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ENCEPHALITIS IN AUSTRALIA, 1979–2006: TRENDS AND AETIOLOGIES

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Abstract

The acute encephalitis syndrome has heralded the emergence of multiple virulent pathogens, including Murray Valley encephalitis, Hendra virus and Australian bat lyssavirus, which may result in severe morbidity and mortality. In Australia, encephalitis is not notifiable and there has been no analysis of trends in encephalitis death rates or causation. Australian Bureau of Statistics mortality and population data for the period 1979–2006 were obtained and cause of death data were extracted using ICD-9 (1979–1998) and ICD-10 (1999–2006) codes that included all relevant encephalitis related diagnoses. Encephalitis-associated deaths were analysed by cause, year, age and gender. Between 1979 and 2006 there were 1,118 encephalitis-associated deaths in Australia. The average annual death rate was 2.3 per 1 million population (range 1.3–3.6). There was a significant decline in encephalitis-associated deaths, particularly due to 'known' pathogens (4.3% decline per year, 95%CI 3.1–5.4%, $P < 0.0001$). The aetiology of 576 deaths were unknown and the proportion of deaths due to 'unknown' encephalitis increased from 47.0% between 1979 and 1992, to 57.2% from 1993 to 2006. Downward trends in encephalitis deaths due to 'known' causes can largely be explained by changes in treatment and prevention methods, particularly for herpes encephalitis (use of acyclovir), and measles encephalitis and subacute sclerosing panencephalitis (measles vaccination). The high proportion of encephalitis deaths from 'unknown' pathogens in Australia highlights the importance of monitoring encephalitis morbidity and mortality with a view to improving pathogen diagnosis and identifying emerging infectious diseases. *Commun Dis Intell* 2009;33:192–197.

Keywords: encephalitis; viral encephalitis; infectious encephalitis; Australia; emerging infectious disease

Introduction

The syndrome of encephalitis frequently presents with fever, headache and an altered level of consciousness,^{1,2} signifying the underlying pathology of an inflammatory process in the brain's

parenchyma.^{1,3,4} Treatment in many cases is supportive, and outcomes often include severe morbidity and even death.

A variety of pathogens cause encephalitis, with herpes simplex virus being the most commonly identified pathogen reported in developed countries.^{5,6} While many encephalitis causing pathogens do not have an effective treatment, herpes simplex virus is a notable exception. Acyclovir significantly reduces the mortality associated with herpes encephalitis^{7,8} from 70% when untreated to approximately 25%–30%.^{2,9,10} Other pathogens, such as rabies and rabies-like viruses, carry a mortality approaching 100%.¹¹

Often no pathogen is identified in people presenting with the encephalitis syndrome.^{12–14} This lack of pathogen diagnosis makes this syndrome a public health challenge, as effective control measures usually depend on an understanding of the underlying epidemiology. In the last 70 years there has been a global increase in emerging infectious diseases (EIDs),¹⁵ including several zoonoses and arboviruses that cause an encephalitis syndrome. Some of these pathogens (such as West Nile virus and Nipah virus) have caused large outbreaks allowing relatively rapid detection and public health action.^{16,17} In Australia the emergence of Australian bat lyssavirus¹⁸ and Hendra virus,¹⁹ which presented with very few cases rather than large outbreaks, highlights the need to adequately investigate all cases of encephalitis, so that novel pathogens are not missed.

Several studies from the United States of America (USA) and Europe have considered the burden of disease associated with encephalitis and trends in causation over time. Khetsuriani et al analysed national data for the USA between 1988 and 1997 to estimate the burden of both viral and non-viral encephalitis hospitalisations.¹⁴ They found that the hospitalisation rate for encephalitis in the USA was 7.3 per 100,000 population and 59.5% did not have a specific cause identified.¹⁴ During the study period a case-fatality rate of 7.4% was recorded.¹⁴

A trend analysis of USA mortality statistics over a longer period showed that the rate of encephalitis related deaths in the USA population between 1979 and 1998 remained stable.²⁰ This was shown to be

largely due to the impact of HIV infection trends while there was a 27% decline in the rate of encephalitis related deaths for non-HIV infected people, which fell from 4.7 per 1 million between 1979 and 1988 to 3.6 per 1 million between 1989 and 1998.²⁰ The authors attributed this latter decrease in part to the widespread use of acyclovir, which resulted in a decline in deaths from herpes encephalitis.²⁰

A review from the United Kingdom (UK) of viral encephalitis hospitalisations over the period 1989 to 1998, found a hospitalisation rate of 1.5 cases per 100,000 population.¹² During the study period, there were 419 deaths, of which 50% were attributed to an unknown viral aetiology.¹² A Finnish study found that a similar proportion (49%) of patients hospitalised with encephalitis between 1967 and 1991 had no aetiology identified.²¹

A recent investigation into the causes of encephalitis hospitalisation in New South Wales between 1990 and 2006 found an average annual rate of encephalitis hospitalisation of 5.2 per 100,000 (range, 4.2–6.7), with 69.6% of the total admissions due to ‘unknown’ pathogens (Huppatz et al, unpublished). The case fatality rate for encephalitis during this time period was 4.6% (Huppatz et al, unpublished).

In Australia, public health surveillance of encephalitis is limited to laboratory confirmed encephalitis cases due to a limited number of specific patho-

gens. There is no active or passive surveillance for encephalitis as a syndrome, and the burden of disease associated with encephalitis is not known. This study aimed to document the burden and trends in encephalitis-associated deaths in Australia between 1979 and 2006.

Methods

Mortality and population data for Australia were obtained for the 28-year period 1979 to 2006 from the Health Outcomes and Information Statistical Toolkit (HOIST), a collection of databases maintained by the Epidemiology and Surveillance Branch of the NSW Department of Health. Datasets used were from the Australian Bureau of Statistics ‘population’ library and ‘death’ library, the latter of which allows data extraction using International Classification of Diseases (ICD) codes. Encephalitis-associated deaths were extracted using ICD-9 (1979–1998) and ICD-10 (1999–2006) codes. To maximise comparability, data prior to 1979, which used ICD-8 codes, were not included and data after 2006 were not included, as it was incomplete at the time of analysis.

An encephalitis-associated death was defined as a death for which the primary cause of death was an ICD-9 or ICD-10 code for encephalitis (Table). These codes were further classified by investigators as ‘known pathogen’ or ‘unknown pathogen’ codes (Table).

Table: ICD-9 and ICD-10 codes most frequently used for primary cause of death for encephalitis-associated deaths, Australia, 1979 to 2006

Primary cause of death ICD Code (ICD 9; ICD 10)	Number of deaths	% of total
All encephalitis deaths	1,118	100
Known pathogen codes	542	48.5
Herpesviral encephalitis (54.3; B00.4)	300	26.8
Subacute sclerosing panencephalitis (46.2; A81.1)	81	7.2
Measles – postmeasles encephalitis (55.0; B05.0)	44	3.9
Late effects/sequelae of viral encephalitis (139.0; B94.1)	26	2.3
Zoster encephalitis (B02.0 in ICD 10)	17	1.5
Australian encephalitis (0.62.4; A83.4)	13	1.2
Other specified non-arthropod-borne viral diseases of the central nervous system (49.8; A85.8)	13	1.2
Listerial meningitis and meningoenkephalitis (A32.1 in ICD 10)	11	1.0
Varicella encephalitis (052.0; B01.1)	8	0.7
Meningococcal infection – meningococcal encephalitis (36.1 in ICD 9)	6	0.5
Other known pathogen codes (= 10 codes)	23	2.1
Unknown pathogen codes	576	51.5
Encephalitis, myelitis, and encephalomyelitis – unspecified cause of encephalitis (323.9; G04.9)	327	29.2
Unspecified non-arthropod-borne viral diseases of the central nervous system or unspecified viral encephalitis (49.9; A86)	238	21.3
Encephalitis, myelitis, and encephalomyelitis – other cause of encephalitis (323.8; G04.8)	11	1.0

Encephalitis-associated deaths were analysed (using SAS version 8) by aetiological category, year, age and gender. Death rates for total, and 'known' and 'unknown' encephalitis deaths were calculated for individual years using mid-year population data from the Australian Bureau of Statistics. Negative binomial regression was used to analyse trends in the crude death rate of all encephalitis deaths and those due to 'known' and 'unknown' aetiology. The regression was repeated with adjustment for population age groups over time.

To compare death rates over time, the average age-specific death rates for the periods 1979–1985, 1986–1992, 1993–1999 and 2000–2006 were calculated using the average number of deaths in each 10-year age group during each time period and the population in the mid-point of each time period. All rates were expressed per 1 million population and the 7 year time periods were chosen to manage small numbers in shorter time periods. Small numbers of deaths in each category precluded determination of rates for individual causes. The annual number of deaths due to the most commonly identified causes were compared over the time periods specified above.

Ethical approval was given by the Hunter New England and the Australian National University Human Research Ethics Committees.

Results

From January 1979 to December 2006, there were 1,118 deaths in Australia with a primary cause of death recorded as encephalitis. The average number of deaths per year was 40.0 (range=26–52). The aetiology of 576 deaths (51.5% of total deaths) were unknown. During the 28 year study period the proportion of deaths due to 'unknown' encephalitis increased from 47.0% between 1979 and 1992 to 57.2% from 1993 to 2006.

The average annual rate of encephalitis deaths was 2.3 per 1 million (range 1.3–3.6). Males accounted for 51.7% of encephalitis deaths.

There was a decline in the crude death rate of all encephalitis deaths and those in the 'known' category (Figure 1) between 1979 and 2006. A negative binomial regression model demonstrated a significant decline of 2.3% per annum in the total encephalitis death rate (95%CI 1.6–3.2%, $P<0.0001$) and a decline of 4.0% (95%CI 3.0–5.0%, $P<0.0001$) in 'known' encephalitis deaths. There was no significant decline in the 'unknown' encephalitis deaths (0.72% decline, $P=0.12$) (Figure 1). When adjusted for age, the decline for total deaths was 3.0% per annum (95%CI 2.1–3.8%, $P<0.0001$) and for 'known' deaths was 4.3% (95%CI 3.1–5.4%,

$P<0.0001$). A small decline was found for the 'unknown' death category (1.5% decline, 95%CI 0.4–2.7%, $P<0.01$).

Figure 1: Death rate (per 1 million population) from total encephalitis, 'known' and 'unknown' causes, Australia, 1979 to 2006

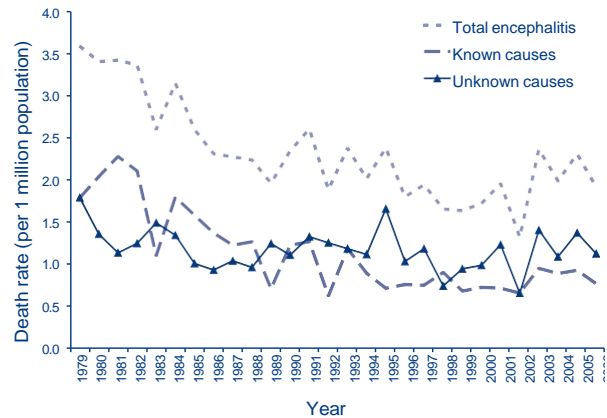
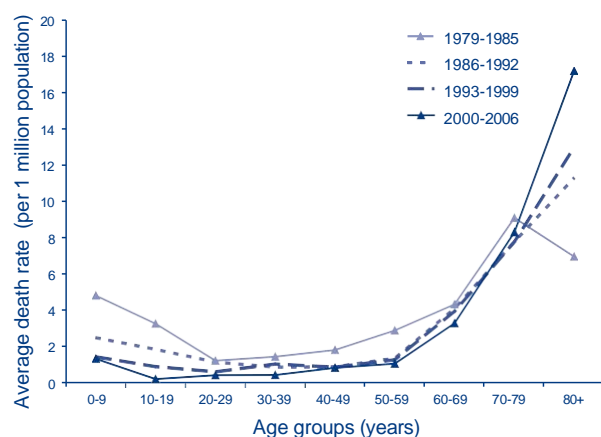


Figure 2 presents the average age-specific death rates for the time periods 1979–1985, 1986–1992, 1993–1999 and 2000–2006. The death rate in all age groups below 60 years decreased, with the most marked reduction in the younger age group (0–9 years). In the oldest age group (80+ years) the death rate increased over time.

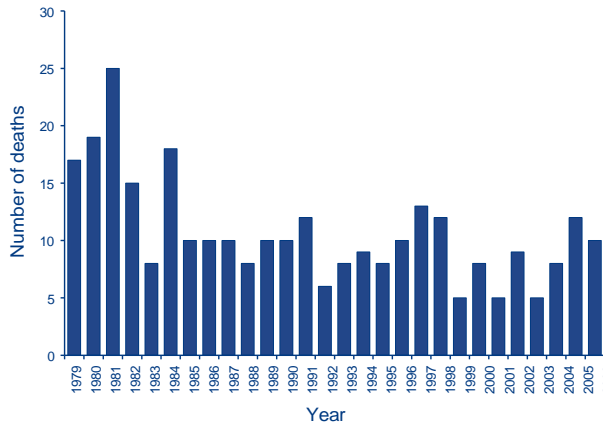
The most frequently identified cause of encephalitis was herpes simplex virus infection, which accounted for 300 deaths (26.8%) (Table). The average number of deaths decreased from 16.0 per year between 1979 and 1985, to 9.4 per year between 1986 and 1992 (Figure 3). Subsequently, the average number of

Figure 2: Trend in average death rates (per 1 million population) from encephalitis, Australia, 1979 to 2006, by 10 year age groups



deaths from herpes encephalitis remained relatively constant (9.3 per year, 1993–1999 and 8.1 per year, 2000–2006).

Figure 3: Number of herpes encephalitis deaths per year, Australia, 1979 to 2006

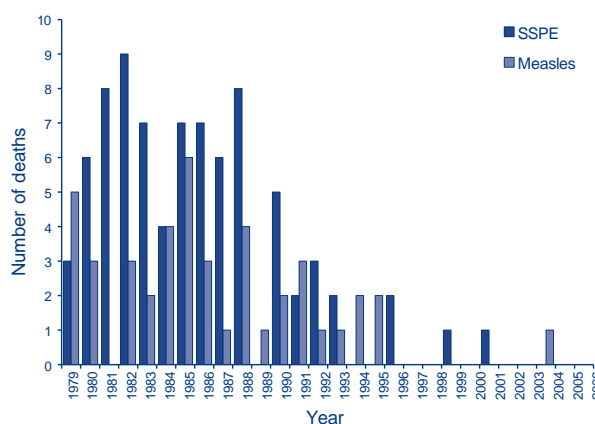


Over the study period, there were 81 deaths (7.2% of total encephalitis deaths) from subacute sclerosing panencephalitis (SSPE) (Table), with the average number of SSPE deaths decreasing from 6.3 per year between 1979 and 1985, to 4.4 per year in 1993 to 1999 (Figure 4). After 1999, the average deaths per year from SSPE was less than one. Measles encephalitis showed a similar decline (Figure 4), decreasing from 3.3 deaths per year (1979–1985) to 2 deaths per year (1986–1992), to fewer than 1 death per year after 1992.

Discussion

There were a total of 1,118 deaths associated with encephalitis in Australia in the 28-year period, 1979 to 2006, with an annual death rate of 2.3 per

Figure 4: Number of subacute sclerosing panencephalitis and measles encephalitis deaths per year, Australia, 1979 to 2006



1 million population (range 1.3–3.6). As 51.5% did not have a pathogen diagnosis, this raises questions about the potential aetiologies of encephalitis deaths in Australia. The increase in the proportion of deaths due to ‘unknown’ encephalitis from 47.0% to 57.2% over the study period, provides further motivation for improving pathogen identification. The wider availability of polymerase chain reaction confirmation for herpes simplex encephalitis over the study period to explain cases that may have previously been coded as ‘unknown’ may mean that there has been an even greater relative increase in encephalitis due to unknown causes.

The changes in death rates by age group over time are likely to represent improvements in medical care during the study period. The decrease in death rates observed in children, aged 0–9 years is likely to be in part due to improvements in paediatric intensive care.^{22,23} Similarly, the increase in death rates seen in older people (>60 years) may be the result of Australia’s ageing population living longer due to improvements in treatment for chronic diseases such as cancer, heart disease and diabetes,²⁴ with older people being more prone to immunosuppression and hence susceptible to diseases such as herpes encephalitis, *Listeria meningoenephalitis* and zoster encephalitis. Unfortunately, the small number of deaths from individual pathogens precludes further detailed analysis. It is worth noting that an improvement in death rate may not necessarily reflect improvement in morbidity for some causes of encephalitis that have important neurological sequelae.

Australia has seen a small decline in the death rate (3.0% decrease) from encephalitis, largely due to a decline in the ‘known’ causes (4.3% decrease) explained by changes in medical care and preventative health activities for two of the more common causative organisms. The observed decline in herpes encephalitis can be attributed to the increasing use of acyclovir in the late 1980s.²⁵ A similar finding was reported from the USA between 1978 and 1998.²⁰

The decline in deaths due to measles encephalitis (Figure 4) can be attributed to the increasing uptake of measles vaccination throughout the 1980s, accelerated by Australia’s first national measles vaccination campaign in 1987.²⁶ SSPE is a rare complication of measles and is a neurodegenerative disorder caused by the persistence of a defective measles virus in the central nervous system.²⁷ SSPE has a reported incubation period of 6–8 years following infection with measles,²⁸ so it is not surprising that a decline in SSPE was observed in the 1990s. The near disappearance of SSPE and measles encephalitis reflects the success of immunisation with measles vaccine in Australia.

The death rate due to encephalitis in Australia is lower than estimates from the USA (2.3 per 1 million in Australia versus 5.1–5.3 per 1 million), however this may in part be due to a difference in study methodology, as the USA study included deaths for which encephalitis was listed anywhere on the death record, whereas our study included only those deaths for which encephalitis was the primary cause.²⁰ In addition, the USA had a higher rate of HIV infection, which accounted for many more deaths in that study. The non-HIV related encephalitis death rate in the USA decreased between 1979 and 1988, and 1989 to 1998, from 4.7 to 3.6 per 1 million population.

Interestingly, the USA study found a much higher rate of ‘unknown’ encephalitis deaths (81.5–86.2%), compared to Australian data. Again, it is difficult to know if this may be a consequence of the data collection, with less likelihood of a pathogen being recorded if encephalitis was not the primary cause of death. Our data showed a proportion of ‘unknown’ encephalitis deaths more in keeping with the findings from the UK, which found 50.0% of encephalitis deaths were from an unknown aetiology.¹²

There are several limitations associated with using ICD coded death certificate data to estimate disease burden. During the time period of this study, the ICD coding system changed with several new encephalitis-associated codes appearing in ICD-10 (1999–2006) that had not been present in ICD-9 (1979–1998), such as those for zoster encephalitis and *Listeria meningoenephalitis*. Patients with these conditions prior to 1999 must have been coded using different codes, however, it can not be definitively determined which were used. Fortunately, such patients account for a small proportion (<3%) of all encephalitis deaths (Table). In addition to limitations due to the ICD coding changes, there may have been differences in diagnostic criteria for encephalitis used by clinicians during the period 1979–2006. Finally, because we used only primary cause of death data, we may have underestimated encephalitis-associated deaths, particularly in people with co-existing medical conditions, who died from another cause (for example a myocardial infarction) while they were ill with encephalitis.

Globally, there has been a dramatic increase in recognition of EIDs since 1940.¹⁵ Many EIDs have been due to zoonotic or arboviral pathogens¹⁵ and presented with outbreaks of an encephalitis syndrome, including West Nile virus, Hendra virus, Nipah virus, Murray Valley encephalitis and Japanese encephalitis.²⁹ The high proportion (51.5%) of encephalitis deaths from ‘unknown’ pathogens in Australia raises questions about our capacity to detect novel pathogens presenting as encephalitis. This highlights the importance of monitoring trends in encephalitis morbidity and mortality in Australia

with a view to improving pathogen diagnosis for encephalitis and rapidly identifying novel emerging encephalitis-causing pathogens that demand public health action.

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