Treatment of Infantile Spasms

Mary L. Zupanc, MD
Professor, Dept of Neurology and Pediatrics
Division Chief, Pediatric Neurology
Director, Pediatric Epilepsy Program
University of CA-Irvine/Children’s Hospital of Orange County
What Is Treatment Response in Infantile Spasms?

- **Treatment response is characterized by**
  - Complete cessation of spasms\(^1\)
  - Resolution of hypsarrhythmia\(^1\)
    - Prolonged EEG is necessary to confirm resolution of hypsarrhythmia\(^2\)
- **Parental observation substantially underestimates number of spasms a child experiences\(^2\)**
- **Studies relying on parental report of complete spasm cessation as sole outcome measure may overestimate positive outcomes**

Early, Aggressive Treatment of IS May Lead to Better Treatment Outcomes

- Seizure and cognitive outcomes are more favorable if IS treated early, regardless of type of medication\(^1\-\text{6}\)
  - True for both cryptogenic and symptomatic cases
- In a study of patients with symptomatic IS\(^2\)
  - 88% responded when treatment was initiated within 1 month of onset of IS
    - Response defined as confirmed cessation of spasms and resolution of hypsarhythmia within 6 weeks of treatment
  - 57% of patients treated \(>\) 2 months after onset did not respond
  - Lower rate of subsequent epilepsy and better cognitive outcomes in responders
- In a study of both symptomatic (\(n = 40\)) and cryptogenic (\(n = 17\)) patients treated for IS, patients treated within 1 month of onset had a significantly better developmental score (DS)\(^4\)
  - Symptomatic group: DS = 53.9 for early treatment and 37.9 for delayed treatment
  - Cryptogenic group: DS = 81.6 for early treatment, 65.5 for delayed treatment
- In a study of 37 patients with cryptogenic IS\(^5\)
  - Of 22 patients treated within 1 month of onset, all had normal cognitive outcomes compared to 40% in the late-treated group
  - Early-treated patients had better seizure outcomes (5%) than late-treated (47%)
UKISS Results: Effect of Lead Time to Hormonal Therapy on Vineland Adaptive Behavior Scales (VABS)

- Based on a multiple regression analysis controlled for the effects of treatment and etiology, there was a significant correlation between VABS score and lead time to treatment for all infants (regression coefficient (SE) = -3.9 (1.7), $P = 0.03$).
- The most striking effect was in patients with no proven etiology (cryptogenic).

ACTH had highest efficacy rating of any IS treatment by the AAN and CNS based on level of evidence*
  - "...ACTH is probably effective for the short-term treatment of infantile spasms and in the resolution of hypsarrhythmia"

AAN/CNS parameter based on review of 14 studies of ACTH therapy
  - 5 randomized controlled trials using no spasms/no hypsarrhythmia as confirmed by video-EEG outcome (3 Acthar)
  - 9 open label/case series (6 Acthar)

*The AAN and CNS conducted an analysis of published studies to date to determine the current best practice for the treatment of IS. Recommendations were based on a 4-tier classification scheme:
Level A = established as effective; Level B = probably effective; Level C = possibly effective;
Level U = data inadequate

ACTH was the only treatment that received a Level B rating as probably effective for the short-term treatment of IS and in the resolution of hypsarrhythmia. No treatment, including prednisone, vigabatrin, or any other AEDs for IS received a Level A rating, which required a prospective, blinded, randomized, controlled trial.

Mackay MT, et al. Neurology. 2004;52:1658-1661,
Additional Treatments for IS

- **Approved therapies**
  - Vigabatrin (approved August 21, 2009)

- **Other reported treatments**¹
  - Oral steroids
  - Valproate
  - Topiramate
  - Zonisamide
  - Pyridoxine
  - Ketogenic diet
  - Levetiracetam

- **Surgery**
  - In selected cases where there is evidence of a focal lesion

Other Therapies--Vigabatrin

• Vigabatrin is possibly effective in the treatment of infantile spasms, especially in patients with tuberous sclerosis (AAN and CNS Practice Parameter, 2004)

• There are some preliminary studies that indicate improved outcomes using the combination of Acthar ACTH and vigabatrin

• Vigabatrin can cause peripheral visual constriction, not vision loss or blindness

• The peripheral visual constriction typically occurs after 10 months of therapy.
Oral Steroids

• Older studies using oral prednisone at 2 mg/kg/day demonstrate less efficacy in the treatment of infantile spasms in comparison to Acthar ACTH

• There are no good controlled studies on higher dose steroids, such as 15 mg/kg/day prednisolone

• In addition, these newer studies are open label, using patients who have failed Acthar ACTH and vigabatrin. The studies contain a small cohort of patients.
United Kingdom Infantile Spasm Study (UKISS)

• Comparison of the efficacy of oral steroids vs. synthetic ACTH, not Acthar ACTH
• Fatally flawed study
• Relied on parental reporting only in determination for cessation of infantile spasms, without confirmation of elimination of hypsarrhythmia pattern on EEG
• Synthetic ACTH has been shown in older studies to be less effective than Acthar ACTH in the treatment of infantile spasms
Other Therapies

• None of the oral antiepileptic medications have been shown to effectively treat infantile spasms

• Topiramate—One study of 9 patients demonstrated efficacy in 7 patients. This study has never been duplicated.

• Valproate in young infants carries a significant risk of hepatoxicity: 1/500, most typically in patients with mitochondrial disorders

• Ketogenic diet---Only a few studies have been conducted, with possible efficacy

• Medical marijuana has not been shown to be effective in the treatment of infantile spasms
# Acthar Efficacy Studies

- All studies used the gold standard response criteria: complete cessation of spasms and resolution of hypsarrhythmia

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial (yr)</th>
<th>Patients (N)</th>
<th>Treatment Schedule</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td>Baram (1995)</td>
<td>29</td>
<td>150 U/m²/d divided (75 U/m² bid) Acthar x 2 wks vs 2 mg/kg/d divided (1 mg/kg bid) prednisone x 2 wks</td>
<td>No spasms, No hypsarrhythmia</td>
</tr>
<tr>
<td></td>
<td>Hrachovy (1994)</td>
<td>59</td>
<td>150 U/m² qd Acthar x 3 wks vs 20 U (~50 U/m² qd) Acthar x 2 wks</td>
<td>No spasms, No hypsarrhythmia</td>
</tr>
<tr>
<td></td>
<td>Hrachovy (1983)</td>
<td>24</td>
<td>20 U (~50 U/m²) qd Acthar x 2–6 wks vs 2 mg/kg qd prednisone x 2–6 wks</td>
<td>No spasms, No hypsarrhythmia</td>
</tr>
<tr>
<td>NRCTs</td>
<td>Sneed (1983)</td>
<td>30</td>
<td>150 U/m²/d divided (75 U/m² bid) Acthar x 1 wk vs 3 mg/kg/d divided bid prednisone x 1 wk</td>
<td>No spasms, No hypsarrhythmia</td>
</tr>
<tr>
<td></td>
<td>Sneed (1989)</td>
<td>15</td>
<td>150 U/m²/d divided (75 U/m² bid) Acthar</td>
<td>No spasms, No hypsarrhythmia</td>
</tr>
</tbody>
</table>
## High-dose Acthar vs Prednisone

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Initial Response (no spasms, no hypsarrythmia)*</th>
<th>Crossover Response (no spasms, no hypsarrythmia)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acthar; 150 U/m²/day divided dose (75 U/m² bid)</td>
<td>87 (13/15)*</td>
<td>88 (7/8)</td>
</tr>
<tr>
<td>Prednisone, 2 mg/kg/day divided dose (1 mg/kg bid)</td>
<td>29 (4/14)</td>
<td>50 (1/2)</td>
</tr>
</tbody>
</table>

*P = 0.0015 for initial response to Acthar compared to prednisone
†Response criteria were complete cessation of spasms and resolution of hypsarrythmia

---

1. H.P. Acthar Gel (repository corticosteroid injection) prescribing information, Questcor Pharmaceuticals, Inc.
Overall Response Rate in Patients With Acthar

Overall Response: No Spasms, No Hypsarrhythmia

Acthar Dosage Regimen

*RCI Questcor Analysis
ACTH Mechanisms of Action: Peripheral and Central

- Exact mechanisms of action for ACTH in treatment of infantile spasms are not fully understood.
- Action on adrenal gland produces maximal effects on release of corticotropins with relatively low doses of ACTH.
- In animal studies, high doses are needed to produce the central effects.
  - These data suggest Acthar has a direct effect on the central nervous system.

• Acthar should be administered intramuscularly at 150 U/m²/day divided into 2 daily injections of 75 U/m² for 2 weeks
• After 2 weeks of treatment, dosing with Acthar should be tapered, gradually eliminating Acthar administration over 2-week period
• Acthar typically dosed based on body surface area (BSA)
  – BSA calculation readily available through most formularies
  – Average BSA for a 6-month old is 0.4 m²
Suggested Tapering Regimen for Treatment of IS

- After the recommended treatment regimen of 150 U/m²/d (divided into 2 daily IM injections of 75 U/m²) over a 2-week period, the dose of Acthar should be gradually tapered over a 2-week period.
- One suggested schedule for tapering the dose:
  - 30 U/m² in the morning for 3 days
  - 15 U/m² in the morning for 3 days
  - 10 U/m² in the morning for 3 days
  - 10 U/m² every other morning for 6 days
Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of Infants and Children Under 2 Years of Age Treated With Acthar

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Event</th>
<th>Recommended 75 U/m² b.i.d. n = 122 (%)</th>
<th>150 U/m² q.d. n = 37 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac hypertrophy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cushingoid</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Convulsion</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nasal congestion</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

- The side effects of Acthar treatment are typically reversible or resolve once treatment is stopped
  - Patient may need careful monitoring during treatment with Acthar and for a period following the discontinuation of therapy
  - Side effects are similar to those with corticosteroids
  - Prolonged use of Acthar may increase the risk of side effects
Contraindications

- **Acthar is contraindicated**
  - In children under 2 years of age with suspected congenital infections
  - For any indication accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction
- **Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar**
- **Acthar is contraindicated in patients with**
  - Scleroderma
  - Osteoporosis
  - Systemic fungal infections
  - Ocular herpes simplex
  - Recent surgery
  - History of or presence of a peptic ulcer
  - Congestive heart failure
  - Uncontrolled hypertension
  - Sensitivity to proteins of porcine origin

H.P. Acthar® Gel (repository corticotropin injection) prescribing information, Questcor Pharmaceuticals, Inc.
• Infantile spasms is a neurological emergency that, once recognized, must be treated rapidly and effectively
• Acthar effectively eliminates spasms and hypsarrhythmia in 87% of patients treated with the FDA-approved dosage regimen
  – Best patient outcomes follow early effective treatment
• Adverse events are known and recognizable
• Benefits outweigh the risks of the drug and the consequences of inadequate treatment