Murray Valley encephalitis virus

David W Smith

PathWest Laboratory Medicine WA
The University of Western Australia
Encephalitic arboviruses

- **Alphaviruses:**
  - Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, California encephalitis virus
  - Rare cases of encephalitis due to chikungunya virus

- **Flaviviruses:**
  - Japanese encephalitis virus (JEV), Murray Valley encephalitis virus (MVEV), West Nile virus (WNV), Kunjin strain of WNV (KUNV/WNV), St Louis encephalitis virus, tick-borne encephalitis virus, louping ill virus, Kyansanur Forest disease virus

- **Phleboviruses:**
  - Rift Valley fever virus

- **Bunyaviruses**
  - California encephalitis group
MVE/Kunjin (Australian) Encephalitis
1917 to 1999

- Murray Valley/Kunjin encephalitis
  1975-1999

- Australian X Disease
  1917-1925

- Murray Valley/KUN encephalitis
  1950-1974
Human MVEV 1975-2010

Mainly the 2000 season
MVEV/KUNV illness in Australia since 1974
MVEV cases in relation to rainfall data: Note that rainfall may not exactly match groundwater/flooding patterns.
Human MVEV & KUNV infections 2011

Circle = MVEV. Star = KUNV. Open circle = not lab confirmed. Red outline = encephalitis. White outline non-encephalitic.
Flaviviruses: Who gets infected and who gets encephalitis?

• Who gets infected?
  – Populations in enzootic/endemic areas with regular exposure
    • Many infected in childhood or early adulthood
    • Disease in older adults is unusual, e.g. JEV in SE Asia, MVEV in the Kimberley
  – People in endemic areas who are not regularly exposed & people in epidemic areas
    • All susceptible, risk depends on exposure

• Who get encephalitis?
  – MVEV 1:200 to 1:1000
  – This may be explained by partial protection due to previous flavivirus exposure in the indigenous population, age related differences, different genetic susceptibility
  – Disease more likely to be under-diagnosed in developing countries
MVEV encephalitis

Maintained in a waterbird-mosquito (*Culex annulirostris*) cycle

Case-to-infection ratio
• 1:1000 to 1:100

Presentation
• May have nonspecific febrile illness +/- headache
• Anorexia, malaise, fever, vomiting
• Adults – headache, altered mental state, occasional fitting
• Children - fitting

Course
• Variable progression. Involves central cerebral structures, brainstem, spinal cord.
• No specific treatment
Clinical presentations of infection with encephalitic flaviviruses

- Asymptomatic
- Nonspecific febrile illness, usually with headache
- Fever with headache
- Meningitis without encephalitis
- Encephalomyelitis
  - Abortive
  - Classical
  - Acute flaccid paralysis prior to encephalitis (polio-like illness)
    - Up to 1/3 of classical cases also have AFP, but associated with severe neurological diseases
  - Guillain-Barré syndrome (WNV)
What happens when you get it?

- Characteristic features relate to involvement of central cerebral structures including the midbrain, basal ganglia, brainstem and medial temporal lobes.
- Cerebellum and upper spinal cord may be affected, particularly the anterior horn cells of the latter.

- Clinical manifestations
  - coma, respiratory failure and flaccid paralysis
  - cranial nerve palsies, tremor, cogwheel rigidity, cerebellar ataxia and upper limb weakness
  - late onset parkinsonism and neuropsychiatric disease
Clinical and radiological predictors of outcome for Murray Valley encephalitis

- Ten cases hospitalised in WA 2008-2011
- All patients acquired infection between March and May, the age range was 2-68 years
- Two children, six males
- Nine infected in WA, one in NSW
- Nine encephalitic, one non-encephalitic
- Investigations
  - All patients developed a raised C-reactive protein, and most developed acute liver injury, neutrophilia and thrombocytosis.
  - MRI
Clinical and radiological predictors of outcome for Murray Valley encephalitis: MRI findings

- CT scans rarely showed any abnormalities
- MRI findings within 1 week of onset
  - All patients with encephalitis developed cerebral peduncle involvement on early magnetic resonance imaging (MRI).
  - The absence of limbic system MRI hyperintensity, with or without leptomeningeal enhancement, predicted a better neurological outcome.
  - Those with widespread abnormalities involving the limbic system and cerebral cortex or the cerebellum had devastating neurological outcomes.
- Later MRI scans showed destruction of the thalamus and basal ganglia, cortex or cerebellum.

MRI

Male
61yo
2011

Male
29yo
2011

Male
26yo
2002
# Outcome of MVE encephalitis: WA/NT 1978-2011

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mortality</th>
<th>Sequelae</th>
<th>Normal</th>
</tr>
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<tbody>
<tr>
<td>Adults</td>
<td>38</td>
<td>6 (16%)</td>
<td>17 (45%)</td>
<td>15 (39%)</td>
</tr>
<tr>
<td>Children</td>
<td>27</td>
<td>6 (22%)</td>
<td>12 (44%)</td>
<td>9 (34%)</td>
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</tbody>
</table>

- Worst outcomes in adults over 50 years and children under 2 years
- Little evidence of improvement in survival or neurological sequelae since 1974
- Improving survival may increase number with severe neurological sequelae
MVEV encephalitis outcomes

![Bar chart showing the number of patients for MVEV encephalitis outcomes by time period and age group.]

- Murray Valley 1951
- Murray Valley 1974
- WA/NT 1978-93
- WA/NT 1978-2000

Number of patients

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Children</th>
<th>Adults</th>
<th>Total</th>
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<tbody>
<tr>
<td>1951</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
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<td></td>
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<tr>
<td>1978-93</td>
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<td>1978-2000</td>
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Diagnosing flavivirus encephalitis

- CSF shows variable pleocytosis and variable proportion of neutrophils. Usually mildly elevated protein, normal glucose.
- Detection of virus by culture is rare in premortem samples (CSF or blood).
- Detection of virus by PCR is uncommon in premortem samples (CSF or blood) for most flaviviruses.
- Detection of IgM in CSF is helpful and diagnostic of flavivirus encephalitis, but only found in ~75%.
- Detection of IgM in serum may be helpful but does not necessarily mean recent infection and may not indicate which flavivirus.
- Rising levels of IgG between acute and convalescent samples is very helpful in confirming recent flavivirus infection, but may not tell you which one it is.
  - Species specific serology should be performed – neutralisation or epitope-blocking EIA.
- Patients with second flavivirus infections, e.g. MVEV infection in someone with past Kunjin infection.
  - IgM may be absent
  - Early IgG response may be directed at the previously infecting flavivirus
- REMEMBER
  - Serological diagnosis can be tricky
  - You never have enough CSF!
PCR for MVEV in CSF

- Target is the envelope protein sequence
- Nested in-house (plus tandem nested real-time 2008 onwards)
- 20 samples tested from 17 patients with known date of onset of illness
  - 3 positive
- One additional patient had positive PCR on postmortem brain tissues
18 patients, 23 samples
Overall, 13/18 (72%) of patients had IgM detectable in CSF
Treatment of flavivirus encephalitis

• Supportive care the only current recommendation for treatment
• Corticosteroids
  – Dexamethasone - no benefit against JEV encephalitis in double-blind placebo-controlled trial
  – Glucocorticoids increase WNV viraemia in dogs
  – Isoquinolone compounds are effective in vitro
• Interferon
  – Recombinant interferon-α promising in open trial, but no benefit for JEV encephalitis in a placebo controlled double blind trial
• Ribavirin
  – Shown to inhibit WNV in vitro, but no benefit in WNV patients treated during 2000 outbreak in Israel or for JEV encephalitis in a placebo controlled trial in India.
  – Does not effectively cross the blood–brain barrier
• Intravenous immunoglobulin (IVIG) therapy
  – Monoclonal antibodies are apparently effective in animal models
  – Case reports and mouse studies suggest IVIG containing high titres of anti-WNV antibodies improves WNV encephalitis outcomes, particularly in immunocompromised patients
  – Phase I/II clinical trials of WNV-specific IVIG have recently been completed in the US, but results are yet to be reported.

Prevention

• Risk monitoring and public warnings
  – Travel to areas with activity
  – Mosquito avoidance

• Vaccine?
**What’s needed to get human infections?**

<table>
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<tr>
<th>Risk condition</th>
<th>Monitoring the risk</th>
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</thead>
<tbody>
<tr>
<td><strong>Weather conditions</strong> - Needs to have heavy rains and flooding, and warmth</td>
<td>Meteorological data, satellite data</td>
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<tr>
<td><strong>Vectors</strong>: Needs mosquitoes – <em>Culex annulirostris</em></td>
<td>Mosquito trapping*</td>
</tr>
<tr>
<td><strong>MVEV present in the mosquitoes</strong></td>
<td>Testing trapped mosquitoes*</td>
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<td><strong>Amplifying hosts</strong>: Mainly water birds that have not been previously exposed</td>
<td>Nil</td>
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<td><strong>Infected mosquitoes biting humans</strong></td>
<td>Sentinel chicken monitoring</td>
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<td><strong>People getting exposed to infected mosquitoes</strong>: Possible dose effect – ? need lots of bites to get encephalitis</td>
<td>Clinical cases</td>
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* Often not feasible during the wet season due to limited access
Sentinel chickens
Sentinel chicken MVEV seroconversions and human cases Jan 2009- May 2012

Data from Arbovirus Surveillance and Research Laboratory, University of Western Australia
If people act on warnings, could they avoid infection?

- 50 yo female – regular mosquito exposure in evenings
- 41 yo female – regular night fishing
- 61 yo male – camping by roadside
- 29 yo male – outdoor job
- 25 yo male – regular evening outdoor activities
- 25 yo male – fishing and camping
- 67y yo female – camping at beach and other locations
- 2 yo female – many mosquito bites
MVEV vaccination

- No specific MVEV vaccine available
- Current flavivirus vaccines: JEV, TBEV, (WNV), (DENV)
- JEV most closely related to MVEV
  - Inactivated JEV vaccines- enhance MVEV infection in mouse model
  - Chimeric vaccine protects against JEV in mice – would it do the same in humans?
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WA
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