The introduction of an assay for the CSF 14-3-3 protein (a non-specific marker of neuronal degeneration) has over the last few years significantly increased the number of prospective referrals of suspect CJD cases to the Registry.[12] This test has shown 90 per cent sensitivity and specificity in appropriately evaluated patients with suspect CJD.[13] However, acknowledging the small but definite false positive and negative rates of this non-specific test, final inclusion on the register depends on review of all available clinical information. 14-3-3 negative cases are followed-up nine months after testing as a safeguard against a false negative result. Patients ultimately classified as CJD through this notification mechanism are currently included under neurologists' personal communications.

The ANCJDR records predominant occupation following consideration of lifetime employment history. The Australian Standard Classification of Occupations (ASCO)[14] was used for classification. Groups of interest include farmers subsumed under group 1 as managers/administrators and butchers/abattoir workers under group 4. The ANCJDR has included a home duties/childcare group, not recognised by ASCO. Disparity between the ANCJDR data classification of predominant occupation versus census data hinders comparative analysis. Australian Bureau of Statistics (ABS)[15] data were used to generate disease incidence rates, as well as age adjusted data.

Results

There has been a steady increase in the annual incidence of CJD since 1970, with probable plateauing during the late 1990s (Figure). When 'incomplete' cases are taken into account, the 1988 to 1999 average annual incidence is 1.1 cases per million (0.6 prior to 1988). Using probable and definite cases alone for the same time period the annual incidence is 1.0 case per million (0.6 prior to 1988). The

Figure. Classification of deaths from transmissible spongiform encephalopathies



increase for definite and probable cases has been reasonably uniform across Australia with absolute numbers reflecting regional population distributions: New South Wales (including the Australian Capital Territory) 139; the Northern Territory 1; Queensland 69; South Australia 48; Tasmania 4; Victoria 105; and Western Australia 39.

Acknowledging their salient demographic similarities, definite and probable cases have been aggregated for statistical analysis. The overall composition of probable and definite cases is 90.4 per cent sporadic, 7.4 per cent genetic and 2.2 per cent health care acquired. Analysis by gender reveals 173 males and 193 females with sporadic CJD, 13 males and 17 females with genetic TSE, and 4 males and 5 females with health care acquired disease. Age at death for sporadic CJD typically occurs between 56–75 years (mean 65.6 years), with an average duration of illness of 6.5 months. Age at death in genetic CJD ranges from 20 years through to 82 years, with the average age at death 56.8 years, and the mean duration of illness 17.6 months. The health care acquired cases include the 4 recipients of gonadotrophin (one probable and three pathologically proven), the single possible case arising from human growth hormone, and five cases related to the implantation of Lyodura (dura mater) grafts (three probable and two definite). Age at death for health care acquired CJD ranges from 26–62 years, with an average age at death 42.3 years. The average duration of illness is 7.8 months.

Analysis of cases by occupation (summarised in Table 3), reveals no groups to be over-represented. A closer look at the spectrum of health care workers developing CJD reveal all cases but one to be sporadic CJD; a radiologist; a dental surgeon; a registered nurse, and three general practitioners. One general practitioner was confirmed with genetic CJD. None of the health care workers are known to have had professional contact with CJD patients. Specifically, the nurse worked in a rural hospital where no known CJD cases had been recorded. A second nurse was a recipient of human derived pituitary gonadotrophin. Fifteen cases have no recorded occupation and one health care acquired case is known never to have worked.

After age adjustment, sub-group comparison by country of birth reveals 68.3 per cent of the general population to be Australian born whereas 66.0 per cent of ANCJDR cases were born in Australia. There is also no excess of cases amongst any immigrant sub-group.

Discussion

Although the catalyst for formal national surveillance of TSE in Australia was to monitor further instances of human pituitary hormone-related CJD, the activities of the ANCJDR have broadened to include vigilance for vCJD. The additional health care acquired cases recognised (as of September 2001) have been as a consequence of dura mater grafts with the most recent death occurring in 2000. One of these patients had an incubation period of approximately 17 years, equivalent to the longest seen so far for this type of iatrogenic transmission. It has now been approximately 10 years since the last death from gonadotrophin-related CJD in Australia, raising the likelihood that no further cases of this type of transmission will be seen domestically in contrast to continuing growth-hormone related cases occurring in other countries such as France.[3] Nevertheless, given the known potential for unpredictable and lengthy incubation periods, continued vigilance for many more years is required.

Over the 30 year surveillance period, the incidence of human TSE in Australia has increased considerably. This

Table 3. Cases by standard occupation

	Cases on Register		Working Australian population
Occupation group	n	%	%
1. Managers and administrators	55	13.6	9.4
2. Professionals	39	9.6	11.3
Medical professionals	4		
Health professionals	1		
Nurse professionals	1		
3. Para-professionals	16	4.0	4.8
Enrolled nurse	1		
4. Trades persons	40	9.9	12.2
5. Clerks	32	7.9	13.4
6. Salespersons and personal service workers	23	5.7	12.6
7. Plant and machine operators, and drivers	29	7.2	5.6
8. Labourers and related workers	51	12.6	12.0
9. Home duties/childcare	94	23.2	18.7
Total	379	93.7	100

phenomenon is analogous to the experience of other long-term comprehensive national CJD surveillance programs and is thought to reflect better case ascertainment stemming from improved recognition, confirmation and reporting. There has been a relative plateauing in annual incidence since the late 1990s, suggesting current ascertainment methods have been optimised. A combination of factors (including the diagnostic CSF 14-3-3 protein test, PRNP genotyping and enhanced post-mortem rates) have contributed to this improved classification and identification of CJD cases across Australia. These investigations have especially increased the ascertainment of non-typical and familial cases. Nevertheless, our non-systematic approach to PRNP genotyping is likely to have contributed to the lower percentage of genetic cases compared with international CJD surveillance programs utilising systematic genetic analysis.

Excessive temporo-spatial grouping of apparently sporadic CJD cases is occasionally seen,[16] and the ANCJDR has undertaken a comprehensive investigation of such a cluster in an Australian rural city which is the subject of a separate report.

At the time of writing, vCJD has not been diagnosed in Australia. Acknowledging the likely zoonotic basis of vCJD from BSE, Australia's continued verified freedom from the latter and the relatively small number of variant cases so far in the UK compared to the total number of BSE affected cattle, the likelihood of occurrence is low but not zero. This is especially so given the extensive flux of citizens between Australia and the UK over the past 2 decades with the possibility of 'importing' vCJD. For a number of reasons, particularly its increased heat stability and the presence of protease-resistant prion protein in lymphoreticular organs,[17] vCJD is believed to constitute a greater public health risk than its classical counterpart. Therefore, any vCJD occurrence in Australia will pose similar public health and safety issues as in the UK. Hence, the low but potential risk of vCJD arising in Australia mandates continued careful monitoring to enable early detection, and safeguard as much as possible against untoward outcomes, especially inadvertent health care related transmission.

The true significance of occupation is tentative and further research will be needed to elucidate potential risks. A case-control study of risk factors for sporadic CJD has been undertaken by the ANCJDR with the results already reported in detail.[18] Importantly, the risk of sporadic CJD progressively increased with the number of surgical treatments to a maximum of three procedures (odds ratio 2.13, 95% CI 1.34-3.41)) and did not appear related to site or complexity of the procedure. There was also an increased risk of CJD with employment or residence on a farm ($p<0.001$) or market garden ($p=0.002$) for periods longer than 10 years ($p=0.002$). These findings raise interesting possibilities with regards to under-recognised or potentially novel transmission events but await validation from further studies.

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