

Neurological disease caused by flavivirus infections



Tristan Gibbs

Department of Microbiology,
PathWest Laboratory Medicine WA
(LMWA), Queen Elizabeth II (QEII)
Medical Centre, Hospital Avenue,
Nedlands, WA 6009, Australia
School of Medicine, Faculty of
Health and Medical Sciences,
University of Western Australia,
35 Stirling Highway, Crawley,
WA 6009, Australia
Email: tristan.gibbs@health.wa.gov.au



David J Speers

Department of Microbiology,
PathWest Laboratory Medicine WA
(LMWA), Queen Elizabeth II (QEII)
Medical Centre, Hospital Avenue,
Nedlands, WA 6009, Australia
School of Medicine, Faculty of
Health and Medical Sciences,
University of Western Australia,
35 Stirling Highway, Crawley,
WA 6009, Australia

The *Flavivirus* genus contains dozens of species with varying geographical distributions. Most flavivirus infections in humans are asymptomatic or manifest as a non-specific febrile illness, sometimes accompanied by rash or arthralgia. Certain species are more commonly associated with neurological disease and may be termed neurotropic flaviviruses. Several flaviviruses endemic to Australia and our near northern neighbours are neurotropic, such as Murray Valley encephalitis virus, West Nile (Kunjin) virus and Japanese encephalitis virus. Flavivirus neurological disease ranges from self-limiting meningitis to fulminant encephalitis causing permanent debilitating neurological sequelae or death. The recent Zika virus outbreak in South America has highlighted the dramatic effects of flavivirus neurotropism on the developing brain. This article focuses on the neurotropic flaviviruses endemic to Australia and those of international significance.

Neurotropic flaviviruses of Australia

Murray Valley encephalitis virus (MVEV) and Kunjin virus (WNV_{KUN}), a clade of West Nile virus (WNV), are endemic to Australia, causing sporadic neurological disease and occasionally outbreaks associated with increased mosquito activity during the wet season. Both viruses are maintained in mosquito-waterbird cycles primarily in northern Western Australia, the top end of the Northern Territory and possibly northern Queensland^{1,2}. However, heavy rainfall with flooding may lead to spread of these viruses into normally arid areas, carried by waterbirds³. There were several outbreaks of MVEV on the east coast of Australia in 1951 and 1974 along the Murray-Darling River basin that gave the virus its name.

The last widespread outbreak of MVEV occurred in 2011, with 17 cases across WA, NT, SA and NSW.

It is estimated that between 1 : 150 and 1 : 1000 of those infected with MVEV will develop encephalitis, which may manifest as seizures, altered mental state, focal neurological abnormalities, coma, or flaccid paralysis¹. Characteristic thalamic involvement may be seen on brain MRI (Figure 1) but the changes may take several days to develop. The case fatality rate is 15–30% with long-term neurological sequelae occurring in 30–50%⁴. WNV_{KUN} follows a similar

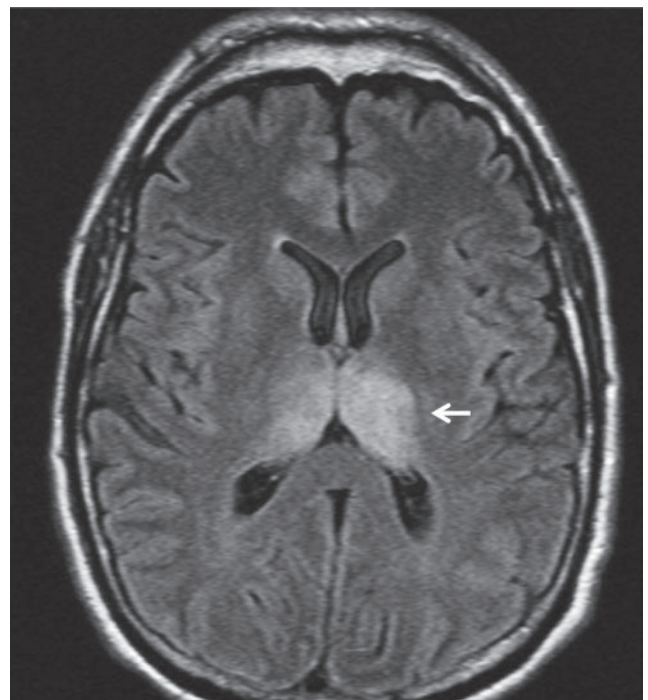


Figure 1. MRI brain scan of Murray Valley encephalitis 8 days after illness onset. FLAIR MRI scan demonstrating increased signal intensity in the thalami (arrow).

epidemiological and clinical pattern to MVEV, although neurological disease tends to be milder, with no recorded cases of fatal infection³.

The public health management of MVEV and WNV_{KUN} includes surveillance using antibody testing in sentinel chicken flocks and, more recently, detection of viral RNA in trapped mosquitoes. These data serve as an early warning system for increased flavivirus activity

and potential increased risk of human cases to prompt timely public health advice to the public for mosquito avoidance measures and to medical services for appropriate diagnostic test ordering⁵.

Neurotropic flaviviruses outside Australia

The most important neurotropic flaviviruses for human health worldwide are Japanese encephalitis virus (JEV), WNV and Zika

Table 1. Distribution, clinical features, vectors and vertebrate hosts of selected neurotropic flaviviruses.

Flavivirus	Geographical distribution	Incubation period	Neurological manifestations	Arthropod vector	Vertebrate host(s)
Murray Valley encephalitis virus	North-western Australia Occasional outbreaks in other parts of Australia Papua New Guinea	5–15 days	Seizures, altered mental state, focal neurological abnormalities, coma, acute flaccid paralysis	<i>Culex annulirostris</i> ^{19,20}	Waterbirds
West Nile virus	Asia Europe Africa Middle East North and South America	2–14 days	Meningitis, encephalitis, altered mental state, extrapyramidal symptoms, focal neurological abnormalities, acute flaccid paralysis	<i>Culex pipiens</i> , other <i>Culex</i> spp.	Birds
WNV-Kunjin virus clade	North-western Australia Occasional outbreaks in other parts of Australia Papua New Guinea	5–15 days	Similar to Murray Valley encephalitis but usually milder	<i>Culex annulirostris</i>	Waterbirds
Japanese encephalitis virus	Asia Western Pacific islands	5–15 days	Meningitis, encephalitis, focal neurological abnormalities, seizures	<i>Culex tritaeniorhynchus</i> , other <i>Culex</i> spp.	Waterbirds, pigs
Zika virus	Asia Africa Central and South America Caribbean	3–14 days	Congenital Zika syndrome, Guillain–Barré syndrome, meningoencephalitis, transverse myelitis	<i>Aedes aegypti</i> , <i>Ae. albopictus</i>	Humans
St Louis encephalitis virus	North and central America	7–14 days	Meningitis, meningoencephalitis, cranial nerve dysfunction	<i>Culex</i> spp.	Birds
Tick-borne encephalitis virus	Northern and eastern Europe Northern Asia	7–14 days	Meningitis, encephalitis, transverse myelitis, acute flaccid paralysis	<i>Ixodes persulcatis</i> , <i>Ix. ricinus</i>	Small mammals, birds
Powassan virus	Canada USA Russia	7–14 days	Encephalitis, paralysis, altered mental state, seizures	<i>Ixodes cookei</i> , <i>Ix. persulcatis</i> , <i>Haemaphysalis longicornis</i>	Small mammals, birds

virus (ZIKV). Infection with these viruses should be suspected in travellers returning from areas where these viruses are endemic who develop compatible symptoms within the relevant incubation period. Depending on the travel and exposure history, the differential diagnosis may include other neurotropic arboviruses, such as alphaviruses and bunyaviruses.

JEV is widespread in Asia with over 50 000 cases of JEV encephalitis reported every year, mostly in children, with a case-fatality rate of 20–30% and neurological sequelae in 70% of survivors⁶. JEV vaccination programs have been implemented in several countries including China, India, Japan and Thailand, though data on the effectiveness of these programs is still emerging.

WNV was endemic only to Africa and Eurasia until it was introduced to New York in 1999, then spread across North and South America⁷. Since 2007, a yearly average of over 1000 cases of neurological disease has been reported in the USA⁸. Between 1 : 150 and 1 : 240 of those infected develop neurological disease^{9,10}, with the risk increasing with age¹¹.

ZIKV was restricted to Africa and Southeast Asia until outbreaks occurred in Micronesia in 2007, French Polynesia in 2013 and Brazil in early 2015. By July 2016, more than 150 000 cases were reported in Brazil and the virus had spread to central and South America and the Caribbean^{12,13}. It is estimated that 80% of Zika infections are asymptomatic. An increase in cases of Guillain-Barré syndrome (GBS) was reported following the outbreak in French Polynesia and subsequently also reported in Brazil, Colombia, and El Salvador^{13,14}. Less commonly, ZIKV may cause meningoencephalitis and transverse myelitis in adults.

During the 2015 outbreak in Brazil, an increase in congenital microcephaly was noted and suspected to be linked to maternal Zika virus infection. Retrospective investigation of the outbreak in French Polynesia outbreak also found an increase in microcephaly notifications. Further data support a causal link between maternal ZIKV infection and congenital Zika syndrome, manifestations of which include microcephaly, obstructive hydrocephalus, cerebral calcifications, congenital contractures, and hypertonia^{13,15–17}. The full neurological spectrum of congenital Zika syndrome will become clearer with longer term follow-up studies of the ZIKV infected infants.

Dengue virus has the most extensive geographical distribution of all the flaviviruses known to infect humans and is the most frequently diagnosed flavivirus infection in travellers returning to Australia. While severe dengue infection usually manifests as shock from plasma leakage or haemorrhage, rare neurological

complications of dengue such as encephalitis, meningitis, transverse myelitis and Guillain-Barré syndrome have also been described¹⁸.

See Table 1 for further information on selected neurotropic flaviviruses.

Laboratory diagnosis of flavivirus neurological disease

IgM antibody may be the earliest serological marker in flavivirus encephalitis²¹ and, in patients who develop an encephalitic illness, detection of flavivirus IgM antibody in serum confirms the diagnosis²². Recent flavivirus infection is usually confirmed by IgG or haemagglutination-inhibiting antibody seroconversion or a significant titre increase, or detection of flavivirus by cell culture or RT-PCR. Interpretation of flavivirus antibody titres is made more difficult in those with immunological memory from previous flavivirus exposure due to ‘original antigenic sin’. Given the high proportion of mild or asymptomatic cases, confirmation of infection with a neurotropic flavivirus does not necessarily indicate neurological disease. Where invasive specimens are available, definitive diagnosis can be made by detection of flavivirus in cerebrospinal fluid (CSF) or brain biopsy by cell culture or RT-PCR, or by detection of specific flavivirus IgM antibody in CSF.

When requesting diagnostic testing for flavivirus, it is important to consider the range of likely infecting flaviviruses, which is seasonally and geographically dependent. Relevant clinical and travel history should be provided to the testing laboratory to assist with test selection and interpretation.

References

- Selvey, L.A. *et al.* (2014) The changing epidemiology of Murray Valley encephalitis in Australia: the 2011 outbreak and a review of the literature. *PLoS Negl. Trop. Dis.* **8**, e2656. doi:10.1371/journal.pntd.0002656
- Prow, N.A. (2013) The changing epidemiology of Kunjin virus in Australia. *Int. J. Environ. Res. Public Health* **10**, 6255–6272. doi:10.3390/ijerph10126255
- Smith, D.W. *et al.* (2011) The viruses of Australia and the risk to tourists. *Travel Med. Infect. Dis.* **9**, 113–125. doi:10.1016/j.tmaid.2010.05.005
- Knox, J. *et al.* (2012) Murray Valley encephalitis: a review of clinical features, diagnosis and treatment. *Med. J. Aust.* **196**, 322–326. doi:10.5694/mja11.11026
- Selvey, L.A. *et al.* (2014) Rainfall and sentinel chicken seroconversions predict human cases of Murray Valley encephalitis in the north of Western Australia. *BMC Infect. Dis.* **14**, 672. doi:10.1186/s12879-014-0672-3
- Campbell, G.L. *et al.* (2011) Estimated global incidence of Japanese encephalitis: a systematic review. *Bull. World Health Organ.* **89**, 766–774. doi:10.2471/BLT.10.085233
- Gould, E.A. and Solomon, T. (2008) Pathogenic flaviviruses. *Lancet* **371**, 500–509. doi:10.1016/S0140-6736(08)60238-X
- Centers for Disease Control and Prevention (2018) West Nile virus statistics. <https://www.cdc.gov/westnile/statsmaps/cumMapsData.html> (accessed 29 January 2018).

9. Williamson, P.C. *et al.* (2017) Incidence of West Nile virus infection in the Dallas–Fort Worth metropolitan area during the 2012 epidemic. *Epidemiol. Infect.* **145**, 2536–2544. doi:10.1017/S0950268816000042
10. Petersen, L.R. *et al.* (2003) West Nile virus. *JAMA* **290**, 524–528. doi:10.1001/jama.290.4.524
11. Krow-Lucal, E. *et al.* (2017) West Nile virus and other nationally notifiable arboviral diseases – United States, 2015. *MMWR Morb. Mortal. Wkly. Rep.* **66**, 51–55. doi:10.15585/mmwr.mm6602a3
12. da Silva, I.R.F. *et al.* (2017) Neurologic complications associated with the Zika virus in Brazilian adults. *JAMA Neurol.* **74**, 1190–1198. doi:10.1001/jamaneurol.2017.1703
13. Musso, D. and Gubler, D.J. (2016) Zika Virus. *Clin. Microbiol. Rev.* **29**, 487–524. doi:10.1128/CMR.00072-15
14. Parra, B. *et al.* (2016) Guillain-Barré syndrome associated with Zika virus infection in Colombia. *N. Engl. J. Med.* **375**, 1513–1523. doi:10.1056/NEJMoa1605564
15. Brasil, P. *et al.* (2016) Zika virus infection in pregnant woman in Rio de Janeiro. *N. Engl. J. Med.* **375**, 2321–2334. doi:10.1056/NEJMoa1602412
16. Chimelli, L. and Avvad-Portari, E. (2018) Congenital Zika virus infection: a neuropathological review. *Childs Nerv. Syst.* **34**, 95–99. doi:10.1007/s00381-017-3651-3
17. Moore, C.A. *et al.* (2017) Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. *JAMA Pediatr.* **171**, 288–295. doi:10.1001/jamapediatrics.2016.3982
18. Carod-Artal, F.J. *et al.* (2013) Neurological complications of dengue virus infection. *Lancet Neurol.* **12**, 906–919. doi:10.1016/S1474-4422(13)70150-9
19. Mackenzie, J. *et al.* (2008) Arthropod-borne viral encephalitides. In *Control of Communicable Diseases Manual*, 19th edn. (Heymann, D.L. ed.) pp. 42–49, Apha Press.
20. Hills, S.L. and Fischer, M. (2015) Arboviral encephalitides. In *Control of Communicable Diseases Manual*, 20th edn. (Heymann, D.L. ed.) pp. 36–42, Apha Press.
21. Speers, D.J. *et al.* (2013) Clinical and radiological predictors of outcome for Murray Valley encephalitis. *Am. J. Trop. Med. Hyg.* **88**, 481–489. doi:10.4269/ajtmh.12-0379
22. Australian Government Department of Health (2018) Australian national notifiable diseases and case definitions. <http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm> (accessed 29 January 2018).

Biographies

Dr Tristan Gibbs is a Clinical Microbiologist at PathWest Laboratory Medicine WA and a Clinical Senior Lecturer for the School of Medicine, University of Western Australia. He is a fellow of the Royal College of Pathologists of Australasia.

Dr David Speers is an Infectious Diseases Physician at Sir Charles Gairdner Hospital, Head of Microbiology, QEII Network at PathWest Laboratory Medicine WA and a Clinical Associate Professor for the Department of Medicine and Pharmacology, University of Western Australia. He is a fellow of the Royal Australasian College of Physicians, the Royal College of Pathologists of Australasia, and the Australasian College of Tropical Medicine.

Results of ASM Members' survey

Recently we asked members to participate in a brief survey. Five hundred members took the time out, not only to answer the questions, but also to write comments. This was a fantastic result and we are most grateful to those of you who answered the questions. This kind of information and insight is most useful and helps guide our decision-making.

Although survey participants have already been given this information I thought other members might be interested in seeing the outcomes.

Regarding *Microbiology Australia*

- Q1. 75% of respondents received a printed copy of *Microbiology Australia* (MA).
- Q2. 66% of respondents thought we should maintain the print version of MA.
- Q3. 70% of respondents found it easier and more convenient to read a printed copy of MA than to read it online.
- Q4. 35% of respondents always read MA from cover to cover.
- Q5. 87% of respondents considered receiving MA, either as a hard copy or online, as an important membership benefit.

Our response?

We have just re-signed our contract with Team Macreadie who put the four editions of MA together, and are about to resign with CSIRO who are responsible for both the print and electronic versions. The survey results give us confidence that this is something members want and consider a worthwhile expenditure item.

Regarding our annual scientific meeting

- Q6. 30% of respondents regularly attended the ASM scientific meeting.

- Q7. 25% of respondents did not attend because they did not find it was relevant or helpful to them in their work.
- Q8. 57% of respondents did not attend because of the total cost.
- Q9. 21% of respondents did not attend because their workplace manager would not support them taking time off work.
- Q10. 40% of respondents did not attend because their workplace manager would not support them financially to attend.

Our response?

We have introduced a very generous incentive to come to the Brisbane meeting this year in response to the response about cost but regret that we cannot do much about travel and accommodation costs.

Regarding membership

- Q11. 77% of respondents thought that ASM membership represented good value for money.

Our response?

A sigh of relief that our hard work has not been in vain but a desire to make the figure 100 not 77.

We are still working through the two hundred comments and finding some excellent suggestions and ideas to make ASM more relevant and useful!

Congratulations to Alice McCarthy, MASM, who works with the Forensic and Analytical Science Service and who won a year's free membership to ASM for participating.

And make sure you apply for one of the 100 reduced price registrations for the Brisbane conference!

Executive standing committee