Short Title: Long term outcomes of Murray Valley encephalitis cases in Western Australia – what have we learnt?

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Abstract

Background

Murray Valley encephalitis virus (MVEV) is a mosquito-borne flavivirus that causes encephalitis in some cases of infection. It is endemic in Northern Australia and cases occasionally occur in South Eastern Australia. The long-term sequelae of MVEV infection have not previously been well-described.

Aim

To investigate the long-term sequelae of MVEV infection.

Methods

This was a descriptive case series of all clinical MVEV infections using data linkage and standard surveys. Hospital admissions, emergency department, psychiatric outpatients and mortality data were obtained. We attempted to follow up all 53 cases of MVEV clinical infection that occurred in WA from 1978 to 2011 inclusive. Two cases opted out of the study.

Results

We followed up 39 surviving cases. Seven of the nine with paralysis or paresis were under five years and they fared worse than other patients, requiring lengthy hospitalisation (median duration 133 days). Two died due to complications of

quadriplegia following a total of 691 days in hospital. Nine surviving patients, including two with non-encephalitic illness, required care for depression and other psychiatric conditions following MVEV infection. Two patients who were discharged with neurological sequelae had no further documented hospital occasions of service but reported ongoing challenges with cognitive dysfunction and inability to work.

Conclusions

This is the first study of long-term outcomes of Murray Valley Encephalitis that included cases with no obvious sequelae at discharge. In spite of the small numbers involved, the study demonstrated the significant medical and social burden due to MVEV in Australia.

Key Words

Murray Valley encephalitis virus;

Flavivirus;

encephalitis, arbovirus;

sequelae;

Australia

Introduction

Murray Valley encephalitis virus (MVEV) is a mosquito-borne flavivirus that causes encephalitis in a small proportion of infected individuals. Human infections occur in Australia and New Guinea.[1] Up to 1974, when there were 58 documented cases,[1]

MVEV encephalitis occurred as large outbreaks of MVEV infection in Eastern Australia, but since then the majority of symptomatic human infections have occurred in Western Australia (WA), mostly in outbreaks associated with heavy rainfall events, the most recent of which occurred in 2011.[2,3] Activity in Eastern Australia was confined to sporadic cases in Queensland, until cases occurred in New South Wales in 2008 and 2011 and in South Australia in 2011.[3]

Neurological disease of varying severity develops in some infected individuals following a non-specific prodrome of fever and headache, with 1/150 to 1/1000 progressing to encephalitis. Non-encephalitic symptomatic cases experience the clinical prodrome and headache but do not progress to significant neurological disease. Symptomatic disease occurs in 1/150 to 1/1000 infections. The case-fatality rate for encephalitis is between 15 and 30% and short-term neurological sequelae occur in 30-50% of survivors,[2] but little is known about long-term sequelae.

Several follow up studies have been undertaken of patients with illness due to the closely related West Nile virus (WNV) and Japanese encephalitis virus (JEV), both of which cause a similar clinical illness to MVEV.[4-13] Follow up studies of JEV encephalitis in children living in endemic areas[4,8] found that the neurological deficit could persist for 27 years or longer, and late sequelae such as lower IQ and seizures were seen.[4,8] In contrast, a large study of adult JEV cases in India found that most cases resolved.[7]

Acute WNV cases tend to be milder than other flavivirus infections with rates of encephalitic illness increasing with age.[5,14] Despite this, a number of patients with

WNV encephalitis develop cognitive and psychological sequelae in the longer term, including memory loss, fatigue, anorexia and depression. These sequelae also occur in patients with WNV fever but no neuroinvasive disease.[5,6,10,12,13] However, this is not a consistent finding, with another study[11] finding that physical and mental outcomes following WNV encephalitis returned to US population norms approximately one year post-infection.

A 1996 study followed up 16 MVE cases for up to 9 years (median three years),[15] but this is the first study to examine the long-term impact of the broader spectrum of clinical MVEV infection, including patients with apparent full recovery. This is important in determining of the true burden of MVEV infection in Australia and providing better prognostic information for patients and family members.

Methods

This is a descriptive case series of all surviving clinical cases of MVEV infection in WA who were infected from 1978 to 2011 inclusive. Data were retrieved from patient records and databases held within the WA Department of Health, and via questionnaires.

Data about laboratory-confirmed clinical MVEV infections 1978, when clinical case were first recognised in WA, were obtained from PathWest Laboratory Medicine WA (PathWest) PathWest undertakes all of the testing for suspected MVEV infection within WA and information was retrieved from clinical and laboratory data held in clinical files by one of us (D Smith). The criteria for laboratory confirmation of

MVEV infection have been described previously.[16] Briefly, serological testing was performed by an in-house haemagglutination inhibition assay, a monoclonal antibody epitope blocking enzyme immunoassay, and an IgM in-house indirect immunofluorescence immunoassay. From 2000, molecular testing was performed using an in-house nested or tandem reverse transcriptase PCR using primers for the MVEV envelope and NS5 gene, respectively.[17]

Additional information about the early clinical outcome of some cases was obtained from published reports.[18,19] MVEV infection became a notifiable disease in WA in 1996, and data after 1996 were cross-checked for completeness against the WA Notifiable Diseases Surveillance System. No additional cases were identified. Cases were identified as Aboriginal if noted as such by the attending clinicians.

Identifying information was provided to the WA Health Data Linkage project team for initial data matching with the WA Mortality Register and the Australian Electoral Roll (to obtain addresses for survivors). Letters inviting participation in the study were sent to surviving cases at the addresses provided, or, if that was not available, to the most recent address from PathWest records. Respondents could opt out of the study or participate in a survey either over the telephone or by completing a written questionnaire. Non-respondents were sent a reminder letter one month after the initial mail out.

Two survey tools were used – SF36v2 questionnaire (QualityMetrics) and a post-encephalitis quality of life survey used in the United Kingdom.[20] The SF36v2 questionnaire data were scored using the QualityMetrics scoring tool and comparisons were made to the Australian SF36 population norms.[21]

De-identified linked data from the WA Hospital Morbidity Data System (WAHMDS), the WA Emergency Department Data Collection (WAEDDC), the WA Mortality Data (WAMD) and the WA Mental Health Ambulatory Data Collection (WAMHADC) were obtained for all cases for which a match was available and who did not opt out. The WAHMDS contains information about all private and public hospital admissions throughout WA. The WAEDDC includes information about all occasions of service provided by emergency departments in WA from 2002 onwards. The WAMHADC contains information about all public ambulatory mental health occasions of service and the WAMD contains information about all deaths in WA, including the cause of death. Data were linked using a common linkage code. The data obtained for each case were from the period from the initial hospital admission for MVE infection until 30 December 2013.

The data were analysed using SPSS v22. We considered subsequent admissions to be related to the initial MVEV infection if they were being treated for complications of the infection such as rehabilitation for quadriplegia, if a past history of encephalitis was included in their diagnosis codes or if the admission/occasion of care was related to mental health. We did not consider admissions for other reasons to be related to the MVEV infection and therefore did not include these in the number of admissions or the duration of hospitalisation. We also noted any other diagnosis codes that may have contributed to the admission.

This study was approved by the WA Department of Health Human Research Ethics Committee (2013/37) and the Curtin University Human Research Ethics Committee (HR179/2013).

Results

There were 53 cases of MVEV infection diagnosed in WA from January 1978 to December 2011. Of these, nine (17%) were known to have died in the acute phase of their MVEV encephalitis illness, and three further deaths were identified from the WA Mortality Register.

Data were not accessed for two cases who opted out, and linked data were available for 44 (83%) of the remaining 51 cases. Of these, 21 were Aboriginal, 22 were non-Aboriginal, and one unknown. Data were available for 20 of the 22 cases (90%) aged 16 and under at onset, and 24 of the 31 cases (77%) aged over 16 at onset. Linked data were available for all of the nine 2011 cases.

The initial outcome of the 44 cases is shown in Table 1. The outcome of the initial presentation of two cases was unknown as they were transferred to a hospital interstate after two days or less.

Longer-term outcomes based on linked and survey data of the 39 cases who survived their initial presentation were as follows:

a) Cases with limb paralysis (9 cases) (Table 2)

Of the nine cases, seven were aged less than five years at onset and two were adults. Six of the children were Aboriginal. Two of the cases, both children, were transferred to an interstate hospital early in their illness. Of the remaining seven cases, the median duration of hospital admission for their first admission with MVE was 96 days (range 21 – 718 days) with a median total duration of admission of 133 days

(range 21 – 718 days). Two cases subsequently died from complications of quadriplegia, one 10 years and the other 20 years after onset.

b) Cases with other neurological sequelae (15 cases) (Table 3)

Of the 15 cases, three were aged less than five years at infection onset and the remainder were adults. Five cases were Aboriginal. Two cases were non-encephalitic of which one was not admitted to hospital. One case was discharged to an interstate hospital. Of the other 13 cases, the median duration of the first hospital admission was 27 days (range 1-200 days) with a median total duration of admission of 36 days (range 1-814 days). Ten cases received ongoing episodes of care relating to cognitive impairment, pain and/or mental illness. This included two who developed schizophrenia, one of whom committed suicide at age 22 years.

c) Cases with no apparent ongoing neurological sequelae (15 cases)

Four of the 15 cases were less than five years of age at the onset of MVE; two were children between 5 and 10 years and the remainder were adults. Eight were Aboriginal. The median duration of the first hospital admission was 11 days (range 0 – 27 days) and there were no further MVE-related admissions.

Data received from patient questionnaires

We attempted to contact 41 surviving individuals, and received responses from 11 (including two people who opted out). Twelve letters were returned unopened, there was no response to twelve letters and addresses were not available for the remaining six people. Questionnaire data were available for eight respondents (one of the

respondents did not complete the questionnaires). Of these eight, two had non-encephalitic illness, three had encephalitis that resolved during the acute admission or the outcome was unknown, and three had neurological sequelae after the acute phase.

a) Cases with neurological sequelae

One of the three cases had two admissions for depression following their encephalitis. This case reported having depression for two years following the initial illness (Table 3, case 8) but their SF36 score indicated that they now had average or above average physical and mental health. Of the other two, one (Table 3, case 10) described significant disability following the encephalitis; being unable to work, and describing problems with cognitive function, mood and emotions, and considerable grief for the loss of his previous life. This individual had above average physical health and significantly below average mental health SF36 scores. The other, (Table 3 case 11) had a prolonged hospital admission in the acute phase (200 days), but no further admissions. He retired young and is uncertain about whether or not he can perform paid work. He described problems with cognition and emotional instability with poor coordination and balance following the encephalitis. He also expressed grief for the loss of his previous life. He had average physical health and below average mental health SF36 scores.

b) Encephalitic cases that resolved during the acute admission

All three cases had SF36 mental health scores that were average or above average. One case had a poorer physical health score than average for her age. The remaining two had physical health scores that were average for their age. Of the three cases, one described no ongoing problems due to MVEV infection and the other two described

mild cognitive problems such as difficulties with problem solving, coordination and reading and answering questions (Table 3, cases 5 and 15). One case said that they were unable to work for two years following their illness (Table 3, case 5).

c) Non-encephalitic illness

One case described symptoms of depression relating to MVEV infection (Table 3, case 9). Their SF36 mental health score was below average and physical health score was average. The other (Table 3, case 13) described herself as "very lucky", but experienced headaches, nausea and vomiting for 18 months post-MVEV infection. Both her physical and mental health scores were average.

Discussion

We found that there were at least two additional deaths attributable to MVEV in WA, increasing the case fatality rate in WA from 17% to 21%. The deaths, both in people under 25 years, followed a total of 691 bed-days or more. We also found that more severe cases required hospitalisation for long periods, thus incurring significant financial, social and psychological costs to the individual, their family and the health system. This was exemplified by cases 8 & 10 in Table 3, young men without obvious residual physical disability, but impaired work and social function and perceived loss of the life they had hoped to lead.

The cases with the most severe outcomes were those that were complicated by paralysis, and these were predominantly children under the age of five years at onset.

This contrasts with WNV encephalitis where children usually had less severe disease.[14,22]

A number of MVEV cases experienced symptoms of mental illness following their illness. While depression is common in the community (around 11% of 18 to 65 year olds reported experiencing a mild, moderate or severe depressive episode in their lifetimes),[23] those who responded to the questionnaire linked their depression to MVEV infection. Long term follow up studies of WNV infection found that over 20% of cases experienced depression post-infection,[5,6,10,12] and in one study 26% of cases described depression five years following infection.[12] Interestingly, these depressive symptoms were not consistently related to the severity of the acute illness,[6] similar to our findings.

Two cases infected as children developed schizophrenia later in life. Our small sample size does not allow an estimation of whether this association is significant. Other studies have found an association between childhood viral central nervous system infections and the onset of schizophrenia in adults but with a low relative risk.[24-26]

Long term follow up studies of WNV and JEV disease have predominantly focussed on neuropsychological and physical functioning rather than subsequent hospital admissions.[4-13] Most follow up studies of WNV infection found, in addition to depression, that other symptoms, such as cognitive dysfunction, memory loss and poor physical health were not uncommon up to eight years post-infection, with higher

rates amongst those cases initially presenting with neuro-invasive disease. [5,6,10-12] This is consistent with our findings in relation to MVE.

There are limited data on the economic impact of viral encephalitis, but the economic impact of cerebral palsy, a disease with a range of neurological outcomes, has been well documented.[27-29] An Australian study estimated the financial average cost to be $43,431 per person per annum in 2008 dollars, increasing to $115,000 per person per annum if the value of lost wellbeing is included.[29] The lifetime cost of cerebral palsy in the USA in 1992 was estimated to be USD 503,000.[28] The paralysis experienced by MVEV cases with severe disease would be likely to incur similar economic costs.

There were a number of limitations with our study. The low incidence of MVEV clinical disease necessitated including cases infected over a time period of 34 years. We expect that we missed some non-encephalitic MVEV infection, but encephalitic illness is very likely to have been captured as they require hospitalisation. The quality of data from admissions early in the study period was limited due to minimal information having been recorded for each case. Also, as MVEV occurs in remote regions of WA, and cases were dispersed over a large geographical area, we had great difficulty contacting the cases and direct examination of cases was not possible. The long period of follow up, exacerbated by having a high proportion of cases living in remote Aboriginal communities where postal addresses are often not available, resulted in very few respondents to our questionnaire. We therefore had to rely on data linkage for follow up of our cases but this did not provide information about all cases. This highlights some of the challenges with data linkage, particularly amongst Aboriginal cases in remote settings where name changes are not infrequent.[30] A very

low response rate for the questionnaire was also a limitation of the study, and probably occurred due to the long period of follow up, exacerbated by having a high proportion of cases living in remote Aboriginal communities where postal addresses are often not available. Because of the potential for bias the responses cannot be considered to be representative, but the survey is still a useful source of qualitative information allowing further interpretation of the data from the patients' medical records, particularly for those with initially less serious disease, a common characteristic of the respondents.

Due to the geographical distribution of MVEV in WA, many of the cases were likely to have come from disadvantaged social and economic circumstances. It may be difficult to distinguish these impacts from the impacts of MVE. However, two studies using SF36 amongst Australians found that mental and physical health was not lower amongst people in the lowest SEIFA quintiles or in remote areas compared to the rest of the population.[31,32]

Despite the limitations of our study, we were able to demonstrate that clinical MVEV infection in WA has significant physical, mental and social repercussions beyond the reported acute case fatality and morbidity rates. These data indicate that, as for JEV and WNV encephalitis, longer term studies beyond the acute admission are required to assess the true burden of MVEV infection. Furthermore, ongoing assessment and appropriate support, even for apparently mild cases, may help reduce the psychological and social impact of this disease.

Conclusions

This is the first study of long-term outcomes of MVE that includes cases with no obvious sequelae at discharge. In spite of the small numbers involved, the study demonstrated the significant medical and social burden due to MVE in Western Australia.

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Table 1. Summary of 44 MVEV cases for whom linked data were available

Initial Outcome of MVEV infection	**Number (%)**
Fatal acute illness	5 (11.3)
Limb paralysis/paresis	9 (20.5)
Cognitive dysfunction, behavioural difficulties, dysphagia, ataxia	12 (27.3)
Recovered without apparent neurological sequelae	16 (36.4)
Unknown	2 (4.5)
TOTAL	**44**

Table 2 – Cases with limb paralysis/paresis on longer-term outcome[a]

Case	Age at onset (years)	Year of onset	Last admission year	Number of Admissions	First admission duration (days)	Total admission duration (days)	Outcome after first discharge	Long-term outcome
1	7 mnth	1978	1998	>12	1	592[b]	Discharged to interstate hospital. Quadriplegia/quadraparesis	Died 1998 from complications of quadriplegia
2	5 mnth	1979	1999	8	35	79	Spastic quadraparesis.	Spastic quadriplegia continued. One episode of acute respiratory failure. Wheelchair-bound.
3	4 mnth	1981	1982	3	96	119	Spastic quadraparesis.	Uncertain longer term. No further hospital admissions/occasions of care recorded after 1982
4	5 mnth	1984	1993	9	29	99	Spastic quadraparesis, intellectual disability	Died 1993 from respiratory failure
5	55	2000	2000	1	718	718	Quadriplegia, dysphagia, tracheostomy (ventilator dependent). Transferred to hospital in Victoria	Unknown (moved interstate)
6	4	2009	2012	5	102	133	Spastic quadriplegia	Spastic quadriplegia continued. Complicated by muscle contractures
7	29	2011	2011	1	226	226[b]	Quadriplegia, speech, brain disorder, limb deformities.	Ongoing rehabilitation in Australia and overseas
8	2	2011	2013	7	2	252[b]	Paraplegia, required gastrostomy. Transferred interstate initially	Paraplegia continued. Complicated by muscle contractures
9	2	2011	2011	1	21	21	Hemiplegia, ataxia	Three subsequent Emergency Room presentations for musculoskeletal problems

[a] Cases were classified as having quadriplegia or paraplegia only where that was specifically recorded in clinical notes. Otherwise they were classified as having quadraparesis or paraparesis.

[b] Total duration of hospitalisation uncertain because a portion of the hospital care occurred interstate or overseas. This total includes only hospital admissions in WA

Table 3 – Cases with other neurological sequelae on longer-term outcome

Case	Onset age (years)	Year of onset	Last admission year	Number of admissions	First admission duration (days)	Total admission duration (days)	Initial outcome	Long-term outcome
1	20	1978	1978	1	136	136	Short term memory loss, upper limb weakness	Multiple mental health episodes of care, mild cognitive impairment
2	4	1978	1995	4	24	68[a]	Behavioural difficulties. Discharged to interstate hospital	Schizophrenia/psychosis, suicide 1996
3	2	1981	2013	>8	13	814	Speech delay and hearing difficulties	Schizophrenia/psychosis, multiple drug abuse, multiple drug overdoses, incarceration
4	26	1981	1983	5	27	36	Back and leg pains	Four additional admissions for back pain
5	24	1993	1993	1	2	2[a]	No record. Was transferred interstate after 2 days in hospital.	Was unable to work for two years after the initial illness. Continues to have mild cognitive difficulties. No further related admissions/occasions of service
6	10 mnth	2000	2002	3	57	66	Bulbar palsy and irritability	Scholastic developmental disorder noted at age 5
7	64	2000	2002	3	33	68	Resolving cognitive dysfunction, depression, polyneuropathy.	266 mental health episodes (depression, alcohol, drug abuse)
8	32	2000	2002	3	9	12	Resolving short-term memory loss, dizziness, lethargy.	Two psychiatric admissions in 2000 and 2002. Depression now resolved. Mild cognitive problems
9	55	2000	-	0	0	0	No hospital admission - non-encephalitic	No further related admissions/occasions of service. Described having depression following MVEV infection.
10	26	2002	2002	1	16	16	Personality change, cognitive disorder and flattened affect	Unable to work, problems with cognitive function, mood and emotions.

								No further related admissions/occasions of service.
11	49	2009	2009	1	200	200	Initial admission included dysphasia, dysphagia, cognitive dysfunction, convulsions. Prolonged admission for rehabilitation. No outcome following rehabilitation was recorded	Retired young and unsure if he can work. Problems with cognition, emotional instability, coordination and balance. No further related admissions/occasions of service
12	42	2011	2011	2	29	36	Not recorded	Seven days of rehabilitation for ataxia post initial discharge. 3 subsequent psychiatric outpatient presentations in 2011 and 2013
13	50	2011	2011	1	1	1	Non-encephalitic - headaches	Three Emergency Room presentations for 'nervous system disorder'. Described having headaches, nausea and vomiting for 18 months post MVEV infection
14	25	2011	2011	1	22	22	Not recorded	Two Emergency Room presentations for nervous system disorder/headache 2012
15	67	2011	2011	1	32	32	Not recorded	Difficulties in memory, coordination and problem-solving. No further related admissions/occasions of service

[a] Total duration of hospitalisation uncertain because a portion of the hospital care occurred interstate or overseas.