Neurological disease caused by flavivirus infections

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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 waterbirds[3]. 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 paralysis[1]. 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

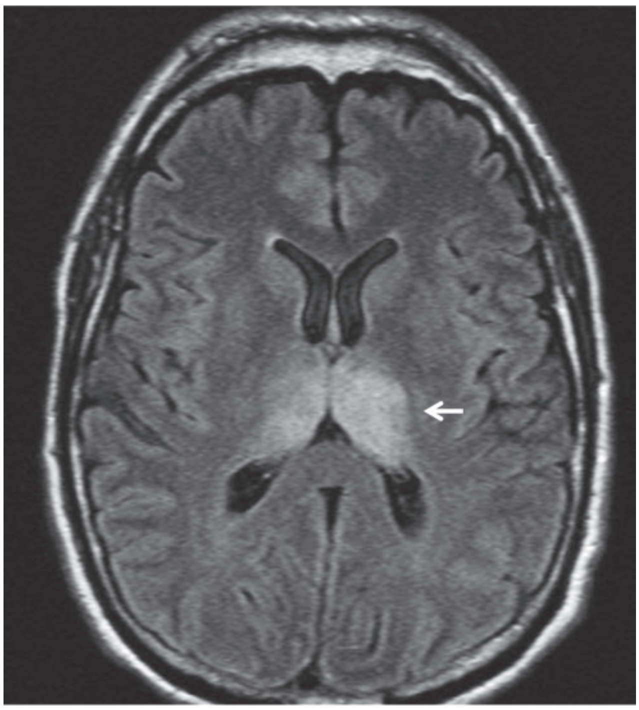

Figure 1. MRI brain scan of Murray Valley encephalitis 8 days after illness onset. FLAIR MRI scan demonstrating increased signal intensity in the thalami (arrow).

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epidemiological and clinical pattern to MVEV, although neurological disease tends to be milder, with no recorded cases of fatal infection[3].

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 ordering[5].

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	*Culex annulirostris*[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	*Culex pipiens*, other *Culex* 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	*Culex annulirostris*	Waterbirds
Japanese encephalitis virus	Asia Western Pacific islands	5–15 days	Meningitis, encephalitis, focal neurological abnormalities, seizures	*Culex tritaeniorhyncus*, other *Culex* spp.	Waterbirds, pigs
Zika virus	Asia Africa Central and South America Caribbean	3–14 days	Congenital Zika syndrome, Guillain–Barré syndrome, meningoencephalitis, transverse myelitis	*Aedes aegypti*, *Ae. albopictus*	Humans
St Louis encephalitis virus	North and central America	7–14 days	Meningitis, meningoencephalitis, cranial nerve dysfunction	*Culex* spp.	Birds
Tick-borne encephalitis virus	Northern and eastern Europe Northern Asia	7–14 days	Meningitis, encephalitis, transverse myelitis, acute flaccid paralysis	*Ixodes persulcatis*, *Ix. ricinus*	Small mammals, birds
Powassan virus	Canada USA Russia	7–14 days	Encephalitis, paralysis, altered mental state, seizures	*Ixodes cookei*, *Ix. persulcatis*, *Haemaphysalis longicornis*	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 survivors[6]. 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 America[7]. Since 2007, a yearly average of over 1000 cases of neurological disease has been reported in the USA[8]. Between 1 : 150 and 1 : 240 of those infected develop neurological disease[9,10], with the risk increasing with age[11].

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 described[18].

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 encephalitis[21] and, in patients who develop an encephalitic illness, detection of flavivirus IgM antibody in serum confirms the diagnosis[22]. 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.

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Biographies

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