AED treatment in infantile spasms

Kwon Soonhak
Department of Pediatrics
Kyungpook National University Hospital
Even if West syndrome is a well known pediatric epileptic syndrome, there is no agreement about the first- and second-line treatments. In the past years, however, a great progress in the development of new AEDs allow us to have more treatment options to control the seizures.

This lecture may outline the effectiveness of a variety of different antiepileptic drugs for the treatment of West syndrome.
West Syndrome

1. Onset: peaks between 4Mo and 7Mo
2. Symptomatic, Probably symptomatic, Idiopathic
3. a) infantile spasms (epileptic spasms):
   flexor, extensor, lightning, nods, or mixed
   b) arrest of psychomotor development
   c) hypsarrhythmia or modified hypsarrhythmia
4. Overall prognosis → poor
Flexor spasm
Treatment of West Syndrome

1. Antiepileptic drug therapy
2. Hormonal therapy: ACTH, PDS, TRH, etc
3. Immunoglobulin
4. Ketogenic diet
5. Resective neurosurgery/callosotomy, etc
6. Others
ACTH versus Pulsatile Dexamethasone in the Treatment of Infantile Epilepsy Syndromes

1. A retrospective study,
   **Group 1**: 11 with West syndrome and 3 with LGS, **ACTH** (1989-2001)
   **Group 2**: 7 with West syndrome, 5 with ESES, and 2 with LGS, **pulsatile dexamethasone** therapy (2003-2006)

2. **Group 1:**
   For weeks 1 and 2, **15-20 IU/day of synthetic corticotropin** was given IM; increased by another **20 IU/day every 2 weeks**, up to a **maximum of 120 IU/day** in therapy-resistant seizures. In case of response, the dose was reduced by **20 IU/day every 2 weeks thereafter**.
   **Group 2**: **20mg/m² dexamethasone IV daily for 3 days**, with an interval of **4 weeks** between each cycle. Every patient received at least **5 cycles**.

Haberlandt E, et al. Pediatr Neurol 2010;42
Seizure response to ACTH in patients with West Syndrome \((n = 11)\) or LGS \((n = 3)\).
In 9/11 West syndrome patients became seizure free, but none with LGS \((0/3)\).
Seizure response to pulsatile corticoid therapy with dexamethasone in West Syndrome ($n = 7$) and in LGS/ESES ($n = 7$).
4/7 West syndrome patients became seizure-free, 1/2 with LGS exhibited seizure-frequency reduction, and 2/5 patients with ESES exhibited significant improvement according to electroencephalograms.
### Adverse events in two treatment groups

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>ACTH (n=14)</th>
<th>PCT (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections, viral</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Infections, bacterial</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Infections, viral, repeated</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Elevation of liver enzymes</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Increase of appetite</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial hypertrophy</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Exanthema, erythema</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Melena</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
In conclusion, pulsatile corticoid therapy was an effective alternative treatment to adrenocorticotropic hormone, but should be investigated in a larger group of patients.

Haberlandt E, et al. Pediatr Neurol 2010;42
Topiramate and adrenocorticotropic hormone (ACTH) as initial treatment for infantile spasms

- a retrospective study
- Children's Hospital of Philadelphia using the International Classification of Diseases → 50 patients, chart reviewed.
  → 31 patients (ACTH, n = 12; TPM, n = 19) as a first-line treatment for infantile spasms.
- 26 patients, symptomatic and 5 cryptogenic.
- 6 patients (50%) treated with ACTH had resolution of clinical spasms and hypsarrhythmia within a month, but 3 relapsed.
- Of the 19 patients treated with TPM, 4 patients (21%) eventually, though over a period of 0, 1, 8, or 69 months, had resolution of spasms and hypsarrhythmia.

Topiramate in children with west syndrome: a retrospective multicenter evaluation of 100 patients

- a retrospective, questionnaire-based data collection.
- median starting dosage 1.6 mg/kg/d (max 12.0 mg/kg)
- 61 patients: on additional 1 ~ 3 AEDs
- The most effective dose was 10 mg/kg
- **17.5% Sz free, 47%, Sz ↓ by at least 50%,**
- EEG (-) in 18 of 83 cases (22%)
- Side effects in 25% → sedation, loss of appetite, weight loss, and metabolic acidosis
- **TPM discontinued because of side effects (17%)**
  - worsening of seizures (4%)
- **In 44% of patients, treatment was continued for > 3 mo**
  
TPM is a useful drug in treating West syndrome. However, future prospective controlled studies should be performed

To evaluate the efficacy and tolerability of first-line TPM treatment for infantile spasms

20 patients

an initial dose of 1mg/kg/day → ↑1 mg/kg a week until their spasms were controlled or a maximum dose of 12 mg/kg/day

1) Six of 20 subjects (30%) had cessation of spasm and disappearance of hypsarrhythmia as seen via the video EEG;
2) 70% of the patients, including the spasm-free patients, had a reduction in their seizure frequency (>50%)
3) The clusters of spasm frequency decreased from 10.6 +/- 8.5 to 3.5 +/- 1.4 clusters/day.

TPM is effective and tolerated in those patients suffering from infantile spasms → new first-line drug for infantile spasms?

As initial therapy for infantile spasms caused by tuberous sclerosis, viagabatrin was treatment of choice.

As initial therapy for infantile spasms that are symptomatic in etiology, vigabatrin was also treatment of choice, with adrenocorticotropic hormone (ACTH) and prednisone other first-line options.

Wheless JW - Epileptic Disorder. 2007; 9(4):
Visual fields at school-age in children treated with vigabatrin in infancy

- VF of 16 children treated with VGB for infantile spasms (by Goldmann kinetic perimetry), at age 6-12 years.
- VGB started at a mean age of 7.6 (range, 3.2-20.3) months. mean duration of therapy: 21.0 (9.3-29.8) months cumulative dose 655 g (209-1,109 g)
- 8 children only on VGB, 5 ACTH & VGB, 3 VGB & other AEDs → 15 children had normal visual fields
  - Mild VAVFL in one child (6%): VGB for 19 months a cumulative dose of 572 g.

CONCLUSIONS: The risk of VAVFL may be lower in children who are treated with VGB in infancy compared to patients who receive VGB at a later age.

Gaily E, et al. Epilepsia 2009; 50(2)
Vigabatrin: 2008 update (I)

- Prevalence and incidence of the VGB-induced VFD
  25% to 50% in adults, 15% in children
  retinal defect in infants 15% to 31%
- A bilateral nasal defect → a concentric, bilateral FD
- Central visual acuity is almost always preserved.
- Onset after VGB exposure (earliest/mean time to onset)
  9 months/4.8 years in adults
  11 months/5.5 years in children
- The earliest sustained onset of the VGB-induced retinal defect in infants → 3.1 months.

Willmore LJ, et al. Epilepsia 2009; 50(2)
Vigabatrin: 2008 update: RECOMMENDATION (II)

- Cognitive, age-appropriate visual field testing is required at baseline and then repeated at intervals.
  → **Infants**: at baseline and at 3-month intervals for the first 18 months of treatment, and then every 6 months thereafter.
  → **Adults with CPS**: at baseline and at 6-month intervals.
- To select patients who are appropriate for VGB therapy.
- **Effectiveness of VGB can be detected within 12 weeks of initiating therapy**
  - weigh risk vs benefits
  - → off or continue VGB with close, periodic monitoring

The risk of developing the peripheral VFD with short-term exposure seems to be low, therefore, VGB is an appropriate option for patients with IS or refractory CPS who receive a clinical benefit from its effectiveness, given the clinical consequences of uncontrolled seizures and spasms.

Willmore LJ, et al. Epilepsia 2009; 50(2)
Current treatment of West syndrome in Japan

To elucidate current practice, a questionnaire was sent to 113 institutes. (1) the drugs used for the treatment (2) their dosage (3) the dosage and the schedule of ACTH therapy.

- Response rate was 51.3%.
- Vitamin B(6) was used most frequently as the first-choice drug followed by valproic acid, zonisamide, and ACTH.
- The most frequently used dose of ACTH was 0.0125 mg/kg/d.
- ACTH was administered every day for 2 weeks and then tapered off in more than 80% of the institutes.
- 2 alterations were observed: an increased use of zonisamide and a shortened duration of ACTH therapy.

Tsuji T, et al. J Child Neurol. 2007; 22(5)
Levetiracetam monotherapy in newly diagnosed cryptogenic West syndrome.


LEV was used initially in the treatment of five patients with newly diagnosed cryptogenic West syndrome.

LEV(30 mg/kg) tablets were crushed and administered via nasogastric tube.

2 → seizure free, 2 → 50% ↑ reduction
1 → no improvement

No relapses in the two patients at 6 months

It appears that LEV may be effective in the initial treatment of selected patients with cryptogenic West Syndrome.
Treatment of infantile spasms.
Hancock EC - Cochrane Database Syst Rev. 2008(4)

- Few well-designed RCT
- The numbers of patients enrolled have been small
- Overall methodology has been poor, hence it is not clear which treatment is optimal.

- Hormonal treatment > vigabatrin (?)
- If prednisone or vigabatrin are used then high dosage is recommended.
- Vigabatrin may be the treatment of choice in tuberous sclerosis.
Resolution of the EEG features may be important (?)

Further research using large studies with robust methodology is still required.
Despite the limited specificity of the available AEDs, some therapies might be considered syndrome-specific. Giving these therapies might be appropriate for children with certain epileptic encephalopathies, such as administration of stiripentol to children with Dravet syndrome, hormone therapy (eg, corticosteroids or adrenocorticotrophic hormone) and vigabatrin to children with infantile spasms, and benzodiazepines and hormone therapy to children with Landau-Kleff ner and other syndromes with continuous spike-wave of sleep.

*Lancet Neurol* 2008; 7: 57–69
VGB, ACTH
Freely
Vt B6, ZNS

ACTH, PDS

VPA, CLZ, TPM, LEV, LMT, FMT, etc
Conclusion

1. Within the limits of expert opinion and with the understanding from new research data, the experts' recommendations provide helpful guidance in situations where the medical literature is scant or lacking.

2. ACTH, VGB, TPM, ZNS, and other new AEDs such as LEV, VPA may be initially used for the children with West syndrome
   1<sup>st</sup> line: ACTH, VGB
   1<sup>st</sup> or 2<sup>nd</sup> line: TPM, ZNS, LEV, VPA
Thank You for Your Attention