MRI findings in Children on Vigabatrin Therapy
Case study

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Introduction

- Infantile spasm (IS)
  - Rare refractory type of childhood epilepsy characterized by spasms, arrested psychomotor development.
  - EEG hypsarrhythmia
  - 2 to 5 per 10,000 live births.
Pathophysiology of IS

- Non specific age-dependent reaction of the immature brain to injury (diffuse or focal).
- Abnormal brainstem activity, hypothalamic activity.
Prognosis of IS

- 50% have chronic refractory epilepsy.
- 20-50% develop Lennox-Gastaut syndrome.
- Mental retardation in 70-80%
- 10-33% of Children with IS die before age 3.
Treatment

- ACTH and predonisone.
- Vigabatrin.
Vigabatrin

- Specific irreversible inhibitor of gamma aminobutyric acid (GABA) transaminase.
- Increase GABA levels in brain.
- GABA = principal inhibitory neurotransmitter in CNS.
- Increase the threshold for seizures.

<table>
<thead>
<tr>
<th>Bodyweight</th>
<th>Daily Dose</th>
<th>No. Tablets/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-15 kg</td>
<td>0.5-1 g/day</td>
<td>1-2 tablets/day</td>
</tr>
<tr>
<td>16-30 kg</td>
<td>1-1.5 g/day</td>
<td>2-3 tablets/day</td>
</tr>
<tr>
<td>31-50 kg</td>
<td>1.5-3 g/day</td>
<td>3-6 tablets/day</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>2-4 g/day</td>
<td>4-8 tablets/day</td>
</tr>
</tbody>
</table>

The drug was first licensed in Britain and Ireland in 1989 and used in clinical practice in over 40 countries.
Non clinical toxicologic studies

- High dose (100-300mg/kg/day) of Vigabatrin is associated with intramyelinal edema (IME) in the brains of mice, rats, and dogs.
- The lesions did not progress to demyelination.

Cohen JA et.al. Epilepsia 2000
Clinical studies

- MRI in 292 pts and autopsy and surgical material in 74 patients demonstrated absence of IME in adults and children with CPS. (3 months to 18 year old)

- The safety of Vigabatrin was evaluated in 2081 epileptic patients treated in clinical trials.

- The relationship of adverse events to Vigabatrin therapy was not clearly established as patients were taking other antiepileptic drugs concomitantly.

- The most frequently reported adverse events were somnolence (12.5%), fatigue (9.2%), and weight gain (5%).

Snead OC et al. 1994
Visual field defects

- The drug is “not approvable” according to the US FDA in 1998.
- Three patients developed severe and persistent concentric visual field defects.
- Incidence of visual field defect is 30% for more than one year.
5 month old male baby with IS. Seizures began at 2-3 months of age. ACTH was started at 4 month old. GERD. Neuroexam: Normal.
May 5 2006
First seen at UCLA

May 20 2006
Diagnosed IS

Zonegran 25mg po q day,
ACTH 40 units IM,
Kepra 250mg po bid

May 23 2006
ACTH 20 units IM QOD (on taper schedule)
Zonegran 0.5mg po QAM,
1mg PO QHS --> supposed to be 50mg po q am and 100mg po q pm
Vigabatrin 250mg PO BID

May 31 2006
MRI 7-26-2006
Vigabatrin 500 mg PO BID

ACTH 20 units IM QOD (on taper schedule)

June 20 2006
8 weeks after Vigabatrin started

Outside MRI Normal
○ IS controlled and no seizure 3 weeks after starting Vigabatrin.
○ Abnormal eye movement started 6 weeks later.
○ MRI was obtained 8 weeks after the Vigabatrin has started.
Normal 5 month old
Diffusion weighted imaging show restricted diffusion in thalamus, basal ganglia and tegmentum portions of the brain stem.
8 months later
MRI abnormality was found in 12 of 15 IS patients.
- Average dose 143mg/kg.
- Average age 12-13 months old
- After 3-4 months of therapy.
- Resolution after discontinuation.

Pearl PL et al. AES meeting Dec 2006 abstract.
Differential diagnosis

Leigh disease

Extrapontine myelinolysis

Encephalopathy
Summary

- Vigabatrin is effective for IS.
- Animal study showed IME.
  - Hypothalamus, fornix, thalamus etc.
- Recent MRI shows transient T2 change in thalamus, basal ganglia and brain stem.
- Monitoring with MRI necessary?