Infantile Spasms in the Age of Guidelines, Pathways, and Big Data

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Nothing to Declare
Treatment of Infantile Spasms

- Leeches. Calomel, Purgative, Gum Lancing (West. 1841)
- Bromides, phenobarb, phenytoin, etc.
- ACTH. (Sorel & Dusaucy-Bauloye, 1958)
- Corticosteroids (Low, 1958)
- High Dose ACTH (Snead et al., 1983)
Treatment of Infantile Spasms

- Vigabatrin (Livingston et al., 1989)
- UKISS Study (Lux et al. 2004, 2005)
- Canadian protocol (Bitton et al., 2012)
Treatment of Infantile Spasms

Predatory Pharma

• 2001 Quesqor purchased rights for ACTH from Armour. Price went from $100/vial to $28,000 per vial

• 2013 Quesqor/Valeo acquired rights to synthactin; price went from $35.66/vial to $801.19/vial
Treatment of Infantile Spasms

• High dose prednisolone (Hussain et al., 2014)
• US IS consortium (Knupp et al., 2016)
• Steroids + VGB (O,Callaghan et al., 2017)
Treatment of Infantile Spasms

Lux A et al. UKISS VGB vs prednisolone vs. ACTH. Lancet 2004;364:1773

• Randomized multicentre open-label trial

• Followed to 3 mos

• ACTH more effective [76%] than prednisolone therapy alone [70%] than VGB [56%]
Treatment of Infantile Spasms

Lux A et al. UKISS VGB vs prednisolone vs. ACTH. Lancet Neurol 2005;4:712

• Randomized multicentre open-label trial
• Followed to 14 mos
• Corticosteroids same as VGB
• Early treatment leads to better devel outcome in non-symptomatic group
Treatment of Infantile Spasms

Bitton et al. Randomized control trial of flunarizine therapy as add on therapy and effect on cognitive outcome in children with IS. ’ Epilepsia 2012;53:1570

• VGB drug of choice. No response: ACTH
• Response: 96% spasm free within 8 weeks
• Multicentre Canadian study
Treatment of Infantile Spasms

O’Callaghan F et al. Safety and effectiveness of hormonal treatment vs. hormonal treatment + vigabatrin for IS. Lancet Neurol 2017;16:33

- Randomized multicentre open-label trial
- International study [377 pts. 102 hospitals]
- Hormonal +/− VGB
- Outcome: 4 week spasm cessation
Treatment of Infantile Spasms

O’Callaghan F et al. Safety and effectiveness of hormonal treatment vs. hormonal treatment + vigabatrin for IS. Lancet Neurol 2017;16:33

- Hormonal +/- VGB more effective [72%] than hormonal therapy alone [57%]
Treatment of Infantile Spasms

Meta-analyses

- AAN Practice Parameter (MacKay et al., 2004)
- AAN Practice Parameter (Go et al., 2012)
- Cochrane Review. (Hancock et al., 2013)
- German-Speaking Society for Neuropaediatrics (Tibussek et al., 2016)
Treatment of Infantile Spasms

Bottom line from all meta-analyses:

- Vigabatrin controls spasms and eliminates hypsarrythmia 50-60% of time.
Corticosteroids, either ACTH or high dose prednisolone control spasms and eliminate hyps 50-70% of the time.

Early Rx associated with better neurodevelopmental outcome
Treatment of Infantile Spasms

My bottom Line:

• Vigabatrin + high dose prednisolone may result in better outcomes than either alone.

• ACTH controls another 40% of IS who fail vigabatrin + high dose prednisolone
Corticosteroids and vigabatrin alone or together are the most effective first line drugs against infantile spasms.
Treatment of Infantile Spasms
SickKids Protocol

- Seen urgently by acute care team
- Clinical dx made
- EEG confirmation.
- Start VGB and see within the week in IS clinic
- Appropriate diagnostic evaluation done, incl. MRI in everyone
Treatment algorithm for newly diagnosed infantile spasms

**EEG**

- IS

- **EEG**
  - Vigabatrin
  - Prednisolone
    - If VGB contraindicated

- Cessation of spasms and disappearance of hypsarrhythmia (after 2 weeks of treatment)

- **YES**
  - Vigabatrin: Continue on same dose for 6 months then wean over 1-2 months
  - Prednisolone: Continue tapering dose for total of 5 weeks

- **NO**
  - Start ACTH (Synacthen Depot)
    - Wean off vigabatrin over one week if no response or maintain dose if partial response

- **EEG**
  - Relapse of spasms
    - Increase dose to regain control or reinitiate treatment or start another AED

- **EEG**
  - Cessation of spasms and disappearance of hypsarrhythmia (after 1 week of treatment)
    - If unknown etiology, treat with Pyridoxine for 2 weeks then folinic acid x 3 days then P5P x 3-5 days

- **YES**
  - Finish course of ACTH
  - **NO**
    - Wean ACTH over one week, refer to the Ketogenic Diet Clinic & for urgent G-tube assessment and/or start another AED

- **EEG**
  - Cessation of spasms and disappearance of hypsarrhythmia (after 2 weeks of treatment)
    - **YES**
      - Continue on maintenance dose of AED
    - **NO**
      - Initiate ketogenic diet or optimize AED dose or start another AED
Treatment of Infantile Spasms
Keto Diet


- 13 observational studies
- 67% spasm reduction
- 35% spasm free
In the treatment of infantile spasms, there are several insoluble problems:

- Lack of rigor of clinical trials
- Uneven access to ACTH because of obscene cost
- Lack of standardization of steroid dose and administration protocol to really determine best treatment.
Treatment of Infantile Spasms

What about TSC?

Chiron et al. 1991

Chiron et al. Epilepsy Res 1997;26:389 – Randomized trial of VBG vs. hydrocortisone in TSC w/IS

11 VGB vs 11 HC – prospective, randomized, crossover

11/11 VGB spasm free vs. 5/11 cortisone spasm free

6/6 cortisone failures crossed over to VGB spasm free
Treatment of Infantile Spasms

What about TSC?

Does early treatment with VGB after onset of EEG evidence of focal sz prevent spasms and improve development in TSC?

Infantile spasms are an age-related catastrophic epilepsy syndrome characterized by flexor &/or extensor spasms and severe EEG abnormalities, uniquely responsive to ACTH and Vigabatrin.
Infantile Spasms vs. Epileptic Spasms

- IS Hypsarrythmia
- Cluster of ES
- NO slow spike/w
- Filaminopathy
- Oligodendrogliosis
- FCD type I

- Late onset ES
- Single ES
- FCD type I/II
- Oligodendrogliosis

- TSC
  - LGS
  - Drop attacks
  - Atypical absence
  - Slow spike/w

- EIEE/EME
  - Burst-Suppression

- Focal onset seizure
- Generalized seizure

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Treatment of Infantile Spasms

Thanks to:

- Tina Go
- Blathnaid McCoy
- Jennifer Boyd