General Paediatric Meeting

GMB: Winter blues

Friday 4th October 2013

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Case 1
Causes of Acute Necrotising Encephalopathy (2)

- Influenza A + B
- Human Herpes Virus 6 + 7
- Herpes Simplex Virus
- Rubella
- Measles
- Varicella
- Parainfluenza
INFLUENZA + NEURAL COMPLICATIONS
Neural Complications

• Retrospective cohort of 842 children with laboratory-confirmed influenza: incidence of neurologic complications was 4 per 100,000 person-years (1)

• Encephalopathy/ Encephalitis (2)
• Reye Syndrome
• Seizures
• Myelitis
• Guillain-Barre Syndrome/Paralysis
• Stroke
Prospectively collected data on neurologic complications of H1N1 2009 of 6 major paediatric hospitals in Australia

<table>
<thead>
<tr>
<th>Neurologic complications</th>
<th>Total</th>
<th>Preexisting conditions</th>
<th>Previously healthy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurologic complication, n (%)</td>
<td>49 (9.7)</td>
<td>27</td>
<td>22</td>
<td>0.45</td>
</tr>
<tr>
<td>Seizure, n (%)</td>
<td>38 (7.5)</td>
<td>20</td>
<td>18</td>
<td>0.35</td>
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<tr>
<td>Encephalitis/encephalopathy, n (%)</td>
<td>7 (1.4)</td>
<td>5</td>
<td>2</td>
<td>0.43</td>
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<tr>
<td>Confusion/disorientation, n (%)</td>
<td>5 (1.0)</td>
<td>4</td>
<td>1</td>
<td>0.24</td>
</tr>
<tr>
<td>Loss of consciousness, n (%)</td>
<td>5 (1.0)</td>
<td>4</td>
<td>1</td>
<td>0.24</td>
</tr>
<tr>
<td>Paralysis/GBS, n (%)</td>
<td>2 (0.4)</td>
<td>0</td>
<td>2</td>
<td>0.19</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>1 (0.2)</td>
<td>1</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>ICU admissions, n (%)</td>
<td>15 (2.9)</td>
<td>7</td>
<td>8</td>
<td>0.53</td>
</tr>
<tr>
<td>LOS in hospital, d, mean; median (range)</td>
<td>6.5; 3 (1–49)</td>
<td>8.5; 3 (1–49)</td>
<td>3.9; 2 (1–16)</td>
<td>0.008</td>
</tr>
<tr>
<td>LOS in ICU, d, mean; median (range)</td>
<td>4.4; 1.5 (1–30)</td>
<td>7.0; 3 (1–30)</td>
<td>1.8; 1 (1–5)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Encephalopathy

- Acute non-inflammatory encephalopathy
- Most commonly associated with Influenza A
  - Influenza B responsible for 10% cases (2)
- Most severe form: Acute necrotising encephalopathy (20%) (2)
  - Incidence unknown (>240 cases reported from Asia, 5 from North America and 10 from Europe) (3)
  - Symmetrical necrosis
    - Thalamus
    - Other deep brain structures
- Leads to death or severe neurodisability in 70% of affected children (2)
Encephalopathy: Risk Factors

• Young age
  • Peak age: 6 – 18 months

• Demographic
  • Japan and Taiwan

• Genetics
Genetics

- Mutation in gene RANBP2 (2q12.1-2q13)
  - Condition: Acute Necrotising Encephalopathy 1 (ANE1)
  - Autosomal dominant missense mutation in ran-binding protein 2
    - Encodes for nuclear pore
    - Unclear how mutation alters gene function to cause phenotype
    - Mutations can appear de novo
  - 40% chance of ever developing ANE in a lifetime

- Importance
  - Genetic contribution (family members)
    - Identify at-risk population
  - Possibility of recurrence
  - Potential for ameliorating the outcome with early aggressive intervention
Pathology: Cytokine Hypothesis

- Unclear whether:
  - Viral invasion neural tissue
  - Inflammatory cytokines
  - Metabolic disease
  - Genetic susceptibility
- Most likely immune mediated or autoimmune rather than direct invasion of CNS
  - Often no CSF pleocytosis and PCR in CSF negative
- Genetically susceptible young children → hypercytokinaemia → vascular inflammation and leakage of plasma into brain parenchyma → cerebral oedema which triggers brain apoptosis
Clinical Features of Acute Necrotizing Encephalopathy (2)

- Normal growth and development
- 1-3 days after initial influenza symptoms commence
  - Acute encephalopathy
  - Coma
  - Seizure
  - Focal neurological deficits
Diagnostic Criteria for ANE

- Main diagnostic criteria:
  1. Acute encephalopathy 1-3 days following onset of febrile disease
     - Required: Deterioration of consciousness
     - Supportive: Seizures
  2. Brain imaging demonstrating symmetric, multifocal lesions:
     - Required: Bilateral thalami
     - Supportive: Peri-ventricular white matter, internal capsule, putamen, brainstem, cerebellum
  3. Absence of CSF pleocytosis (increase in CSF protein common)
  4. Increase in serum transaminases sometimes present (normal ammonia)
  5. Exclusion of other disease (infectious, metabolic, toxic, autoimmune)
Imaging

- Cerebral oedema (majority)
- 10-20% demonstrate features of acute necrotizing encephalopathy
  - Brain T2-weighted MRI: Multiple symmetrical lesions
    - Thalami (primarily)
    - Upper brainstem tegmentum
    - Periventricular white matter
    - Putamina
    - Cerebellum
- Presence of haemorrhage and/or cavitation associated with more severe clinical outcome
General - Management

- Supportive
  - Ventilation
  - Circulation support
  - Treatment of seizures
- Monitoring and treatment of raised intracranial pressure
- Broad spectrum antibiotics + antivirals
Specific Management

• Recent changes in Japan since 2001 has lead to a decrease in mortality from 30% to 15% \(^{(8)}\)
  • Pulse methylprednisolone
  • High dose y-globulin
  • Plasmapheresis

• Steroids
  • Treatment with steroids in first 24 hours in children without brainstem involvement may improve outcome \(^{(9)}\)
Encephalopathy - Prognosis

- Prognosis \(^{(2)}\)
  - 30%: Fatal
    - Half from multi organ failure
    - Half from brain stem failure
  - 30%: Persisting neuro-disability
    - (secondary to cerebral atrophy)
  - 30%: Recover
References


Case 2
Influenza Updates
• 70% children contract the virus during pandemic years (compared with 10-30% adults)

• Amongst other vaccine-preventable diseases, flu is the leading cause for hospitalisations in children <5 y.o.

Courtesy of Influenza Specialist Group (ISG)
Southern Hemisphere 2013 flu vaccine contains antigens representing the strains:

- A/California/7/2009 H1N1 pdm09-like virus
- A/Victoria/361/2011 H3N2-like virus
- B/Wisconsin/1/2010-like virus
Influenza Situation Report (Week 38)
VIDRL (Victorian Infectious Diseases Reference Laboratory)

- 3,328 laboratory-confirmed influenza cases notified year-to-date in VIC (5,189 at the same time in 2012)

- Australia-wide 18,995 cases year to date (National Notifiable Diseases Surveillance System)
  - 24,248 in 2011
  - 41,505 in 2012
WHO Collaborating Centre for Reference and Research

- 253 influenza isolates in VIC 30/4/13 to 23/9/13 (5 months)
  - 22% A/California/7/2009 H1N1 pdm09-like virus
  - 19% A/Victoria/361/2011 H3N2-like virus
  - 58% B/Massachusetts/2/2012  ---- Antigenic variant of B/Wisconsin/1/2010-like
  - 2% B/Brisbane/60/2008-like
Data from 30/4/13-23/9/13
Laboratory detection of respiratory viruses from all respiratory PCR samples tested at VIDRL 2013
Summary

• Young children are at risk of contracting and being hospitalised from influenza
  • Vaccine recommendations

• Current influenza vaccine: A-H1N1, A-H3N2, B-Wisconsin

• In VIC May-Sept 2013, high proportion ~60% of influenza B (based on WHO data)
  • Majority are B/Massachusetts/2/2012-like *antigenic drift
Summary

• Neurological complications
  • 10% hospitalised cases
  • 55% children had pre-existing medical conditions and 43% pre-existing neurological problems
  • 50% cases in children <5 years
  • Only 60% presented with the triad of cough, coryza and fever and 12% had no respiratory symptoms: think of Flu!

• Underlies importance of early diagnosis, use of antivirals and universal flu vaccination
  • Only 14% children with pre-existing medical conditions had had the flu vaccine and 10.9% overall

Thank you! 😊