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Prion disease in Indigenous Australians

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INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare transmissible, neurodegenerative disorder with an annual incidence of approximately 1-2 per million population.[1–3] CJD represents the most common phenotype of human prion disease,[4] which can be sporadic (~85-90%), genetic (~10-15%) or acquired (<1%). Sporadic CJD (sCJD) typically presents as a rapidly progressive dementia associated with myoclonus and cerebellar ataxia with inexorable clinical decline resulting in death after a median survival of ~4-5 months.[2–4] In addition to sCJD, the spectrum of human prion disease includes Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia. The detection of

kuru in the 1950s established that prion diseases occur in Indigenous peoples albeit aetiologically linked to the culturally peculiar Fore practice of endocannibalism. Epidemiological studies of prion disease in specific ethnic groups are limited[5] ; however, a global epidemiological survey revealed that CJD occurs worldwide,[6] including Indigenous peoples from Oman and Papua New Guinea.[7,8] Indigenous Americans and Alaskans were later reported to also develop CJD.[5]

Encompassed in the investigation of neurodegenerative disorders occurring in Indigenous Australian (Aboriginal and Torres Strait Islander) communities, including Huntington's disease,[9] spinocerebellar ataxia[10] and early onset dementia,[11] is the study of CJD and other forms of human prion disease. Systematic epidemiological studies of neurodegenerative disorders in Indigenous Australians can be problematic for reasons that include geographical remoteness from clinical services and socio-cultural attitudes to medical evaluation, including performance of neuropathological studies. Herein, we selectively report for the first time, all ANCJDR ascertained cases of CJD in Indigenous Australians, highlighting a Western Australian Indigenous person dying from likely prion disease. This patient illustrates some of the potential challenges faced in the diagnosis and management of prion diseases in Indigenous Australians living in remote communities. Incidence rates, indirect age-standardised mortality ratios and the clinical phenotype of sCJD in Indigenous Australians are compared to non-Indigenous Australians from the ANCJDR database.[12,13]

METHODS

The ascertainment and classification of Indigenous (Aboriginal and Torres Strait Islander) and non-Indigenous Australians with prion disease occurred as part of routine surveillance activities of the ANCJDR, employing updated case classification criteria.[13] ANCJDR data and relevant population data

from the Australian Bureau of Statistics (ABS)[14,15] allowed estimation of crude annual incidence rates for specific reference years (2006, 2011 and 2016). In addition, indirect age-standardisation of all CJD to calculate the standardised mortality ratio (SMR) for the Indigenous Australian population in comparison to the all-resident Australian population was undertaken. Indirect age-standardisation was performed because case numbers for the Indigenous Australian population for the years 2006 to 2018 were small rendering age-standardised mortality rates a less robust calculation. Indirect age-standardised mortality ratios for the Indigenous population for the years 2006 to 2018 in comparison to non-Indigenous Australians represents the period during which Indigenous persons were diagnosed and classified as dying from sCJD. Due to the lack of resident Aboriginal and Torres Strait Islander population data by age group for the years 2017 and 2018, the 2016 estimate was used for these years. Indigenous ethnicity was as reported by the patient, family or caring medical practitioners.

The ANCJDR is funded by the Commonwealth Department of Health and is responsible for the national surveillance of clinically suspected and confirmed human prion disease in Australia and is based at The Florey Institute, The University of Melbourne. ANCJDR surveillance activities are approved by The University of Melbourne Human Research Ethics Committee (ID# 1341074) to collect and monitor limited personal and health information from Indigenous and non-Indigenous Australians in relation to CJD and disseminate de-identified and aggregate data for reporting and research purposes; approvals were not obtained from other sources. Written permission to release additional data for publication was obtained for the illustrative case report.

RESULTS

Illustrative case report

This patient was a 55-year-old male Indigenous Australian residing in a remote region of Western Australia at the time of illness onset. Approximately 6 weeks prior to admission, the patient developed progressive unsteadiness of gait associated with blurred vision, tinnitus, short-term memory loss and slurred speech. He was a non-smoker, did not take illicit drugs or alcohol and there was no known family history of a neurodegenerative disorder. There was no past surgical history nor any history of blood transfusions or treatment with any other medical products. Upon admission to hospital gait was impaired but he was able to walk without assistance, his Mini-Mental State Examination score was 22/30, and he was intermittently confused with disorientation to year, month and day. He had left upper limb dysmetria. Rapid decline in cognition and gross motor function continued such that by approximately ten days after admission the patient was only able to provide one or two word answers, was unable to stand independently and could not follow commands to allow a detailed neurological examination. Myoclonic jerks became evident in the upper limbs.

A MRI scan revealed increased T2 signal with restricted diffusion in the left caudate nucleus and putamen, as well as the posterior cingulate gyrus on both sides, raising the likelihood of CJD. Routine CSF parameters were unremarkable with cytology negative for malignant cells; microbiological studies were negative for bacteria, viruses and fungi; 14-3-3 protein testing was positive. EEG five days after admission showed a non-specific excess of slower frequencies consistent with an

encephalopathy while a repeat study at 12 days after admission showed diffuse periodic complexes at 1 hertz, strongly increasing the likelihood of CJD.

A working diagnosis of probable sCJD and the attendant poor prognosis was explained to the family. It was the family's preference that the patient be transferred for palliative care at "home and country". The patient died with his family in his local community after an illness duration of approximately two months; the patient's family declined an autopsy.

Summary of ascertained CJD affecting Indigenous Australians

As part of comprehensive, national surveillance, eight persons identified as Indigenous Australians have been classified as dying from sCJD by the ANCJDR (Table 1). Although dealing with a small number of Indigenous Australians with sCJD, basic demographic features are similar to the broader Australian population with a median age at death of 61 years (IQR=16 years) and median disease duration of 3 months (IQR=1.6 months). Two of the patients were known to share Irish, Scandanavian and English ancestry. The patients were geographically, widely dispersed across the continent spanning from South Hedland to the eastern seaboard. Definite CJD was confirmed through post-mortem neuropathological examination in five persons, while three cases (including the illustrative case report from Western Australia) fulfilled classification criteria for probable CJD. One patient presented with prominent visual symptoms in keeping with the Heidenhain sub-type of sCJD while the others presented with typical sCJD evincing rapidly progressive dementia accompanied by myoclonus. There was no family history of similar neurological illness in any of the eight Indigenous persons, with genetic testing performed in three patients showing codon 129

methionine homozygosity and absence of disease-associated prion protein gene (*PRNP*) mutations. CSF 14-3-3 protein was positive in six of the eight patients tested.

Using data from the ANCJDR and the ABS (populations based on three reference years 2006, 2011 and 2016), we estimated overall crude annual rates of sCJD in Indigenous Australians compared to the remainder of the Australian population (after subtracting the number of Indigenous people): 0–3.87 per million for Indigenous Australians and 0.94–1.83 per million for the remainder of the Australian population (Table 2). In addition, indirect age-standardisation was utilised to estimate a standardised mortality ratio for the Indigenous population for the years 2006 to 2018, representing the period in which Indigenous persons were diagnosed and classified as dying from sCJD. Using the ABS estimated populations for both resident Aboriginal and Torres Strait Islanders (2006-2016)[16] and all-resident Australians (2006-2018),[17] age-specific Australian mortality rates were used to calculate the number of Indigenous CJD cases expected if the Indigenous population had the same age-specific mortality rates as the entire Australian population. Compared to the eight observed Indigenous cases, the overall number of expected CJD cases was calculated to be 5.37, giving a ratio of 1.49 (95% CI, 0.75 - 2.98). Although, this suggests a 50% excess of observed cases compared to the expected number in the Indigenous Australian population, the wide confidence interval range encompassing 1.0 renders this result not statistically significant.

DISCUSSION

The present study re-confirms that CJD occurs in Indigenous populations, with the overall features of the eight Indigenous Australians in keeping with sCJD, which appears phenotypically in keeping with sCJD occurring in non-Indigenous persons with similar geographical dispersion and incidence rates.

Uniformity of phenotype and rates of occurrence for sCJD is well recognised across non-Indigenous populations.[18] Our illustrative patient is the first known Indigenous Australian from that particular remote region of Western Australia to be diagnosed with probable sCJD, dying approximately two months after the onset of symptoms with a typical clinical picture of rapidly progressive dementia, ataxia and myoclonus, positive 14-3-3 protein in the CSF and characteristic MRI and EEG findings. Although permission for post-mortem confirmation is commonly sought for persons suspected to be manifesting CJD, including in this patient, families not infrequently decline for various reasons including cultural, religious and personal preference. This rare neurodegenerative cause of death in Indigenous Australians stands in contrast with their much more common causes of death, most of which relate to ischaemic heart disease, diabetes mellitus, chronic lung diseases, lung cancer and self-harm.[19,20]

Sporadic CJD has also been reported amongst Indigenous North Americans and Alaskans with 12 CJD deaths recorded from 1981 until 2002, with an annual age-adjusted mortality rate of 0.47 per million population – possibly lower than for Caucasians but close to that reported for African Americans.[6] Potential difficulties with case ascertainment and diagnosis related to remote residence, as well as the possibility of problems obtaining autopsy because of cultural and other influences were described in relation to these Indigenous populations,[5] and these factors may have contributed to the absence of confirmed CJD in Indigenous Australians prior to 2006. This year delineates when CJD became a notifiable disease across all Australian states and territories. Presumably this or other factors mitigated any previous impediments up to around 2006 allowing detection and confirmation of CJD in Indigenous Australians at rates broadly comparable to non-Indigenous Australians. Our estimated crude incidence rates and indirect age-standardised mortality ratios for CJD in Indigenous

Australians since 2006 are equivalent to rates in the non-indigenous population. Overall, and in contrast with the findings of Maddox and colleagues suggesting a lower incidence in Indigenous North Americans and Alaskans than in Caucasians,[21] it appears unlikely there are significant differences between the rates of CJD in Indigenous and non-Indigenous Australian populations.

One important limitation of this study is the small number of patients included. This renders incidence rates potentially fragile to the effects of only a small change in detected absolute case numbers. As such, although we found the rate of CJD in Indigenous Australians was not different to the non-Indigenous population, a small increase in CJD cases could engender a relatively marked effect. All Indigenous CJD patients were from regional Australia and under-recognition of Indigenous CJD cannot be excluded where it is possible some doctors might not be aware that prion disease occurs in Indigenous people and furthermore health workers might not have easy access to diagnostic tools such as MRI or CSF biomarker analysis. Of some reassurance however, five out of the eight Indigenous patients had autopsy confirmation of CJD, which approximates the proportion of definite confirmation in the non-Indigenous population and thereby militates against undue concerns regarding difficulties in achieving adequate medical evaluation of suspected CJD in Indigenous patients from remote regions. Another limitation of our study was the lack of uniformity or consensus regarding the definition of Indigenous, which was based on self, family, or practitioner reporting. Given this lack of a definition and our limited understanding of the level of awareness and the attitudes of individuals regarding identification as Indigenous or not, our study is at risk of potential under- or over-reporting of CJD in Indigenous Australians. These limitations underscore the importance of maintaining awareness of CJD amongst practitioners, especially general practitioners

and general physicians servicing Indigenous Australians in remote regions, to ensure high quality national surveillance and accurate incidence rates are achieved.

In conclusion, we confirm that prion disease in the form of sCJD occurs in geographically dispersed Indigenous Australians, with the overall incidence rate and phenotype approximating that observed in non-Indigenous Australians. In combination with previous epidemiological studies, it appears likely that all human populations, regardless of genetic background and residential location, are susceptible to the pathophysiological disturbances culminating in prion disease.[22]

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Table 1. Creutzfeldt-Jakob disease in Indigenous Australians*

Year of death	Sex	Death age (years)	Illness Duration (months)	ANCJDR Classification	CSF 14-3-3 result
2006	F	67	3	Definite	NT
2006	M	48	8	Definite	Positive
2007	F	61	6	Definite	Positive
2009	M	58	1.3	Definite	Positive
2011	F	80	3.8	Definite	Positive
2011	F	71	3.5	Probable	Positive
2015	M	61	2.3	Probable	NT
2018	M	55	2.2	Probable	Positive

NT = not tested.

* Ethics approval was granted from the NH&MRC to collect and disseminate this information.

Table 2: Crude annual rates of sporadic Creutzfeldt-Jakob diseases in Indigenous and non-Indigenous Australians.

	INDIGENOUS			NON-INDIGENOUS		
Year	**Population**	**CJD cases**	**CJD rate**	**Population**	**CJD cases**	**CJD rate**
2006	517,043	2	3.87	20,180,837	37	1.83
2007	549,234	1	1.82	20,478,698	27	1.32
2008	577,366	0	0.00	20,776,559	34	1.64
2009	605,499	1	1.65	21,074,421	30	1.42
2010	633,631	0	0.00	21,372,282	29	1.36
2011	669,881	2	2.99	21,670,143	36	1.66
2012	689,895	0	0.00	21,968,004	32	1.46
2013	718,027	0	0.00	22,265,865	25	1.12
2014	746,160	0	0.00	22,563,727	27	1.20
2015	774,292	1	1.29	22,861,588	29	1.27
2016*	798,365	0	0.00	23,392,542	22	0.94
2017	830,556	0	0.00	23,690,403		
2018	858,688	2	2.33	23,988,264		

* provisional figure
Estimated population based on three referenced years reported by ABS in 2006, 2011 and 2016.

ABSTRACT

Background: Indigenous Australians are of increased risk of developing dementia – Alzheimer's disease and mixed dementia diagnoses are the most common. Whilst prion diseases have been reported in Indigenous peoples of Papua New Guinea and the United States of America, the occurrence and phenotype of prion disease in Indigenous Australians is hitherto unreported.

Aim: Report the incidence rate and clinical phenotype of Creutzfeldt-Jakob disease (CJD) in Indigenous Australians.

Method: Calculation of crude sporadic CJD (sCJD) incidence rates and indirect age-standardisation of all CJD to calculate the standardised mortality ratio (SMR) for the Indigenous Australian population in comparison to the all-resident Australian population, along with analysis of clinical phenotype.

Results: Illustrative case report of an Indigenous Australian from regionally remote Western Australia dying from typical "probable" sCJD two months after disease onset, with Australian National CJD Registry (ANCJDR) surveillance overall ascertaining eight Indigenous Australians dying from sCJD (5 post-mortem confirmed, 3 classified as "probable") with the clinical phenotype similar to non-Indigenous people, including median age at death of 61 years (interquartile range IQR=16 years) and median duration of illness 3 months (IQR=1.6 months). Indigenous Australians with sCJD were geographically dispersed throughout Australia. The calculated overall crude annual rate of sCJD in Indigenous Australians compared to the remainder of the Australian population was not significantly different (0–3.87/million for Indigenous Australians; 0.94–1.83/million for non-Indigenous). The indirect age-standardised all CJD mortality ratio for the Indigenous population for the years 2006 to 2018 was 1.49 (95% CI, 0.75 - 2.98), also not significantly different to the all-resident Australian population.

Conclusion: CJD occurs in Indigenous Australians with the clinical phenotype and occurrence rates similar to non-Indigenous Australians. These findings contrast with a previous report wherein the incidence rate of CJD in a non-Australian Indigenous populations was reported as decreased.

Prion disease in Indigenous Australians

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