Unusual VIRAL causes of Childhood encephalitis

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Why study encephalitis

- **Causes:** Aetiological diagnosis frequently not made

- **Consequences:** cause of mortality, short-term survivors with significant sequelae, long-term half with cognitive/behavioural sequelae

- ‘**Canary in coal mine**’: ‘marker’ syndrome for emerging and serious infectious diseases
ACE Study - methods

Discovering the Infectious Causes of unknown Encephalitis (DICE)

Active surveillance
“Suspected Encephalitis”

Expert clinical review
- Case categorisation
- Review diagnostics

Specimen salvaging
- Biobanking
- Novel diagnostics

Follow-up
Expert Panel - methods

Suspected Encephalitis

‘Not Encephalitis’

‘Unknown’

Infectious

Encephalitis

Brighton Definition
IEC Definition

Immune mediated

Confirmed Granerod et al.

Probable Granerod et al.

Possible Granerod et al.

ADEM

Brighton Definition

Ab-mediated

Other

Specify diagnosis

ADEM

Brighton Definition

J.J. Sejvar et al. Vaccine 2007
A. Venkatesan et al. CID2013
J.Granerod et al. Epidemioll Infect. 2010

J.Granerod et al. Epidemioll Infect. 2010

J.Granerod et al. Epidemioll Infect. 2010

J.Granerod et al. Epidemioll Infect. 2010
Causality

Confirmed

Probable

Possible

Granerod et al. Epi Infect 2010
### ’Acute encephalitis’ - Clinical pathological spectrum

<table>
<thead>
<tr>
<th></th>
<th>Acute infectious encephalitis</th>
<th>Acute disseminated encephalomyelitis</th>
<th>Acute haemorrhagic leucoencephalopathy</th>
<th>Acute toxic encephalopathy</th>
<th>Septic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ages</strong></td>
<td>All</td>
<td>&gt; 2 years</td>
<td>All</td>
<td>&lt; 2 years</td>
<td>All</td>
</tr>
<tr>
<td><strong>Antecedent infection</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Clinical features:</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Common</td>
<td>Variable</td>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic involvement</strong></td>
<td>Sometimes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Altered level of consciousness</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Seizures common</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Meningism</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Focal CNS signs</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Involvement of PNS</strong></td>
<td>Sometimes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Flavivirus, CMV &amp; EBV encephalitis</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>CSF examination:</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>↑ opening pressure</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td><strong>Pleocytosis</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>↑ protein</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Intrathecal IgG Synthesis</strong></td>
<td>After 10 days</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Detection of microbe by PCR</strong></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>CNS imaging (CT/MRI)</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>EEG</strong></td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td><strong>Brain histopathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Davies et al. Jn Neuro 2006.](#)
## ACE Review Panel to end 2016 (n=519 suspected cases)

<table>
<thead>
<tr>
<th>Confirmed Encephalitis</th>
<th>Confirmed/Probable&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Possible</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong>&lt;br&gt;(n (% confirmed encephalitis; 95% CI)</td>
<td><strong>102 (36; 30-41)</strong></td>
<td><strong>59 (21; 16-25)</strong></td>
<td><strong>161 (56; 51-62)</strong></td>
</tr>
<tr>
<td>Parechovirus</td>
<td>28</td>
<td>1</td>
<td>29 (10; 7-14)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>17</td>
<td>11</td>
<td>28 (10; 6-13)</td>
</tr>
<tr>
<td>‘Bacterial’&lt;sup&gt;*&lt;/sup&gt;</td>
<td>21</td>
<td></td>
<td>21 (7; 4-10)</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>18</td>
<td>18 (6; 3-9)</td>
</tr>
<tr>
<td>HSV</td>
<td>17</td>
<td></td>
<td>17 (6; 3-9)</td>
</tr>
<tr>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td>15</td>
<td></td>
<td>15 (5; 3-8)</td>
</tr>
<tr>
<td>EBV</td>
<td>2</td>
<td>2</td>
<td>2 (2)</td>
</tr>
<tr>
<td>HHV6</td>
<td>1</td>
<td>2</td>
<td>3 (2)</td>
</tr>
<tr>
<td>MVEV</td>
<td>1</td>
<td>1</td>
<td>2 (1)</td>
</tr>
<tr>
<td>CMV</td>
<td>1</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>RSV</td>
<td>3</td>
<td>3</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>2</td>
<td>2</td>
<td>2 (1)</td>
</tr>
<tr>
<td>HMPV</td>
<td>1</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>1</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Norovirus</td>
<td>1</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td><strong>Cryptococcus sp.</strong></td>
<td>1</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Toxocarasis</td>
<td>1</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>15</td>
<td></td>
<td>15 (5)</td>
</tr>
<tr>
<td><strong>Immune Mediated (n (%))</strong></td>
<td><strong>73</strong></td>
<td></td>
<td>73 (26; 21-31)</td>
</tr>
<tr>
<td>ADEM</td>
<td>51</td>
<td></td>
<td>51 (18; 13-22)</td>
</tr>
<tr>
<td>Anti-NMDAR</td>
<td>17 (2)&lt;sup&gt;##&lt;/sup&gt;</td>
<td></td>
<td>17 (6; 3-9)</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>1</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td><strong>Other^</strong></td>
<td>4</td>
<td></td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Unknown (n (%))</strong></td>
<td>51</td>
<td></td>
<td>51 (18; 13-22)</td>
</tr>
</tbody>
</table>
Case

3yo well boy; Asian background

- 3 days fever, cough, vomiting and diarrhea
- Found unresponsive and cyanosed
- CT: low attenuation and swelling of the basal ganglia and upper brain stem
- CSF - WCC 1, Prot 14.69
- AST >21,000, ALT >11,000
- PCR positive for Influenza A
- Death within 48 hours of admission
IAE cases

- 23 cases of Suspected encephalitis; 13 IAE cases
  - Age: median 3.7 years (IQR 1.5 – 7.2)
  - Sex: 8/13 female
  - Clinical: Fever, decreased LOC, seizures, 1/3 no resp.
    - 8 children with specific acute encephalopathy syndromes (4 ANE, 2 AESD, 1 MERS, 1 HHS)
  - CSF: median WCC 1
  - Neuroimaging: normal – specific syndromes
  - 1 death; 3 severe adverse
  - neurologic morbidity occurred in 7 of the 13 children (54%)

One pre-existing neurological dx
None vaccinated
15% received oseltamivir
IAE: Clinico-radiological diversity

Acute necrotising encephalopathy (ANE) Severe; mortality 25%; morbidity 40%

Hemiconvulsion
Hemiplegia
Syndrome (HHS) Moderate-severe; mortality ?; morbidity ?70%

Mild encephalopathy with biphasic seizures and late reduced diffusion (AESD) Moderate-severe; mortality <5%; morbidity 70%

Acute encephalopathy with reversible splenial lesion (MERS) Mild; full recovery by 1 month

**Pathogenesis**

**Diagram Description:**
- **CNS (Central Nervous System):** Apoptosis/death of neurons and glia, brain edema and damage, CNS disorders.
- **Activated Glia:** Cytokines.
- **Damaged BBB (Blood-Brain Barrier):** Metabolic disorders, DIC, hepatic/renal dysfunction.
- **IL-6:** Induce.
- **IL-6, IL-10, sTNFR1:** Induce or aggravate.
- **RANBP2:**

**Legend:**
- BBB: Blood-brain barrier
- CNS: Central nervous system
- DIC: Disseminated intravascular coagulation

**References:**
ACE Outcome (short-term)

- Nine patients died (case fatality proportion 5%),
  - 7 infectious encephalitis (2 influenza-associated, 3 HHV6-associated, 1 parechovirus, 1 Group B streptococcus);
  - 2 with encephalitis of unknown cause.
- ICU admission occurred in 53% of cases
- Median length of stay in hospital was 9 days hospitalisation
  22% of children showed moderate to severe neurological sequelae at discharge from hospital (Glasgow outcome scale score ≤4).

<table>
<thead>
<tr>
<th>Predictor*</th>
<th>Multivariable aOR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>43.5 (3.3-500)</td>
<td>0.004</td>
</tr>
<tr>
<td>Anti-NMDAR</td>
<td>50 (4.2-500)</td>
<td>0.002</td>
</tr>
<tr>
<td>ADEM</td>
<td>6.0 (1.0-34.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0.18 (0.05-0.58)</td>
<td>0.004</td>
</tr>
<tr>
<td>GCS &lt;13§</td>
<td>3.8 (1.0-7.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>7.0 (1.2-39.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
IAND combined analysis - Methods:

**ACE study 2013-2015**
Suspected Encephalitis (n=342); 5 sites

**FluCAN PAEDS Surveillance 2013-2015**
(n=710); 2 sites. ACE co-participating.

**Influenza-associated Suspected Encephalitis**
(n=23; Table 3)

**Influenza with neurological features**
(n=48; Table 2)

Cases from non-FluCAN co-participating sites
(n=8)
- 3 Encephalitis/encephalopathy
- 2 AES: 1 ANE, 1 HHS
- 1 encephalopathy/myocarditis
- 1 ?cerebral vasculitis
- 3 non-specific encephalopathy

Cases from FluCAN co-participating sites
(n=15)
- 10 Encephalitis/encephalopathy
  - 6 AES: 3 ANE, 2 AESD, 1 MERS
- 1 hypertensiveencephalopathy/PRES
- 1 post-influenza myelitis
- 3 non-specific encephalopathy

Cases co-identified
(n=94)

**Influenza-associated neurological disease (IAND)**
from ACE and FluCAN co-participating sites
(n=54; Table 1 and Figure 2)
Results:

Deaths  n = 3

IAE  n = 10
1.4 (0.5-2.3) per 100 admit

IAND  n = 54
7.6 (5.7-9.6) per 100 admit

Incidence of IAE per 1 000 000 population

- 0-4 yrs  6.5 (1.3–20.1)
- 0-14 yrs  2.8 (0.7–7.8)

2014
- 0-4 yrs = 0.66 million
- 0-14 yrs = 1.9 million
# Spectrum of IAND

**Table 2. Demographics, Risk Factors, Treatment, and Outcome of Influenza-Associated Neurological Disease Identified by the Australian Childhood Encephalitis Study and Influenza Complications Alert Network Surveillance, 2013–2015**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Encephalitis/Encephalopathy(^a)</th>
<th>Other Encephalopathy(^b)</th>
<th>Simple/Typical Febrile Seizure</th>
<th>Other Seizure</th>
<th>Acute Ataxia</th>
<th>Other Focal Neurological</th>
<th>Total</th>
<th>(P) Value(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>10 (19)</td>
<td>7 (13)</td>
<td>14 (26)</td>
<td>16 (30)</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td>54 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Median age (y, range or IQR(^b))</td>
<td>2.9 (1.3–6.4)</td>
<td>2.8 (0.1–4.9)</td>
<td>2.5 (1.3–4.6)</td>
<td>5.9 (2.1–9.6)</td>
<td>3.4 (1.3–10.6)</td>
<td>5.9 (10–9.2)</td>
<td>3.8 (1.3–6.6)</td>
<td>.51(^a)</td>
</tr>
<tr>
<td>Aged ≤4 y</td>
<td>7 (70)</td>
<td>6 (86)</td>
<td>11 (79)</td>
<td>7 (44)</td>
<td>3 (75)</td>
<td>1 (33)</td>
<td>31 (63)</td>
<td>.21</td>
</tr>
<tr>
<td>Male sex</td>
<td>3 (30)</td>
<td>5 (71)</td>
<td>7 (50)</td>
<td>12 (75)</td>
<td>1 (25)</td>
<td>2 (67)</td>
<td>28 (58)</td>
<td>.18</td>
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<tr>
<td>Vaccinated</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (6)</td>
<td>0</td>
<td>0</td>
<td>2 (4)</td>
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<tr>
<td>Preexisting neurological disease</td>
<td>1 (10)</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>13 (81)</td>
<td>0</td>
<td>1 (33)</td>
<td>17 (35)</td>
<td>&lt;.01</td>
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<tr>
<td>Other medical comorbidities</td>
<td>0</td>
<td>0</td>
<td>4 (29)</td>
<td>7 (44)</td>
<td>1 (25)</td>
<td>1 (33)</td>
<td>13 (24)</td>
<td>.07</td>
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<td>Specific diagnoses</td>
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<td>...</td>
<td>3</td>
<td>...</td>
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<tr>
<td>S ANE</td>
<td>3</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>1 PRES(^c)</td>
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<td>Hypertensive</td>
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<td>2 AESD</td>
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<tr>
<td>1 transverse myelitis</td>
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<tr>
<td>1 Epsosclerous myelitis</td>
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<td>...</td>
<td>...</td>
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<tr>
<td>1 acute visual disturbance</td>
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<td>...</td>
</tr>
<tr>
<td>Influenza A</td>
<td>6:4</td>
<td>6:1</td>
<td>9:5</td>
<td>6:10</td>
<td>4:0</td>
<td>2:1</td>
<td>33:21</td>
<td>16</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>30 (30)</td>
<td>16 (17)</td>
<td>3/13 (23)</td>
<td>2/13 (15)</td>
<td>1 (25)</td>
<td>0</td>
<td>8/47 (17)</td>
<td>.60</td>
</tr>
<tr>
<td>ICU admission</td>
<td>6 (60)</td>
<td>2 (29)</td>
<td>1 (7)</td>
<td>6 (38)</td>
<td>0</td>
<td>0</td>
<td>15 (26)</td>
<td>.04</td>
</tr>
<tr>
<td>Median LOS (d, range or IQR(^b))</td>
<td>6.5 (3.5–20)</td>
<td>3 (2–9)</td>
<td>1 (1–2.3)</td>
<td>4 (1.3–14)</td>
<td>5.5 (2–20)</td>
<td>4 (2–10)</td>
<td>3 (2–8.3)</td>
<td>.02</td>
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<tr>
<td>Death</td>
<td>2 (20)</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (6)</td>
<td>.5</td>
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<tr>
<td>Incomplete recovery</td>
<td>3/8 (38)</td>
<td>1 (14)</td>
<td>0/13</td>
<td>5 (31)</td>
<td>0</td>
<td>1 (33)</td>
<td>10 (18)</td>
<td>.08</td>
</tr>
</tbody>
</table>

\(^a\) Percentage of total \(n=54\) \(83\%\) of patients with IAND had respiratory symptoms; 62\% had fever. \(^b\) Lactate dehydrogenase (LDH) was available in 45 cases; median LDH was 487 U/L (range 22–3306 U/L). \(^c\) Postoperative or other neurological disease: 2\% had chronic meningitis, 1\% had chronic subdural hematoma, 1\% had aseptic meningitis, 1\% had acute transverse myelitis, 1\% had Guillain-Barré syndrome, 1\% had acute primary polyradiculoneuropathy, 1\% had chronic lower spinal cord injury, and 1\% had traumatic brain injury. \(^d\) \(P\) value for the comparison between patients with and without the respective variable.
IAND: Clinico-pathological Spectrum

Increasing Neurological Sequelae and Mortality

Acute Onset – Cytokine storm

+Reduced seizure threshold*

Febrile seizures ~26%
Exacerbation seizures ~30%

Non-specific encephalopathy ~13%
Non-specific encephalitis ~8%
MERS ~2%
Hypertensive encephalopathy/PRES ~2%

+Excitotoxicity* (AEFCSE)

HHS* AEDS ~4% AIEF

ANE I* (recurrent/familial) ~2%

+Blood Brain Barrier injury*

ANE* (sporadic) ~4%
HSES/ASEM
AHL

Sub-acute Onset – adaptive immune responses

Myositis
Acute cerebellar ataxia* ~7%

ADEM GBS
Transverse Myelitis ~2%
Ospoclonus-myoclonus* ~2%

Fulminant Cerebellitis*
Cerebral vasculitis*

Conclusions

- IAE is associated with a high morbidity and mortality
- Influenza a possible cause of encephalitis syndrome in all children during influenza season
- Incidence of IAE comparable to that in 2009–10 pandemic and in East Asia
- IAND occurs primarily in children younger than 5 years and without preexisting neurological disease
- Specific consideration of these severe syndromes in discussion re. universal child influenza vaccination

State funding for universal ‘under-5’ influenza vaccination from 2018
### Human Herpes Virus-6 B (n=3)

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8y boy Post allogeneic HSCTx ~4-5 weeks</td>
<td>16 mo boy, previously well</td>
<td>13 mo girl, previously well</td>
</tr>
<tr>
<td>CSF – WCC 0, prot 0.31 HHV6 pcr POS. Blood HHV6 pcr POS, then NEG on Rx.</td>
<td>CSF – WCC , prot 0.15 CSF and blood HHV6 PCR pos</td>
<td>CSF – WCC 12, Prot 1.16 CSF and Blood HHV6 PCR pos (log 4.7 in blood) HHV6 IgG pos, IgM pos</td>
</tr>
<tr>
<td>Later died</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** exclusion of chromosomally integrated HHV6 not undertaken in these cases
Human Herpes Virus-6 (B)

Two clear phenotypes:

- **Post Transplant Acute Limbic Encephalitis (PALE)**
  - Clinically: antegrade amnesia, insomnia, delirium, seizures
  - EEG: localised temporal lobe epileptiform discharges.
  - Imaging: localized medial temporal lobe T2, FLAIR, DWI
  - Risk: unrelated donor and cord HSCT recipients
  - Resolution of symptoms with foscarnet and ganciclovir
  - ? up to 40% mortality + up to 80% significant neurologic sequelae

- **Primary HHV-6 associated encephalopathy/encephalitis**
  - Up to 17% IAE in children
  - Clinically exanthem subitum + seizures + encephalopathy
  - Leading secondary cause of IAE clinico-radiological syndromes (ANE, AESD, AIEF, HHS etc.)


# Epstein-Barr Virus (n=2)

<table>
<thead>
<tr>
<th>5yo boy, previously well</th>
<th>12 yo girl, previously well</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 day vomiting illness, GTCS on day 2 admission then 2x GTCS day 3. Irritable, combative post-ictal for 48hrs. Slowly settled. Rx with steroids. Rash.</td>
<td>Headache, fever, visual symptoms and papilloedema. Developed unsteady gait, intention tremor + hyperreflexia.</td>
</tr>
<tr>
<td>MRI - marked T2 hyperintensities caudate + lentiform nuclei + thalami, centrum semiovale and perirrigonal WM. Mild changes paracaline cortex, cingulate gyrus. No DWI</td>
<td>MRI – peri-ventricular WM changes in occipital and R parietal lobe</td>
</tr>
<tr>
<td>EEG – abnormal</td>
<td>EEG – abnormal – R hemispheric slowing</td>
</tr>
<tr>
<td>CSF – WCC 2, prot 0.13 EBV IgM + heterophile Ab pos. CSF EBV PCR pos. Ev/Rhino PCR pos on nasal swab</td>
<td>CSF – WCC 286 (97% Mono), prot 1.78 CSF EBV PCR pos. EBV IgG pos, IgM neg</td>
</tr>
</tbody>
</table>
Epstein-Barr Virus

Primary EBV associated encephalitis

- 5-10% of childhood acute encephalitis
- Pathogenesis?
- Clinically: meningism + progression to lethargy, disorientation and coma; radicular pain often reported
- CSF ‘aseptic meningitis’; Atypical lymphocytes may be seen.
- Diagnosis:
  - Serology showing primary infection (EBV viral capsid antigen (VCA) IgM or EBV VCA seroconversion) **AND** EBV DNA in CSF by PCR.
  - If able EBV specific antibodies in the CSF with an high CSF:serum ratio may increase the specificity
- MRI can be normal; basal ganglia and cerebellar lesions
- Acyclovir is not recommended.
- Majority recover fully, occ. severe adverse outcomes

# Murray Valley Encephalitis Virus cases (n=2)

<table>
<thead>
<tr>
<th>8y boy</th>
<th>2mo girl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, seizures, reduced LOC, lower limb  spasticity</td>
<td>‘Septic’, status epilepticus, flaccid quadriplegia, CN palsies, oral dyskinesia</td>
</tr>
<tr>
<td><strong>MRI</strong> - “Diffuse meningeal enhancement + basal ganglia and <strong>bilateral</strong> thalamic diffusion restriction”</td>
<td><strong>MRI</strong> - “<strong>Focal unilateral thalamic</strong> + rostrum CC diffusion restriction”</td>
</tr>
<tr>
<td><strong>EEG</strong> - abnormal</td>
<td><strong>EEG</strong> - abnormal</td>
</tr>
<tr>
<td><strong>CSF</strong> – WCC 388, prot 0.86</td>
<td><strong>CSF</strong> – WCC 156, prot 2.4</td>
</tr>
<tr>
<td>MVEV IgM pos (IgG neg)</td>
<td>MVEV IgG and IgM pos. CSF MVEV IgM neg.</td>
</tr>
</tbody>
</table>

Both children with severe neurological sequelae at discharge.
# Endemic Flaviviruses

<table>
<thead>
<tr>
<th></th>
<th>Murray Valley Encephalitis Virus (MVEV)</th>
<th>Kunjin Virus (KUNV/WNV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus Vector</strong></td>
<td><em>Flaviviridae; JEV serogroup</em></td>
<td><em>Flaviviridae; JEV serogroup; WNV-like</em></td>
</tr>
<tr>
<td></td>
<td><em>Culex annulirostris</em></td>
<td><em>Culex spp.</em></td>
</tr>
<tr>
<td><strong>Ecology + epidemiology</strong></td>
<td>Enzootic: mosquito-water bird cycle in Northern Australia; mammals as amplifiers</td>
<td>Epizootic: SE + SW Australia ?climactic factors</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>0-2 cases pa since 2001 except 2001(6); 2009(4); <strong>2011 (16)</strong></td>
<td>0-3 cases pa since 2001 except 2001 (5); 2003 (9); 2004 (6).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outbreak in horses in NSW 2011</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>~1% infections = disease. JEV-like. mortality 30%; young children at ↑ risk</td>
<td>Similar to MVE but less severe, no deaths. FAR syndrome.</td>
</tr>
</tbody>
</table>
Testing in the ACE study cohort

- ‘Arbovirus’ testing = \textit{flavivirus} (+/- alphavirus)

<table>
<thead>
<tr>
<th></th>
<th>Suspected Encephalitis N=324</th>
<th>Not encephalitis N=130</th>
<th>Encephalitis with known cause N=156</th>
<th>Unknown encephalitis N=38</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arboviral serology tested</td>
<td>25/308 (8%)</td>
<td>4/119 (3%)</td>
<td>15/143 (12%)</td>
<td>6/36 (17%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Arboviral testing positive</td>
<td>2/25 (8%)#</td>
<td>0</td>
<td>2/15 (13%)#</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher exact testing comparing proportion tested in the encephalitis with known cause and unknown encephalitis groups.
Neuroimaging & Exposure history in untested, ‘Unknown’ encephalitis

- MRI performed in 29 of 30 cases.
- MRI abnormal “consistent with encephalitis” in 18/29
  - With thalamic involvement: n=5
  - With other basal ganglia involvement: n=3

- Mosquito bites: 2 of 30 (7%) cases

- Travel OS: 4/8 of 30 (27%) cases
  - 1 Bali 2/52 prior
  - 1 Malaysia 3 mo prior
  - 1 Hawaii 5 mo prior
  - 1 Pakistan nos

28%

13%
Rotavirus

12 yo boy, previously well

Fever, diarrhoea and vomiting. GTCS. Confused, ‘delirious’ >24hrs post
Clinically dehydrated – but not electrolyte disturbance

CT normal
CSF – WCC 3, Prot 0.17

Rotavirus

- Since 1980’s – seizures (afebrile) and encephalopathy in the context of acute gastroenteritis
- Up to 10% Rotavirus GE with seizures; 6% encephalopathy
- >75% outcome benign; occ. death
- Published cases with:
  - CSF pleocytosis
  - CSF rotavirus NA detection - ?contaminant
  - CSF rotavirus Ab detection

- More recently specific clinic-radiological phenotypes:
  - MERS
  - HHS
  - ‘Cerebellitis’
  - Reye Sx

Emerging and re-emerging

- Australian encephalitides:
  - Murray Valley Encephalitis (MVEV)
  - WNV/Kunjin Virus (KUNV)
  - Australian Bat Lyssavirus (ABLV)
  - Hendra virus

- Regional threats:
  - Rabies (RABV)
  - JEV
  - Dengue
  - Nipah
  - CHKV

Britton et al. JPCH 2014
Britton et al. ID-DT 2014
Japanese Encephalitis Virus

‘encephalitic’ Flavivirus

- 11-69% childhood encephalitis in Asian cohorts
- almost 70,000 cases in Asia annually
- Up to 185 per 100,000 per year; 75% <15y

- Clinical: Specific features associated with JEV encephalitis include a Parkinsonian movement disorder, and weakness, be it bulbar or limb
- Diagnosis: serum AND preferably CSF for JEV-specific IgM. CSF PCR relatively insensitive
- MRI: signal in the thalami, substantia nigra and basal
- No effective treatment;
  - trials of ribavirin, interferon-alpha and dexamethasone have shown no benefit
- Outcome: CFR 20-30% and moderate-severe sequelae up to 40%
  - Risk Factors associated with worse outcome: younger age, greater impairment LOC, dystonia, focal neurologic signs
- Vaccine preventable, but not all countries undertake surveillance and/or have immunization programs (WHO)
Dengue

‘non-encephalitic’ Flavivirus
- FAR + Haemorrhagic fever
- 2-28% of childhood encephalitis in Asian cohorts; 0.5-21% of hospitalized Dengue

- Encephalopathy - indirect mechanisms BUT evidence of detection of Dengue virus within the CNS from clinical and autopsy studies
- CSF pleocytosis + absence of liver failure, metabolic derangement or intracranial haemorrhage differentiate encephalitis from encephalopathy

- Clinical: Altered LOC, seizures, limb rigidity/weakness
- Diagnosis: serum AND CSF specific IgM, and blood/CSF for Dengue RNA by PCR and/or NS1 antigen.
- Outcome: In small series, majority fully recover; death and neurological sequelae described

Chikungunya

alphavirus from family towaviridae

- Most commonly - fever, arthralgia, rash with potential chronic arthritic disease

- Up to 10% of CHKV infections in adults associated with encephalitis

- La Reunion island outbreak 2005-6 - 30 children, 12 encephalitis (decreased consciousness/seizures/focal neurological signs)

  - 2 died, 5 neurological sequelae at 6 months

- Diagnosis: positive PCR or IgM in blood AND positive PCR in CSF

Countries and territories where chikungunya cases have been reported*
(as of April 25, 2018)

Data table: Countries and territories where chikungunya cases have been reported

<table>
<thead>
<tr>
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<th>ASIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>Bangladesh</td>
</tr>
<tr>
<td>Benin</td>
<td>Bhutan</td>
</tr>
<tr>
<td>Burundi</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Cameroon</td>
<td>China</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>India</td>
</tr>
<tr>
<td>Comoros</td>
<td>Indonesia</td>
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<tr>
<td>Cote d'Ivoire</td>
<td>Laos</td>
</tr>
<tr>
<td>Dem. Republic of the Congo</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Djibouti</td>
<td>Myanmar (Burma)</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td></td>
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</tbody>
</table>

<table>
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<tr>
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</table>

*Does not include countries or territories where only imported cases have been documented.


The University of Sydney
Algorithm 1:

‘Suspected Menigo-encephalitis’

- ↑ sensitivity for diagnosis
- ↑ awareness of ‘mimics’
- Addresses: CSF sampling, early and appropriate initiation Aciclovir, imaging

Britton et al. IMJ 2015;45(5):563-76
Britton et al. MJA. 2015;202(11):576-7
Algorithm 2: ‘Probable Encephalitis’

- Universal diagnostics and consultation
- Exclusion HSV
- Directed diagnostics based upon risk factors, clinical and radiologic features
- Role of brain biopsy

Britton et al. IMJ 2015;45(5):563-76
Britton et al. MJA. 2015;202(11):576-7
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- NHMRC ECR fellowship (1054414) Khandaker
- NHMRC CRE critical infections APP1001021 (Jones, Booy)