Arbovirus encephalitis

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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
New World Alphaviruses

Smith DW, Hall RA, Johansen CA Broome AK, Mackenzie JS. The Arboviruses. Manson’s Tropical Diseases (22nd ed)
Map showing approximate global distribution of major neurotropic flaviviruses

JE=Japanese encephalitis; MVE=Murray Valley encephalitis; WNV=West Nile virus; WTBE=Western tick-borne encephalitis; FETBE=Far Eastern tick-borne encephalitis; LI=Louping Ill virus; SLE=St Louis encephalitis.

Solomon T et al. J Neurol Neurosurg Psychiatry 2000;68:405-415
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 and WNV(KUNV) infections of humans 2000-10

- 2001
- 2002
- 2005
- 2006
- 2008
- 2009
- 2010

- MVEV
- WNV (KUNV)
- MVEV/WNV
MVEV/KUNV illness in Australia since 1974
Human MVEV & KUNV infections 2011

Lighter colour and white border = non-encephalitis case
Solid = confirmed MVEV/KUNV
Open circle = non-confirmed MVEV
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?
  – JEV 1:25 to 1:1000, WNV (US) <1:100, 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
Clinical presentations of infection with encephalitic flaviviruses

- Asymptomatic
- Nonspecific febrile illness, usually with headache
- Fever with severe 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)
MVEV encephalitis: clinical features

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

Presentation
- May have nonspecific febrile illness +/- headache
- Anorexia, malaise, fever, vomiting
- Adults - headache
- Children - fitting

Course
- Variable progression. Involves central cerebral structures, brainstem, spinal cord.
- No specific treatment
It’s more dangerous than Wolf Creek!

Mozzie agony: 300 bite man

Tourist wakes from coma

Sport fit for royals to grace Arfutura Games

After coming out of the coma he mouthed the words “Murray Valley Encephalitis.”

The man had been taken to hospital in a coma in Germany after returning home from a six-month holiday in Australia.
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
MRI

• Useful early investigation to aid diagnosis and assist with prognostication
• If the MRI shows significant changes in midbrain, basal ganglia, brainstem and medial temporal lobes basal then the patient is much more likely to have a bad outcome – death or major neurological deficit
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, 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
- BUT
  - Serological diagnosis can be tricky
  - You never have enough CSF!
Nucleic acid detection for flavivirus diagnosis

- Limited availability, at present and many patients seen too late for it to be useful
- Useful for
  - early diagnosis
  - definitive identification and typing of virus,
  - resolving tricky serology
  - molecular epidemiology
PCR for detection of WNV in CSF

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>Serum</th>
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<tr>
<td></td>
<td>TaqMan</td>
<td>RT-PCR</td>
</tr>
<tr>
<td><strong>Seropositive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16/28</td>
<td>0/28</td>
</tr>
<tr>
<td><strong>Seronegative</strong></td>
<td>30/30</td>
<td>0/42</td>
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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
Serological diagnosis of acute flavivirus infections: the criteria and their problems

• Significant rise in IgG between acute and convalescent samples
  – Cross reactive IgG
  – Immune recall (original antigenic sin)
• Detection of IgM
  – Persistent IgM, especially in serum, therefore does not necessarily indicate recent infection
  – Cross reactive IgM may occur, but much less than with IgG
  – Lack of IgM in secondary infections (e.g., secondary dengue, MVEV infection in a patient with past KUNV)
  – Late IgM in some patients, especially seriously ill
Flavivirus encephalitis: Acceptable diagnostic criteria

• Detection of virus by culture or PCR (or antigen detection for some)
• Detection of specific IgM in CSF
• Detection of specific IgM in serum in patients with definite encephalitis
• Rising levels of specific IgG in serum in patients with definite encephalitis
MVE encephalitis 2000-2011
CSF IgM by IFA

18 patients, 23 samples
Overall, 13/18 (72%) of patients had IgM detectable in CSF
MVE/KUN encephalitis 2000-2011
Serum IgM by IFA

42 samples from 18 patients
Positive IgM detected in one case up to 150 days after onset
Specific tests for flavivirus IgG

• Neutralisation tests
  – Relatively specific provided a suitable range of flaviviruses is tested and there is a significantly higher titre to one flavivirus

• Epitope-blocking EIA
  – Measure ability of patient antibody to block binding of monoclonal antibodies directed at virus-specific epitopes
Monoclonal antibody epitope-blocking EIA

- Need to find a monoclonal antibody that will react with a specific epitope and will be blocked efficiently by specific antibodies in patient serum
- May not provide clear results with early antibody responses
- Specific antibody can be detected earlier than with neutralisation assays

Epitope-blocking EIA for differentiation between antibody to MVE and KUN

<table>
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<tr>
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<th>Percent inhibition using</th>
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<tbody>
<tr>
<td></td>
<td>3H6 (Flavi)</td>
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<tr>
<td>MVE</td>
<td></td>
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<tr>
<td>Early</td>
<td>56%</td>
</tr>
<tr>
<td>Late</td>
<td>51%</td>
</tr>
<tr>
<td>KUN</td>
<td>96%</td>
</tr>
<tr>
<td>Mixed</td>
<td>95%</td>
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Specific antibody may not be present in acute serum

Patient’s antibody is blocked by the general and specific flavivirus antibodies
Outcomes of flavivirus encephalitis

• Japanese encephalitis
  – 30% mortality
  – 50% survivors have severe neurological sequelae, especially children
  – Learning difficulties, behavioural problems, and subtle neurological disease occurs in many of the apparently normal survivors
  – Better medical care improves survival, but the additional survivors have significant neurological sequelae.

• West Nile encephalitis
  – 15% mortality
  – Neurological deficits common survivors - movement disorders, fatigue, headache, myalgia, weakness
  – Possible chronic infection
## Outcome of MVE encephalitis: WA/NT 1978-2011

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

- **Supportive care** the only current recommendations 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. Monoclonal antibodies are apparently effective in animal models
- **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 and no benefit for JEV encephalitis in a placebo controlled trial in India.
  - Does not effectively cross the blood–brain barrier
- **Intravenous immunoglobulin (IVIG) therapy**
  - 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 (NCT00069316) but results are yet to be reported.
- **Vaccines (JEV, TBE) and prevention of infection** are the most effective interventions currently available
West Nile/Kunjin Virus Infections

- Ecology very similar to MVE except sporadic activity is found in south-east Australia in the absence of MVE.
- Causes occasional cases of encephalitis that are usually less severe than MVEV encephalitis.
  - Between 1974 and 2000 there were 3 confirmed cases of KUN encephalitis compared with 68 cases of MVE encephalitis.
- More often fever, malaise & possibly polyarthritis.
Acknowledgements

WA
PathWest/UWA?: David Speers, Ian Sampson, Tony Jones, Peter Boan, Karen Sagenschneider, Gerry Harnett, Glenys Chidlow, David Williams, Cheryl Johansen, staff of the Arbovirus Surveillance and Research Laboratory
DoH: Gary Dowse, Paul Armstrong, Mike Lindsay, Sue Harrington, Heather Lyttle
SCGH: Fremantle: John Dyer, Moira Wilson,
Royal Perth Hospital: Paul Ingram, Laurens Manning
Princess Margaret Hospital: Chris Blyth

NT
Jim Burrow, Bart Currie, Peter Markey, Peter Whelan

Qld
Roy Hall

NSW
Linda Hueston, Keith Eastwood

SA
Peter Blumbergs

Vic
Rod Moran, Mike Catton, Jack Richards, John Mackenzie

Others
CDNA, NAMAC members, physicians involved in patient care