Murray Valley encephalitis virus (MVEV)

Pathogen

Murray Valley encephalitis virus (MVEV)

Overview

Whilst MVEV transfusion-transmission has not been reported it is considered likely given other similar viruses can be transfusion-transmitted. Whilst severe disease does occur the vast majority are asymptomatic. It is considered a low risk to blood safety because infection is very rare and cases generally occur in areas away from blood donation centers. The risk of an adverse outcome is low given most cases are asymptomatic.

Classification and morphology

MVEV was first isolated during an outbreak in 1951 in the Murray Valley. MVEV is a member of the *Flavivirus* genus within the *Flaviviridae* family. The flaviviruses are enveloped viruses with a single-stranded positive-sense RNA genome. MVEV belongs to the Japanese encephalitis (JE) antigenic group, along with Japanese encephalitis and West Nile viruses (JEV and WNV, respectively). Four MVEV genotypes (G1 to G4) have been recognised. G1 is the dominant genotype circulating on the Australian mainland and has also been found in PNG while G2 is a minority genotype isolated from the Kimberly region of WA. Single strains of MVEV from PNG have been designated G3 and G4 but do not appear to be circulating in Australia.

[1-3]

Associated disease

Between 1 in 150 and 1 in 1,000 MVEV infections result in symptomatic disease. For MVEV infections that develop clinical symptoms the incubation period is typically one to four weeks (average, two weeks), followed by a prodrome of two to five days that usually includes fever and headache but may also include nausea, vomiting, diarrhoea, macular rash and cough. Neurological features occur early and may include lethargy, irritability and confusion. Seizures almost invariably occur in children, but may also occur in adults. Progression of neurological features varies, and four clinical patterns have been described: relentless progression to death, prominent spinal cord involvement causing flaccid paralysis, cranial nerve/brainstem involvement and tremor, and encephalitis followed by complete recovery. Mild cases of encephalitis not requiring hospitalisation, and non-encephalitic cases with fever and headache have also been described, suggesting a broad spectrum of disease. Long-term neurological sequelae occur in 30–50% of survivors with only 40% recovering completely. The case fatality rate for symptomatic MVEV infection is about 15–30%.

[4-9]

Blood phase

The blood phase of MVEV has not been well characterized. The duration of the viraemic period is uncertain but is believed to be short and the virus is cleared from the blood by the time symptoms appear. There is also considerable uncertainty about the time sequence for serological markers. Based on limited data for MVEV, and comparison with related flaviviruses (WNV and JEV), it is thought that IgM appears four to nine days after disease onset and can persist for months.

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Infection results in life-long immunity.

[10,11]

Chronic carriage

Chronic MVEV infection has not been reported.

Human exposure routes

MVEV is transmitted to humans by infected mosquitoes. It is not transmitted person-to-person (either directly or via mosquito) or animal-to-human. It appears that humans do not have a sufficiently high level of viraemia to sustain ongoing transmission by mosquito.

[12,14]

Vector and reservoir

The major MVEV vector is the *Culex annulirostris* mosquito. The virus has also been isolated from a number of other mosquito species including *Aedes normanensis, C. tritaeniorhynchus and C. pipens*, but it is not known whether they are competent to transmit the virus. Large water birds (herons, egrets and pelicans) are the main viraemic hosts. While a number of domestic and wild animals have antibodies to MVEV, only rabbits and possibly western grey kangaroos develop significant levels of viraemia sufficient to support local transmission. In northern Western Australia and the top end of the Northern Territory, where MVEV is endemic, the virus is maintained in enzootic foci in a cycle involving water birds and mosquitoes. MVEV can also infect horses (causing fatal encephalitis), but they are considered to represent a "dead end" host and are not part of the transmission cycle.

[9,12-14]

At risk populations

MVEV is endemic in PNG, northern Western Australia (Kimberley region), the north of the Northern Territory and northern Queensland. The virus is epizootic in the Pilbara, Gascoyne and Mid-West regions of WA and southern parts of the NT. Occasionally, MVEV spreads from enzootic areas to the south-eastern Australia, where it usually causes significant outbreaks of encephalitis (three of which occurred in 1950-51, 1974 and 2011). In the 2011, high level MVEV activity occurred in south- eastern Australia for the first time since 1974 and was accompanied by increased activity in northern Australia. Outbreaks have been associated with heavy rainfalls and climate favouring vector proliferation.

Individuals without previous exposure to MVEV who visit endemic areas, as well as people living in areas undergoing an epidemic, are at risk of infection. In particular, people engaged in outdoor activities such as camping and fishing during periods of mosquito and virus activity may be at increased risk of infection. MVE may be more severe in the very young and those over 50 years-old, but severe disease and death may occur at any age. Protective measures include avoiding known mosquito infested areas, especially at dawn and dusk when mosquitoes are most active, ensuring that houses are adequately screened, using insect repellents that contain the chemical DEET and reapplying it regularly, and wearing long sleeved shirts and pants.

[9,12-14]

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Transfusion-transmissibility

Transfusion-transmission of MVEV has not been reported but cannot be excluded. MVEV infection includes a viraemic phase and most MVEV infections are asymptomatic. Additionally, in the case of symptomatic infections, the viraemic phase occurs prior to the onset of symptoms. Potential transfusion-transmission of MVEV is also indicated by the reported transfusion-transmission of the related flaviviruses, dengue virus (DENV) and WNV.

[10,11,15-19]

Treatment and efficacy

There is no specific treatment for MVEV infection. An effective human vaccine has not been developed. It is recommended that patients with encephalitis be managed in hospitals with intensive care facilities and expertise in the management of complicated neurological disease.

[10,13]

Assay and algorithm options for screening and confirmatory / diagnostic testing

Immunoassays for detection of MVEV specific IgM and IgG are available. However, both IgG and IgM are broadly cross-reactive among the flaviviruses and therefore cross-reactivity with antibodies to DENV, West Nile virus-Kunjin strain (WNV_{KUN}) and JEV may occur. A reverse transcriptase polymerase chain reaction (RT-PCR) assay to detect MVEV RNA has been developed.

Definitive laboratory evidence of MVEV infection can be one of the following: (i) isolation of MVEV or (ii) detection of MVEV RNA or (iii) IgG seroconversion or significant increase in antibody level or a fourfold or greater rise in titre to MVEV antibodies or (iv) detection of MVEV-specific IgM in cerebrospinal fluid in the absence of IgM to WNV_{KUN}, JEV and DENV or (v) detection of MVEV-specific IgM in serum in the absence of IgM to WNVKUN, JEV and DENV (this is only accepted as laboratory evidence where there is encephalitic illnesses).

[10,20]

Lifeblood risk assessment: blood components

As noted above, although transfusion-transmitted MVEV infection has not been reported, it cannot be excluded as most infections are asymptomatic and symptomatic infections include a pre-symptomatic blood phase. Additionally, transfusion-transmission of related flaviviruses has been reported.

To assess the risk of MVEV to blood safety, a number of factors need to be considered. MVE is predominately reported in northern Western Australia (Kimberley region) where blood centres are either absent or underrepresented. Relatively low numbers of MVE are reported annually. The Commonwealth Department of Health has been reporting MVEV infections since 2001. Between 2001 and 2020 the annual number of reported cases has varied from zero to six cases, except for 2011 when possibly 16 confirmed cases and 1 suspected case were reported. However, under certain conditions, outbreaks of MVEV can occur. There were three known outbreaks during the second half of the twentieth century − 1951 (when the virus was first isolated), 1956 and the last one

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in 1974 when 58 cases of encephalitis were reported. Additionally, due to the apparent low proportion of MVEV infections that are symptomatic (estimated between 1 in 150 and 1 in 1,000), the actual number of infections in the community will be considerably higher than the reported case numbers.

Analysis of the 2011 outbreak has indicated a changing demographic pattern of MVEV infections in humans, with an increasing number of non-Aboriginal workers and tourists living and travelling in endemic and epidemic areas in northern Australia.

Therefore, while MVEV is a potential threat to blood safety in Australia, it currently represents a low risk.

[7,9,10,21,22]

Current Lifeblood risk management strategy for blood safety

Donor deferrals exist for allogeneic/therapeutic donors with current or recurrent infection, past infection and contacts with infectious disease. These deferrals are regularly reviewed and any outbreaks or new developments are constantly monitored.

Proposed strategy should local outbreak occur

In the unlikely event of a significant local outbreak of MVEV, Lifeblood may perform a risk assessment to determine whether additional risk mitigation measures were required. Potential strategies include the implementation of a supplementary question to identify donors visiting/residing in risk areas and restriction to plasma for fractionation for those donors.

Leucoreduction efficacy

No data is available regarding the leucoreduction efficacy for MVEV. However, as the blood phase of MVEV infection in humans includes a short viraemia period, it is unlikely that leucoreduction would have a clinically significant impact.

Pathogen reduction efficacy (fresh products)

There is no licensed pathogen reduction technology (PRT) in Australia. PRT is a possible future option if an effective RBC technology is realised.

The Mirasol Pathogen Reduction Technology System (CaridianBCT Technologies) has been reported to reduce infectious MVEV in platelet concentrates by nearly 2 logs. There is no specific pathogen reduction data for MVEV for the INTERCEPT Blood System (Cerus Corporation) or the THERAFLUX MB-Plasma System (MacoPharma). However, these two systems effectively inactivate other flaviviruses and therefore may be effective against MVEV.

[23-26]

Pathogen reduction efficacy (plasma derivatives)

All of CSL Behring (CSLB)'s plasma-derived products include specific virus inactivation or virus removal steps designed to ensure viral safety.

[27]

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Further information available on the CSL Behring website:

https://www.cslbehring.com/products/safety-and-manufacturing

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