Medical treatments – where are we?

Finbar O’Callaghan
Reader in Paediatric Neuroscience
Plan of the talk

• Should we treat?
• What to treat with?
• Difficulties in evaluating treatment?
• Looking at the evidence
  – Infantile Spasms
  – Ohtahara
  – MPSI
  – TSC
  – Dravet’s
• Possible new avenues
• Conclusions
Should we always be treating?

- James Edwin West
- Born in 1840 in Tonbridge to William James West and Mary Dashwood
- Infantile spasms developed at 8 months
- Developmental regression
- Spasms stopped at 3 years
- Ongoing epilepsy and learning difficulty
- Leeches
- Cold applications to head
- Calomel purgatives
- Lancing of gums
- Warm baths
- Castor oil
- Hydrocyanic acid
Should we always be treating?

- Treatment may be relatively ineffective
- Treatment may be harmful (? GABA agonists in infancy)
- Very difficult to “sit on our hands”
• 5 categories of lead time:
  • < 7 days
  • 8-14 days
  • 15- 28 days
  • 1-2 months
  • > 2 months

• Each category in lead time to treatment lead to reduction in DQ of 3.9 points (95% CI 0.4 to 7.5 p=0.014)
“Infantile spasms should be treated with nitrazepam and a month of corticotrophin followed by 2 months of prednisolone unless the year ends with an odd number, when sodium valproate and prednisolone are de riguer, although you could make do with vigabatrin and 3 weeks of hydrocortisone if your favourite colour is blue and Jupiter is about to collide with Mars.”

“Treatment of infantile spasms”
Arch Dis Child 1995:73;188.
Difficulties in evaluating treatments in infantile epilepsy

- Double-blind RCT is thought to be “gold standard for evaluating treatments.
- Rarity of conditions
  - Lack of power
  - Expense
- Blinding often difficult
What outcomes are important?

- Reduction in spasms
- Abolition
- Electro-clinical
- Development
  - At what stage?
- Future epilepsy
Infantile spasms
Infantile spasms

Treatment of infantile spasms (Review)

Hancock EC, Osborne JP, Edwards SW


Neurology 2012;78;1974-1980

DOI 10.1212/WNL.0b013e318259e2ef
Infantile Spasms

- 18 RCTs
- 12 different pharmacological treatments
  - Vigabatrin
  - ACTH (9 different regimens and preparations)
  - Prednisolone
  - Prednisone
  - Hydrocortisone
  - Nitrazepam
  - Sodium Valproate
  - Sulthiame
  - Ganoxolone
  - Methysergide
  - Alpha-Methylparatyrosine
  - Magnesium Sulphate
Quality of studies

- **Methodology**
  - Only two studies had > 70 participants
  - 6 out of 18 stated method of randomisation
  - 4 reported concealment of allocation
  - In 6 studies assessors were blinded to allocation
Trials of agent versus placebo

• Vigabatrin versus placebo (Appleton et al, 1999)
  – 40 participants
  – 7/20 on VGB spasm free vs 2/20 on placebo
• Sodium valproate versus placebo (Dyken 1985)
  – Significant reduction in “spasm index” on valproate versus placebo
• Sulthiame versus placebo (Debus 2004)
  – 8/23 on sulthiame spasms free versus 1/23 on placebo
Low-dose versus high dose vigabatrin

- High dose regime (100-148 mg/kg/day)
- Low dose (18-36 mg/kg/day)
- 17/107 on high dose versus 8/114 on low dose became spasm free ($p = 0.04$)
Vigabatrin versus hormonal treatment (ACTH, high-dose prednisolone, tetracosactide)

- Vigevano et al. (1997)
  - 11/23 on VGB versus 14/19 on ACTH = spasm free
- Askalan et al. (2003)
  - 6/6 on VGB versus 3/3 on ACTH = spasm free
- Lux et al. (2004)
  - 28/52 on VGB versus 40/55 on hormonal Rx = spasm free

- Combining results:
  - 45/81 on VGB versus 57/77 on hormonal Rx = spasm free (Peto OR 0.42 95% CI 0.21 to 0.8)
ACTH versus high dose prednisolone

- Nested within UKISS study
- Comparison of ACTH 40-60 Units alt die vs Prednisolone 40-60 mg/day

- 19/25 on ACTH versus 21/30 became spasm free ($p = \text{n.s.}$)
ACTH versus low-dose prednisone

- Hrachovy et al. (1983), Baram et al. (1996)
- Prednisone has to be metabolised to prednisolone
- Hrachovy
  - ACTH (20 – 30 units/day) vs Prednisone (2mg/kg/day)
  - ACTH (5/12 spasm free) vs Prednisone (4/12 spasm free)
- Baram
  - ACTH (150 units/m²/day) vs Prednisone (2mg/kg/day)
  - ACTH (13/15 spasm free) vs Prednisone (4/14 spasm free)
High dose versus low dose ACTH

- Hrachovy et al. (1994), Shu et al. (2009)
- Hrachovy
  - High dose (150 units/m$^2$/day for 3 weeks) – 13/30 responded
  - Low dose (20-30 units/day for 2-6 weeks) – 14/29 responded
- Shu
  - High dose (50 IU/day for 3 weeks) – 53% responded
  - Low dose (0.4-1.0 IU/kg/day for 2 weeks) – 60% responded
Conclusions (Cochrane)

• Hormonal treatments lead to faster resolution of spasms and in more infants than vigabatrin
• Response without subsequent relapse may be no different
• If prednisolone or vigabatrin used – use high dose
• Hormonal therapies may be associated with better developmental outcome in those with no proven aetiology
Conclusions (American Academy of Neurology)

- Low dose ACTH should be considered
- ACTH and VGB may be considered for short term treatment of spasms (preference for ACTH)
- Hormonal treatment considered in preference to VGB for “cryptogenic” spasms
- Shorter treatment lag with either hormonal therapy or VGB may be associated with better developmental outcome
Ohtahara Syndrome

- Early onset (first month)
- Tonic spasms and focal seizures
- S-B pattern on EEG
- Underlying structural pathology

Treatments
- Keto diet
- Levetiracetam
- Zonisamide
- High dose phenobaritone
- Valproate
Migrating Partial Seizures of Infancy

- Infantile onset (< 6 mo)
- Almost continuous migrating polymorphous seizures
- Migrating multifocal discharges
- Psychomotor deterioration
- Treatments tried:
  - Keto diet
  - Levetiracetam
  - Rufinamide
  - Stiripentol
  - Bromides

McTague A et al. Brain 2013
Tuberous sclerosis complex

Comparison between vigabatrin (150 mg/kg/day) and hydrocortisone (15 mg/kg/day)

22 patients in trial

11/11 on vigabatrin vs 5/11 on hydrocortisone spasm free at 1 month (p < 0.01)

? Methodological problems
Dravet Syndrome

Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial

C Chiron, M C Marchand, A Tran, E Rey, P d’Athis, J Vincent, O Dulac, G Pons, and the STICLO study group*

Valproate (24 mg/kg/d) and clobazam (0.5 mg/kg/d)

Placebo (n = 20)

Stiripentol (n = 21)

(50 mg/kg/d)

1 month 2 months Open-label Baseline Double-blind

Stiripentol: 71% responders vs 5% placebo (P < 0.0001)
Ketogenic Diet

• Consider if hormonal therapies and vigabatrin fail in spasms
• Consider in malignant intractable epilepsies (e.g. Ohtahara, MPSI)
• ? At least as effective as any new add-on anticonvulsant medication
• Clinical trials
Therapies to be cautious about

Managing Severe Epilepsy Syndromes of Early Childhood

James W. Wheless, MD

<table>
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<tr>
<th>AED</th>
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<th>Report</th>
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<td>Perucca et al\textsuperscript{22}</td>
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New ways forward?

- Prophylaxis
- Combination therapy
- mTOR inhibition
- Neuroprotection
Prophylaxis

• Jozwiak et al. Epilepsia 2007 & EJPN 2011

• Methodology
  – 45 infants: 31 received standard therapy and 14 received prophylactic therapy
  – Significant reduction in LD in prophylactic group at 2 years (48% vs 14% \( p = 0.031 \))
  – Significant higher proportion seizure free in prophylactic group (93% vs 35% \( p = 0.004 \))

• Can we reliably identify children who will go on to develop epileptic encephalopathy?

• Problems of giving treatment with known side-effects (e.g. VFDs) to children who would never develop epilepsy

• Potentially other adverse effects of treatment
  – GABA agonists and the developing brain
Combination therapy

• Some patients will respond to one therapy and not another

• Rationale for
  – Combination of VGB and hormonal therapy vs hormonal therapy alone

• Combine therapies – multiply risk of side-effects/damage
Finding a better drug for epilepsy: The mTOR pathway as an antiepileptogenic target

Aristea S. Galanopoulou¹, Jan A. Gorter², and Carlos Cepeda³

- mTOR overactivation implicated in genetic forms of infantile spasms e.g. TSC, NF-1, PTEN
- Also implicated in multiple-hit animal model of infantile spasms
Rapamycin suppresses axon sprouting by somatostatin interneurons in a mouse model of temporal lobe epilepsy

*†Paul S. Buckmaster and *Xiling Wen

Departments of *Comparative Medicine and †Neurology & Neurological Sciences, Stanford University, Stanford, California, U.S.A.

- Somatostatin interneurons in dentate gyrus decrease in patients with TLE
- Surviving interneurons sprout axons? Pro-epileptogenic
- Rapamycin suppressed axon sprouting in a mouse model of TLE

Figure 1.
GFP-immunostaining of the dentate gyrus in a control mouse (A) and in mice that had experienced pilocarpine-induced status epilepticus and then were treated daily for 2 months with vehicle (B) or 3 mg/kg rapamycin (C). Asterisks in left panels indicate areas shown at higher magnification in right panels. m = molecular layer, g = granule cell layer, h = hilus, CA3 = CA3 pyramidal cell layer. Epilepsia © ILAE
Regulation of cell death and epileptogenesis by the mammalian target of rapamycin (mTOR)
A double-edged sword?

Ling-Hui Zeng,1 Sharon McDaniel,2 Nicholas R. Rensing1 and Michael Wong3
1Department of Pharmacy; Zhejiang University City College; Hangzhou, Zhejiang China; 2Department of Neurology and the Hope Center for Neurological Disorders; Washington University School of Medicine; St. Louis, MO USA

- mTOR inhibition may prevent essential repair of brain in the context of brain injury
- Paradoxical effect of mTOR inhibitors in animal models of status epilepticus
  - Timing of administration

Figure 3. Rapamycin causes paradoxical exacerbation of kainate-induced mTOR activation when administered within one hour of kainate. Adult rats were injected with vehicle (Con), kainate (15 mg/kg, i.p.), or rapamycin (6 mg/kg) at different intervals before or after kainate. Kainate alone (KA) causes increased mTOR activation, as reflected by the ratio of phospho-S6 to total S6 expression measured 7 days after kainate injection, compared to vehicle (Con). Pretreatment with rapamycin one day prior to kainate inhibits the kainate-induced mTOR activation (Pre-1d). In contrast, rapamycin administered within one hour before (Pre-1 h) or after (Post-1 h) kainate causes a paradoxical increase in the kainate-induced mTOR activation. *p < 0.05, ***p < 0.001 by ANOVA, compared to the KA group.
Neuroprotection?

- Vigabatrin vs Vigabatrin + Flunarizine
  - Non-significant difference in spasm cessation
  - Non-significant difference in development @ 24 months
  - BUT – significant difference in development in group with no known aetiology (84.1 vs 72.3 p = 0.03)...
Conclusions

• Evidence base is poor but slowly improving
• Treat early… but
• Beware of polypharmacy and side-effects
• Beware of using drugs that make the situation worse
  – e.g. Carbamazepine
• Infantile spasms
  – Hormonal therapy or vigabatrin
  – Hormonal therapy controls spasms faster and may be associated with better cognitive outcome in no-cause found group
• Some evidence for syndrome/disease specific treatments
  – e.g. Dravet, TSC
• Ketogenic diet
• Promising new avenues
  – e.g. mTOR inhibition, Combination therapy