UNIVERSITY OF EASTERN FINLAND

New developments of Epileptic Syndromes in very young infants

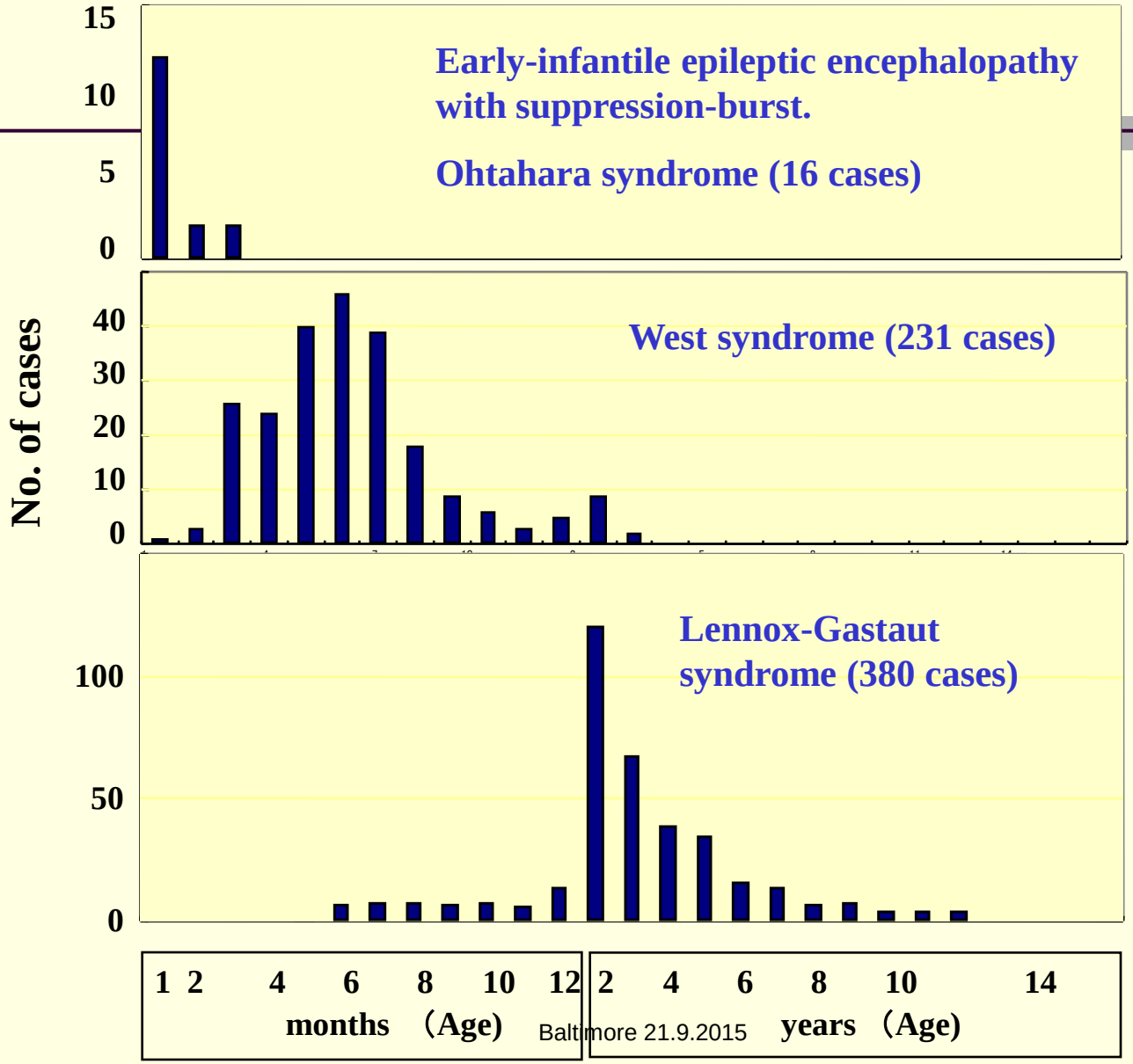
Raili Riikonen
MD, PhD, Professor
Kuopio University Hospital, Finland

I have no disclosers

Epileptic syndromes of very young infants

1. Early myoclonic encephalopathy
2. Early infantile epileptic encephalopathy
3. Migrating partial seizures of infancy
4. Infantile spasms

Age at Onset of Seizures in 3 Syndromes



By courtesy of Prof. Ohtahara 2005

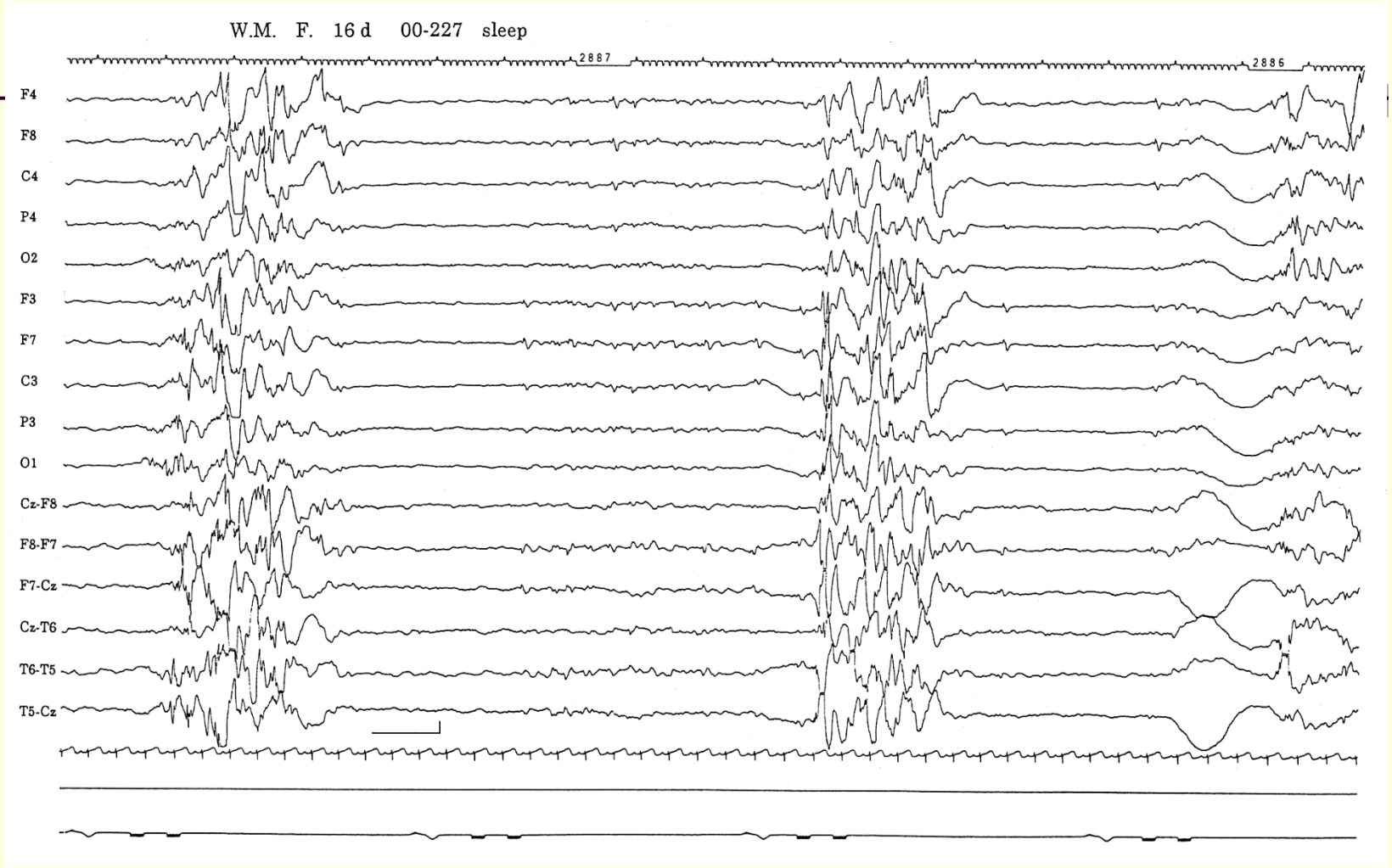
Ohtahara syndrome (EIEE)

- Ohtahara et al 1976

- Within the first 3 months of age
- Tonic spasms and other seizure types
- Continuous burst-suppression pattern
- Structural aetiology (brainstem)

- Variable malformations, metabolic diseases and genetic mutations **ARX, PNKP, SLC25 A22, STXBP1**

- No specific AEDs



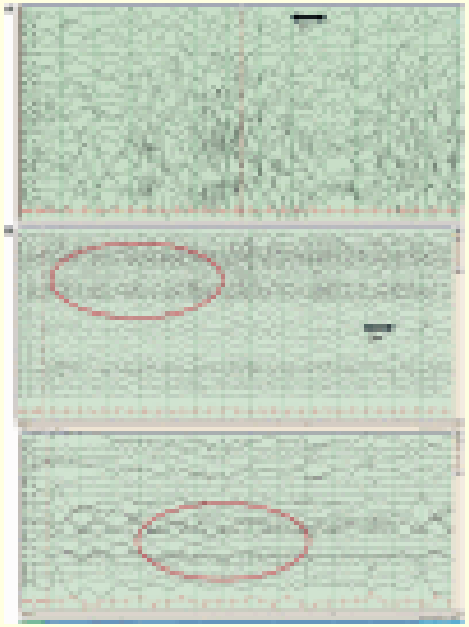
Baltimore 21.9.2015

Migrating partial seizures of infancy

- Coppola et al 1995

- Rare, 2014:100 patients reported
- Focal seizures within the first 6 months of life
- Autonomic features
- Initial MRI normal
- Develepmental stagnation
- No specific AED therapy

Migrating partial epilepsy: EEG



Expansion of electroclinical, radiological and pathological disease spectrum Mc Tague et al Brain 2013

- Multiple gene panel screening of genes
- KCNT1 mutation has been a significant genetic finding in the syndrome
- but also:SCN1A, SLC25A22, PLCB
- KCNT1 gain of function was **reversed by quinidine** (Bearden et al. Ann Neurol 2014)

???

Debate: Does genetic information in humans help us treat patients?

PRO--genetic information in humans helps us treat patients. CON--genetic information does not help at all.

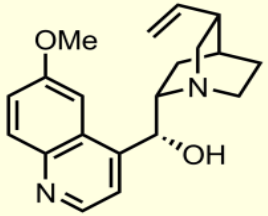
Delgado-Escueta AV, Bourgeois BF.

Epilepsia. 2008

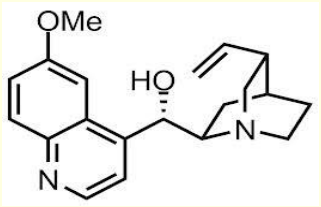
Quinidine

Cinchona Tree Bark





quinine

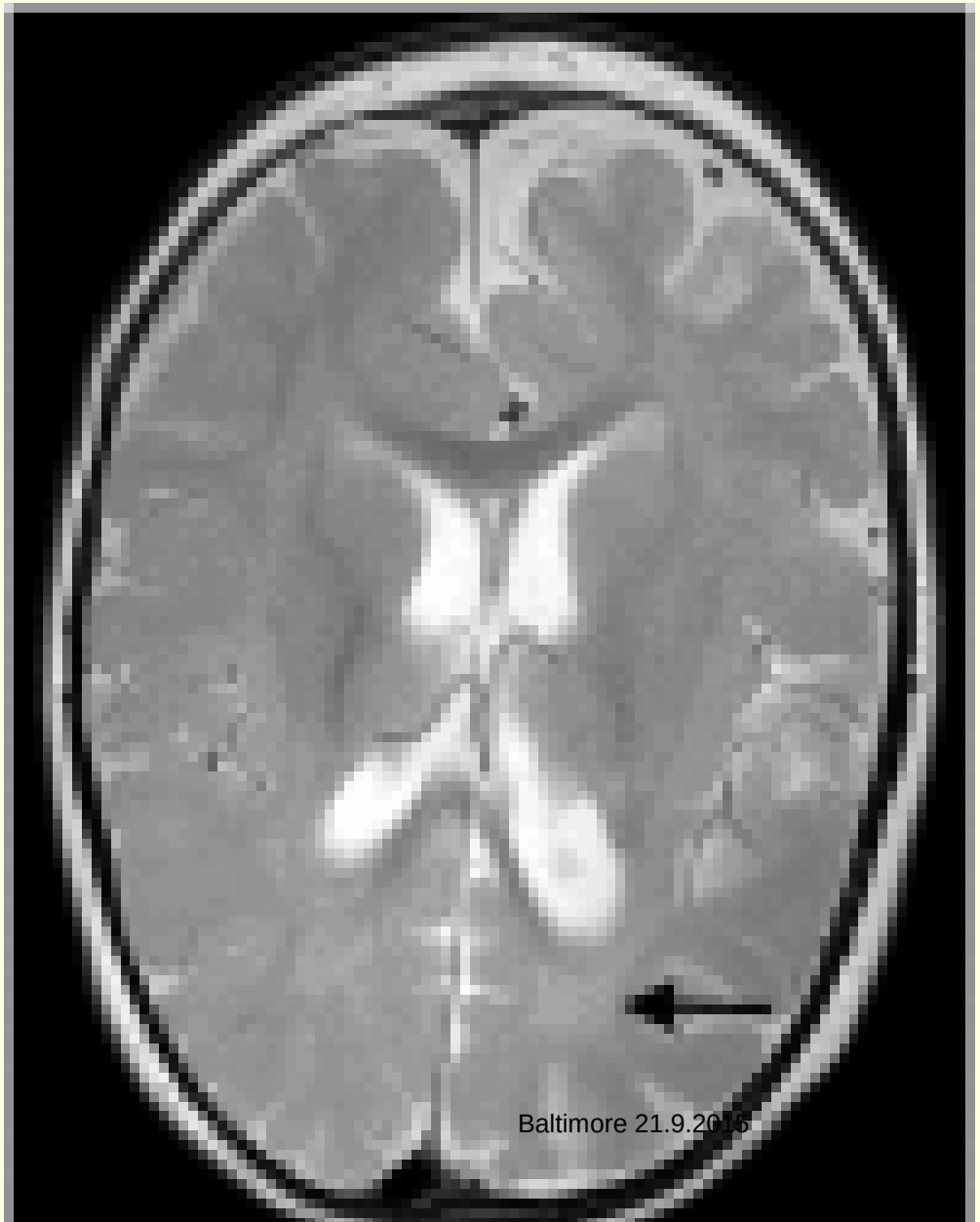


quinidine

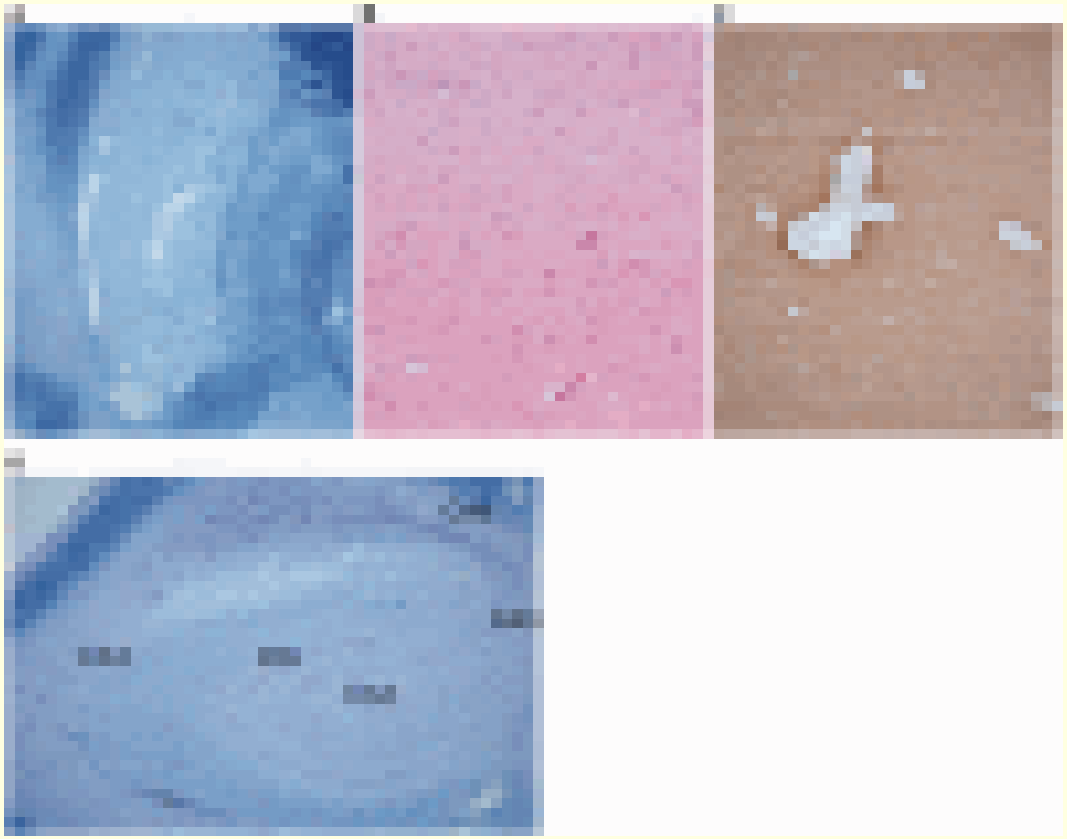
- FDA approved antiarrhythmic drug
- Inhibits rodent SLACK channels (KCNT1)
- Potential therapeutic?

Milligan and Petroe.
Ann Neurol 2014

- MPSI: Hyperintensity of deep WM Mc Tague et al 2913



Migrating focal epilepsy: microscopy: atrophy of the putamina with severe neuronal loss and gliosis (Mc Tague et al 2013



INFANTILE SPASMS

Infantile spasms: 30-40 years ago

- **Some authors used ACTH up to 240 IU/D**
- **Jeavons et al 24-40 IU /d until response**

- **”Side effects not extensively considered”**

- **Jeavons et al 1976: follow-up 4-14 yrs:**
- **Treated 105 pts normal Intelligence 26 %**
- **Untreated 45 pts normal intelligence 27 %**

What are recent advances?

Riikonen CNS Drugs 2014

1. **Increased knowledge of the role of ACTH, corticosteroids, vigabatrin and other antiepileptic drugs**

   Evidence-based studies

2. **Side-effects of VGB**

3. **Specific subgroups for treatment**

4. **New options: rapamycin, surgery**

- **Preventive intervention**
- **Long-term outcome**

Animal models

Genes: TSC1, TSC2,
ARX, CDKL5, FOXG, CRIN12A, MAG1, MEF2C, SLC25A22, SPTAN1, STXB1,15q11q13 (30)

Infantile spasms: highlights

1. Evidence-based treatment guidelines

2. Vigabatrin

3. Specific subgroups for treatment

4. Pathogenetic mechanism

1. EVIDENCE-BASED GUIDELINES

Evidence-based guideline update:

- **Medical treatment of infantile spasms Report of the Guideline Development Subcommittee of the AAN and the Practice Committee of the CNS.**

- **Go et al Neurology 2012**
- **Riikonen Nat Rev Neurol 2012**

Levels of recommendation

■■**Level A: Strong research-based evidence (requires at least two class I studies)** *prospective, randomized, controlled*
a) primary outcome, b) exclusion criteria, c) drop-outs, d) baseline characteristics clearly defined

■■**Level B: Moderate research-based evidence (requires at leas one class I study or two consistent class II studies)**

■■**Level C: Limited research-based evidence**

■■**Level U: data are conflicting or insufficient**

Main questions for the practice

For short-term treatment of infantile spasms:

1. Are other forms of corticosteroids as effective as ACTH ?

2. Are low-dose ACTH regimens effective ?

3. Is ACTH more effective than VGB ?

4. Is there a role for AEDs other than VGB and for ketogenic diet in managing infantile spasms?

5. Does the sucessful early treatment of infantile spasms lead to long-term improvement of cognitive outcomes or decreased incidence of epilepsy?

Recommendation 1

”The evidence is insufficient to recommend the use

of prednisolone, dexamethasone, and methylprednisolone as being as

effective as

ACTH for short-term treatment of infantile spasms (Level U)”

Recommendation 2

”Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).”

	ACTH doses (IE) 20-40 (N=97)	120-160 (N=54)
Good response: spasms	64 %	54 %
Good response: hypsarrythmia	77 %	74 %
Relapses	31 %	34 %
Normal at follow-up*	18 %	6 %

* p=0.038, (power=50%)

Riikonen 1982

Recommendation 3

”ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).”

Is there a role for AEDs other than VGB or ketogenic diet in managing infantile spasms?

- **Class IV:**
- **Valproic acid** *Dreifuss et al 1989, Chandra et al 2012*
- **Nitrazepam** *Chamberlain et al 1996,Volzke et al 1967*
- **Zonisamide** *Suzuki et al 1997,Glauser et al 2002*
- **Topiramate** *Glauser et al* 1998
- **Pyridoxin** *Ohtsuka et al 1987, Pietz et al 1993*
- **Sulthiame** *Debus et al1993*
- **Levetiracetam** *Mikati et al 2008*
- **Ketogenic diet** *Kossoff et al 2008, Hong et al 2010*

Recommendation 4

”Evidence is insufficient to recommend these therapies for treatment of infantile spasms (Level U)”

The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial

*Andrew L Lux, Stuart W Edwards, Eleanor Hancock, Anthony L Johnson, Colin R Kennedy, Richard W Newton, Finbar J K O'Callaghan, Christopher M Verity, John P Osborne on behalf of participating investigators**

Lancet 2004; 364: 1773–78



The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial

*Andrew L Lux, Stuart W Edwards, Eleanor Hancock, Anthony L Johnson, Colin R Kennedy, Richard W Newton, Finbar J K O'Callaghan, Christopher M Verity, John P Osborne, the trial steering committee on behalf of participating investigators**

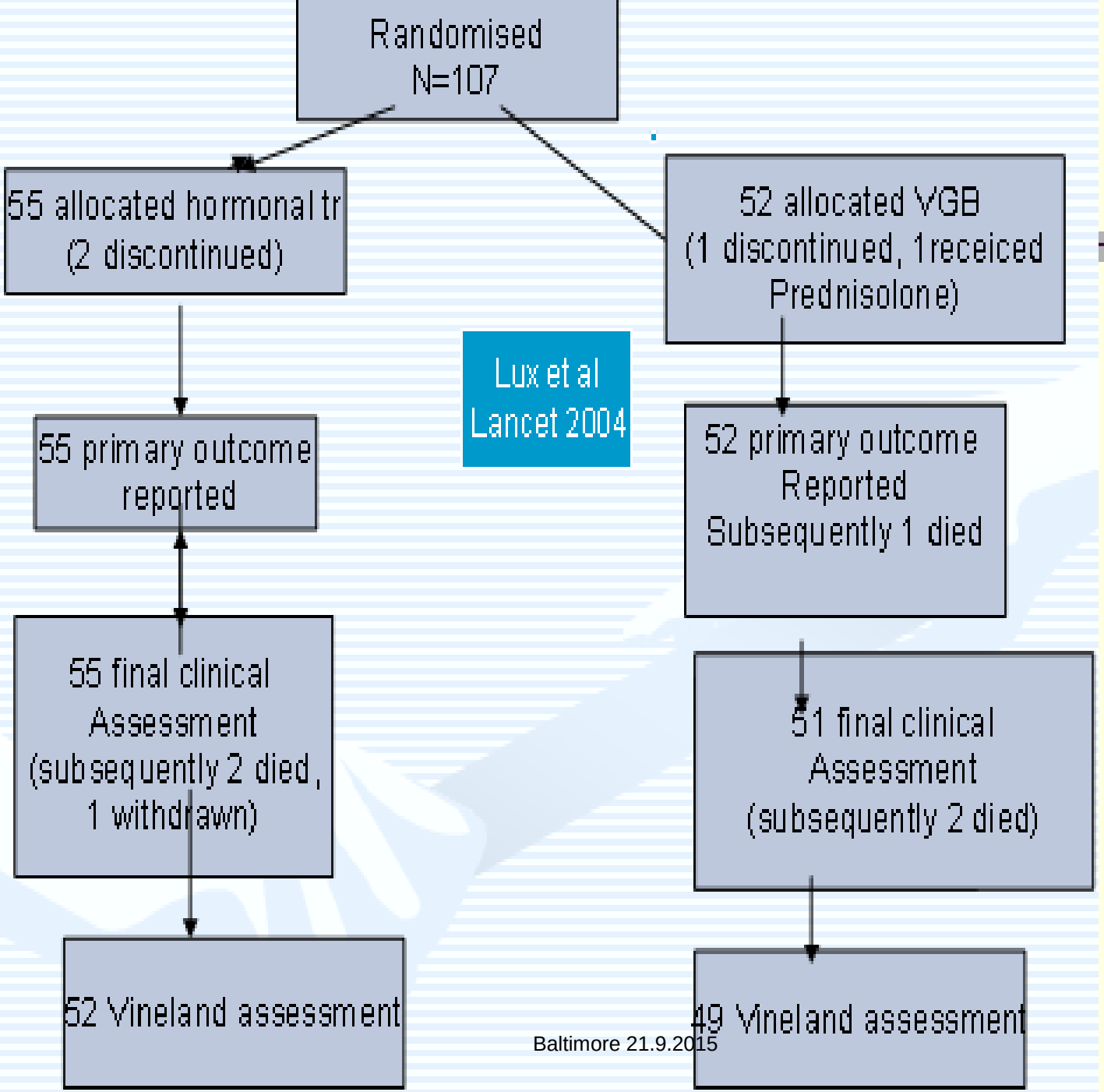
Lancet Neurol 2005; 4: 712–17

UKISS

Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial

Katrina Darke,[1] Stuart W Edwards,[1,2] Eleanor Hancock,[2,3] Anthony L Johnson,[4,5] Colin R Kennedy,[6] Andrew L Lux,[2,7] Richard W Newton,[8] Finbar J K O'Callaghan,[1,2,7,9] Christopher M Verity,[10] John P Osborne[1,2]; the trial steering committee on behalf of participating investigators

Arch Dis Child 2010;**95**:382–386.


Randomised
N=107
55 allocated hormonal tr
(2 discontinued)
52 allocated VGB
(1 discontinued, 1receiced
Prednisolone)
Lux et al
Lancet 2004
55 primary outcome
reported
52 primary outcome
Reported
Subsequently 1 died
55 final clinical
Assessment
(subsequently 2 died,
1 withdrawn)
51 final clinical
Assessment
(subsequently 2 died)
52 Vineland assessment
49 Vineland assessment

Cessation of spasms
Vigabatrin in 56% and ACTH 74%

THE COCHRANE COLLABORATION®

Study or subgroup	Vigabatrin n/N	Hormonal treatment n/N
Lux 2004	28/52	40/55
Vigevano 1997	11/23	14/19
Askalan 2003	6/6	3/3
Total (95% CI)	**81**	**77**

Outcomes at age 4 years
No identified aetiology

Treatment	*Hormonal*	*Vigabatrin*
Number	21	16
Median VABS score	96	63
Interquartile range	56,102	37,92
Mann-Whitney U test	U = 98.5; P = 0.033	
Difference (95%CI)	14 (1 to 42)	

Darke K et al. *Arch Dis Child* 2010;95:382-6

Lead time to treatment and subsequent cognition, no identified etiology (n=37)

- 8-14 days 84.7
- 15 days-1 m 74
- 1-2 m 71
- >2m 66.2
- P= 0.0046

- **O`Callaghan et al Epilepsia 2011**

Recommendation 5

”Hormonal therapy (ACTH or prednisolone) may be considered in preference to VGB in in children with cryptogenic spasms, to possibly **improve developmental outcome** (Level C)”

”**A shorter lag time** to treatment of infantile spasms with either hormonal therapy or VGB may be considered to **improve long-term cognitive** outcomes (Level C)”

THE INTERNATIONAL COLLABORATIVE INFANTILE SPASMS STUDY (ICISS)

A comparison of combined therapy of hormonal therapy + vigabatrin versus hormonal therapy alone in the treatment of infantile spasms

EARLY CLINICAL OUTCOME & ELECTRO-CLINICAL OUTCOME

Dr Finbar O'Callaghan

on behalf of the ICISS Trial Steering Committee, national co-collaborators and local investigators

Combined therapy is associated with

- **increased proportion of patients achieving spasm cessation and EEG response**
- **faster clinical response**
- **response most marked in those children with no identified aetiology**
- **tetracosactide may be superior to prednisolone**

F. Donohoe EPNS CONGRESS Vienna 2015

2. VIGABATRIN

Vigabatrin (VGB)

VGB (inhibitor of GABA transferase)

In many European countries used as 1st-line monotherapy for IS

Tuberous sclerosis – Chiron et al 1997, Elterman at al 2001; TS vs symptomatic 13/15 vs 19/117 ($p<0.001$)

2009 US FDA approvment for the treatment of IS under strict and careful visual field controls

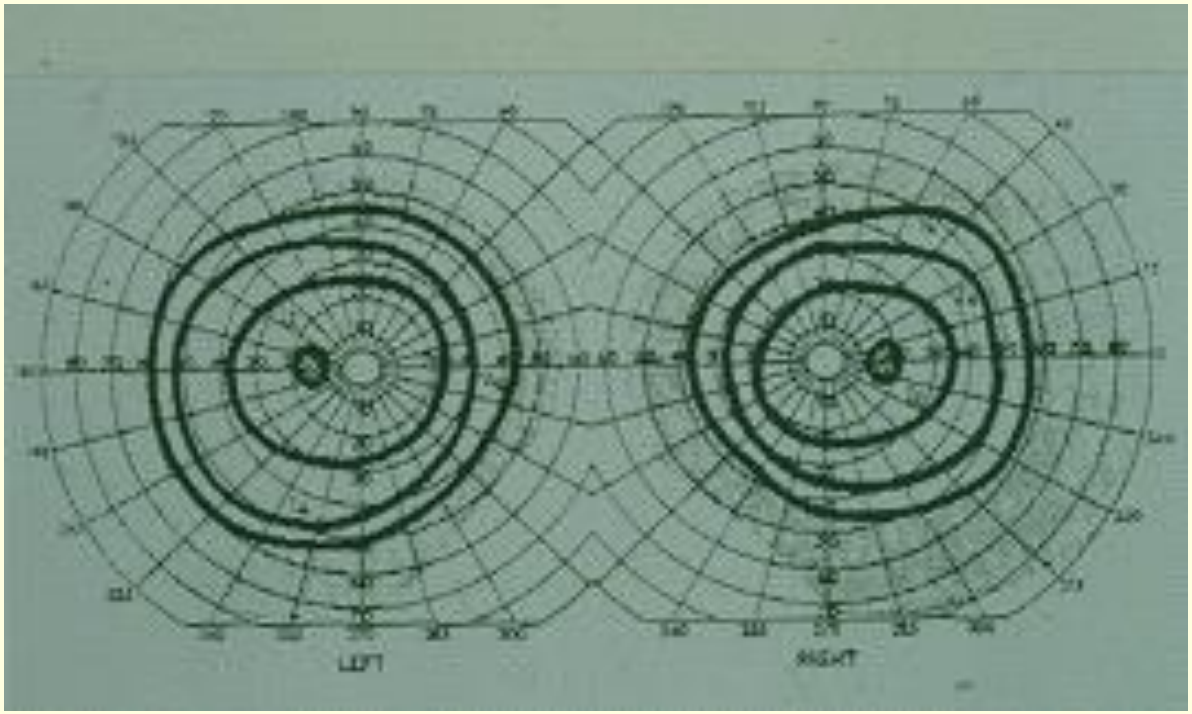
Short periods of treatment. It might prevent relapses.

- **Adverse effects: visual field defects, hypodensities in NMR**

Does VGB treatment for infantile spasms cause VFDs? **Riikonen et al 2015 DMCN**

- **VFDs were found in 34%** of the patients but the rate increased from 9 % (less than one year) to 63 % with a longer duration of treatment (more than 2 years).

Infantile spasms and VFDs



MRI of VGB-treated patient taking VGB for 36 days, Wheless et al 2009



3. SPECIFIC SUBGROUPS FOR TREATMENT

SPECIFIC SUBGROUPS

ACTH to spasms of non-identified etiology

VGB for Tuberous sclerosis and cortical dysgenesis

KD for Glut-1 deficiency

Epilepsy surgery: focal dysplasia or when AED therapy has failed

Tuberous sclerosis and IS

- **VGB the drug of 1st choice**
- **TS is caused by mutations of TSC1 and TSC2 genes**
- **TSC1 and TSC2 genes encode distinct proteins: hamartin and tuberin**
- **Mutations in these genes cause hyperactivation of the mTOR system and result in excessive cell growth and hamartous tumors** *(Crino 2013*)
- **VGB inhibits seizures and mTOR pathway** *(Kotulska et al 2013)*

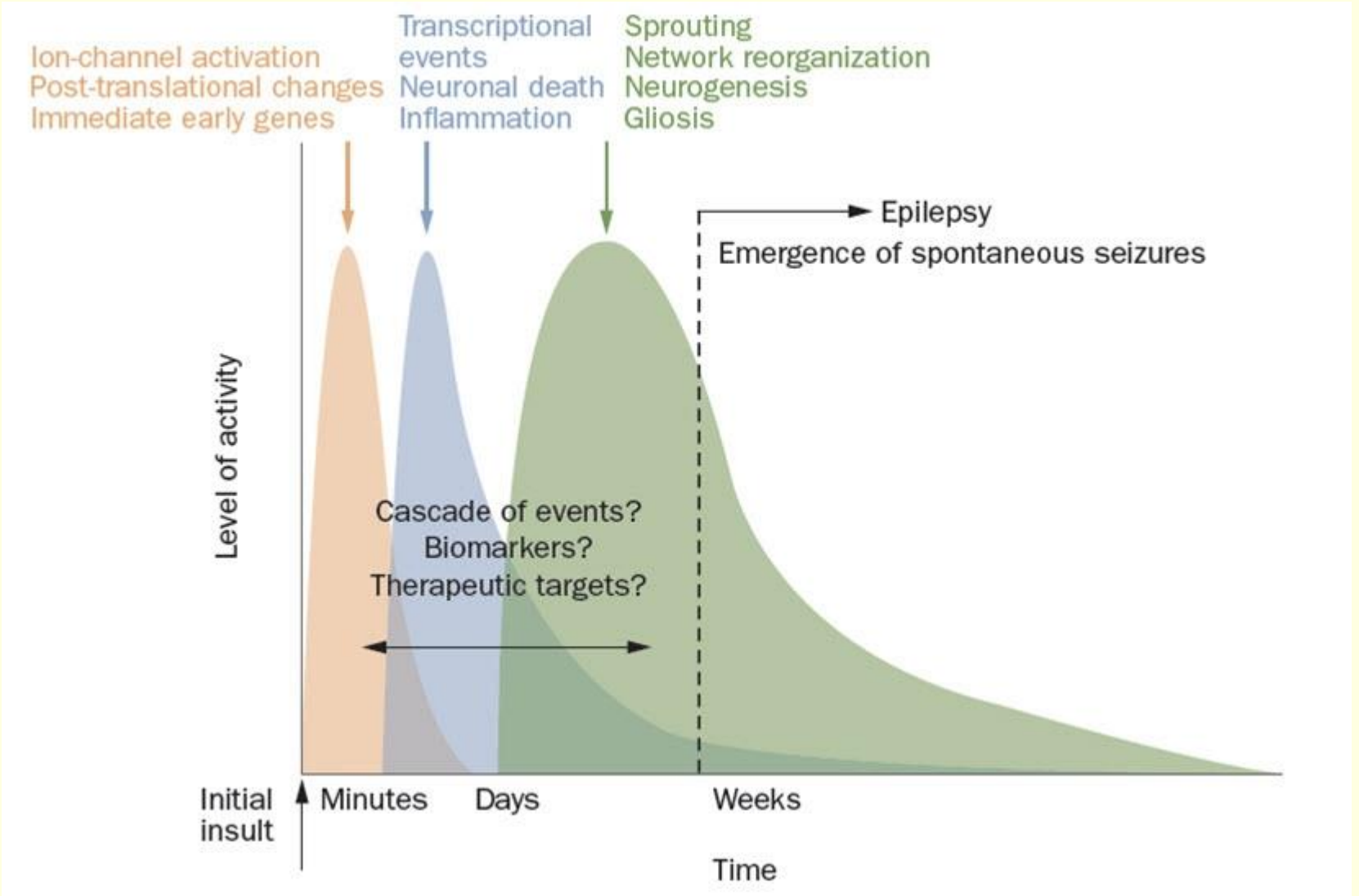
Everolimus=Rapamycin

- New oral selective mTORC-1 inhibitor for treatment of SEGA in TS
- No safety concerns in patients <3 years of age (Kotulska et al 2013)
- Controlled, Phase III trial, EXIT-1 (Franz et al 2013)
- **High-dose rapamycin is a promising new therapy for IS including those not linked to TS** *(Raffo et al 2011, Galanopoulou et al 2012)*
- *A pulse rapamycin therapy for IS is associated better cognitive outcome (Raffo et al 2011) –no human studies*

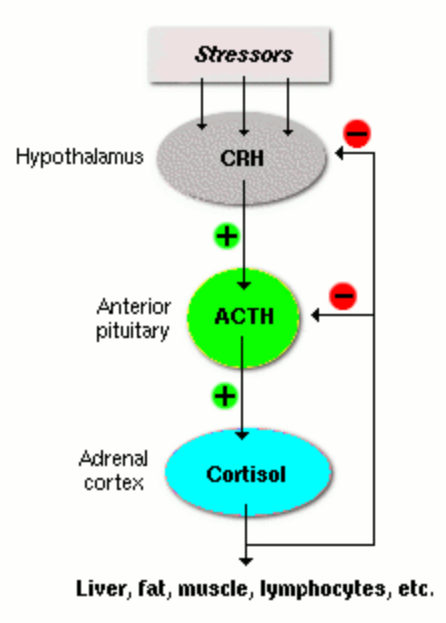
4.PATHOGENETIC MECHANISM of infantile spasms

Pathogenetic mechanism?

- Disturbance of cortical synaptogenesis
- Abnormal cortical-subcortical interaction
- Abnormal brain-adrenal axis


Ion-channel activation
Post-translational changes
Immediate early genes
Transcriptional events
Neuronal death
Inflammation
Sprouting
Network reorganization
Neurogenesis
Gliosis
Epilepsy
Emergence of spontaneous seizures
Level of activity
Cascade of events?
Biomarkers?
Therapeutic targets?
Initial insult
Minutes
Days
Weeks
Time

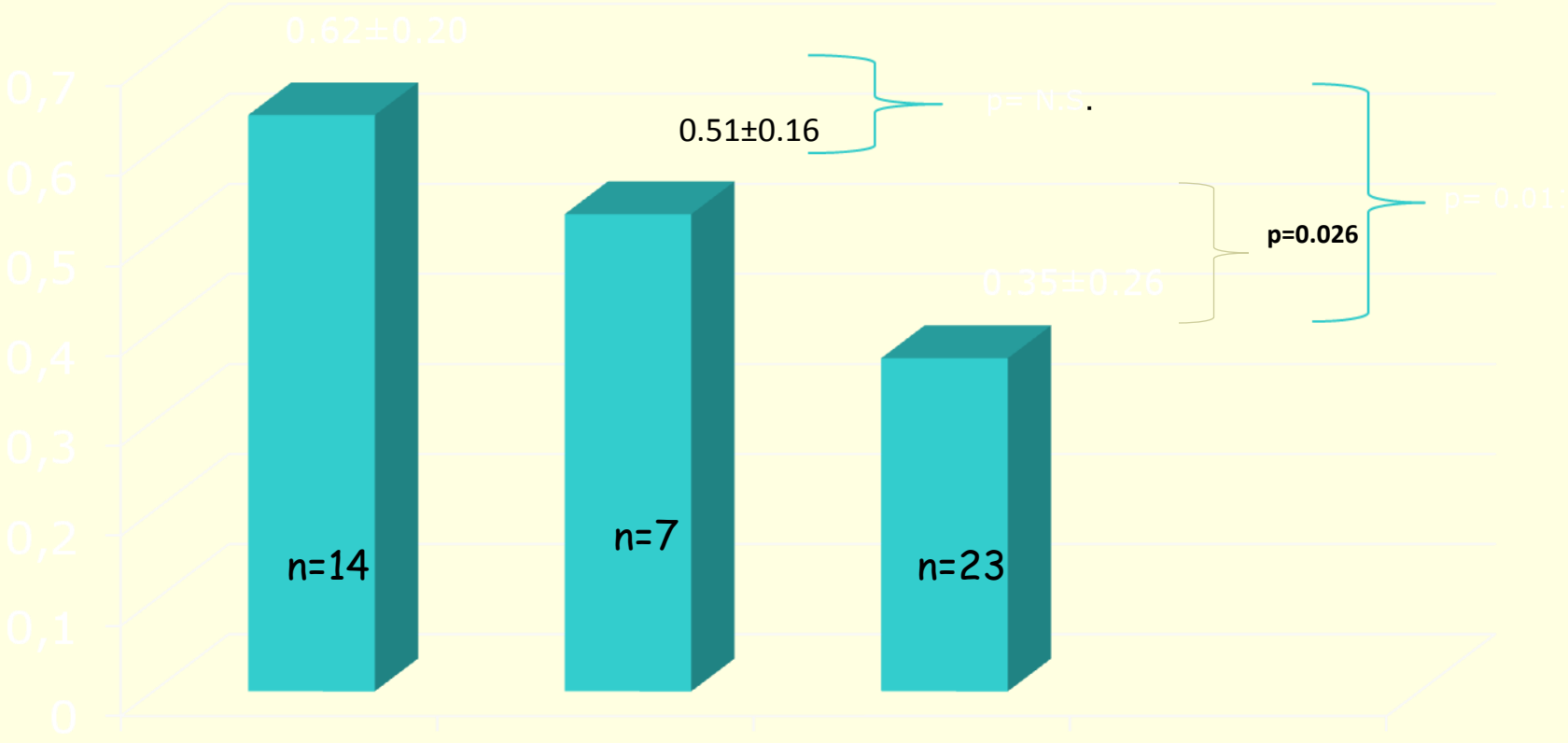
Abnormal early hypopituitary-adrenal axis (HPA) in IS Baram et al Ann Neurol 1993



Pathogenetic mechanism?

- Early insult/stress—increase of CRF (Baram et al.1993)
- Chronically elevated CRF desensitizes CRF receptors and decreases ACTH release—impairment of HPA axis (Brunson et al 2001)
- When stress is repetative—affects synthesis of IGF-1—(because IGF-1 needs stimulation of steroids)
- Synaptic impairment and reduction of certain cognitive functions---Epileptic encephalopathy

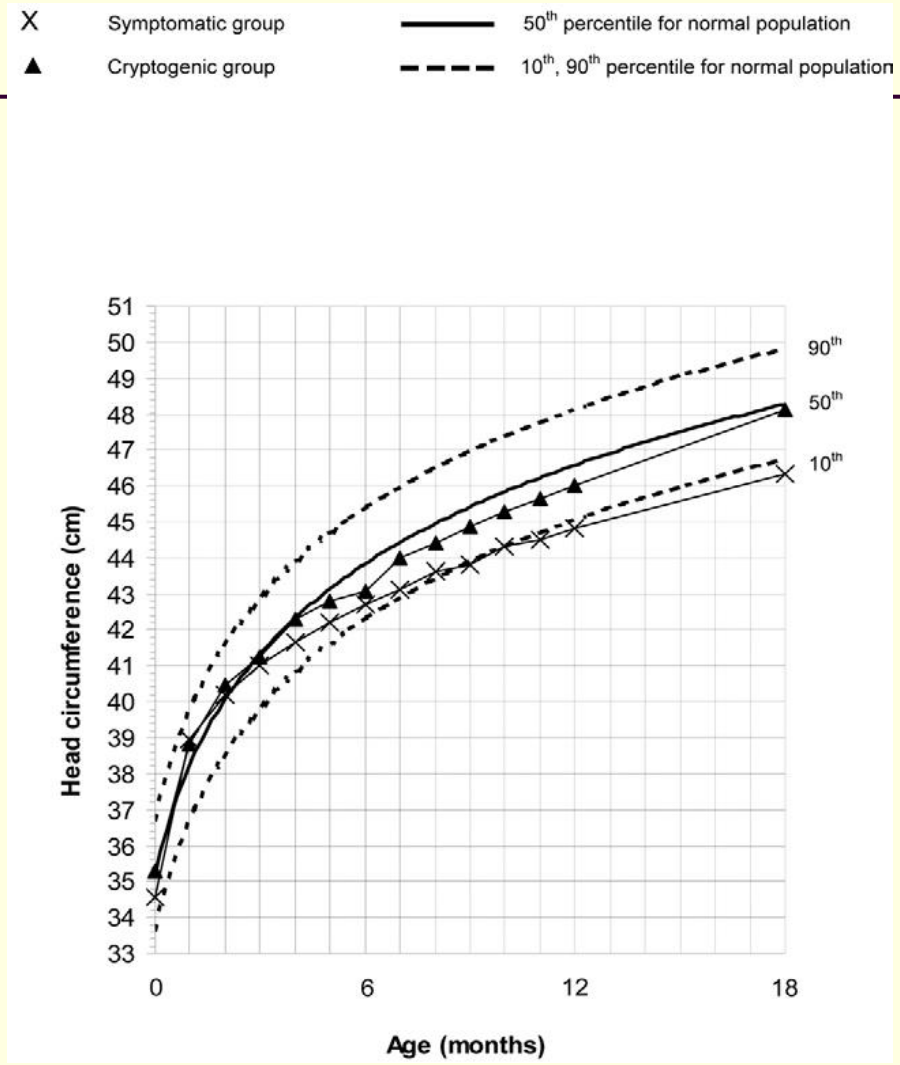
CSF IGF-1 concentration (µg/L) in children with idiopathic infantile spasms (IIS) or with symptomatic infantile spasms (SIS) (Riikonen et al Epilepsia 2010)



Low CSF IGF-1 concentrations correlated with

- Severity of insult/length of stress
- Cortical damage
- Poor response to ACTH therapy
  - **Poor cognitive outcome**

Riikonen et al Epilepsia 2010


X Symptomatic group
▲ Cryptogenic group
50th percentile for normal population
10th, 90th percentile for normal population
Head circumference (cm)
51
50
49
48
47
46
45
44
43
42
41
40
39
38
37
36
35
34
33
0
6
12
18
Age (months)
90th
50th
10th

- In children with IS, insults or stress in early life may affect the synthesis of IGF which might play a role in the reduction of certain cognitive functions

What has changed in 30 years in epileptic syndromes of very early infancy

- Expansion of electroclinical, radiological, pathological and genetic disease spectrum
- Pathogenetic mechanism (theory)
- Treatment: evidence-based data for pharmacological treatments (still ACTH the best!)
- Vigabatrin: new 1 or 2. line therapy
- New options: rapamycin
- Ketogenic treatment and surgery

New options

- Rapamycin (Raffo et al 2011,Zhang et al 2013)
- Insulin-like growth factor (Riikonen et al 2010)
- Cytokines (Vezzani et al 2010)
- Melacortin receptor agonists (Catania 2008)
- Combined Hormonal + Vigabatrin (ICISS)
- Protection of VGB toxicity: taurine (Jammoul et al 2010)

Future Research

- Multicentric RCT trials with multiple treatment arms
- Long-term outcome in children treated with VGB
- Management of relapses
- Understanding and preventing of VFDs following VGB treatment
- Understanding of brain maturation, etiology,mechanisms and genetics underlying infantile spasms may facilitate more effective intervention



Baltimore 21.9.2015

