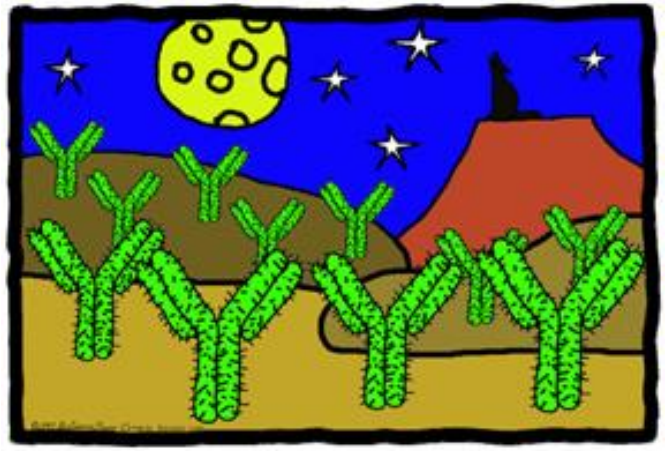
Immune “therapies” in childhood epilepsy ?



Lieven Lagae

Paediatric Neurology

University Hospitals KULeuven

Belgium

The first principle is that you must not fool yourself and you are the easiest person to fool.

(Richard Feynman)

Immunology, inflammation and childhood epilepsy

Treatment success

- Infantile spasms : treatment with ACTH / steroids
- CSWSS / Landau Kleffner
- Other epilepsies (?)

‘Immune epilepsy syndromes’ recognized by ILAE

- FIRES : febrile infection related syndromes
- Rasmussen encephalitis
- Auto-immune encephalitis (anti NMDA,…)

Prevalence epilepsy in auto-immune diseases increased

Epilepsy in systemic autoimmune diseases

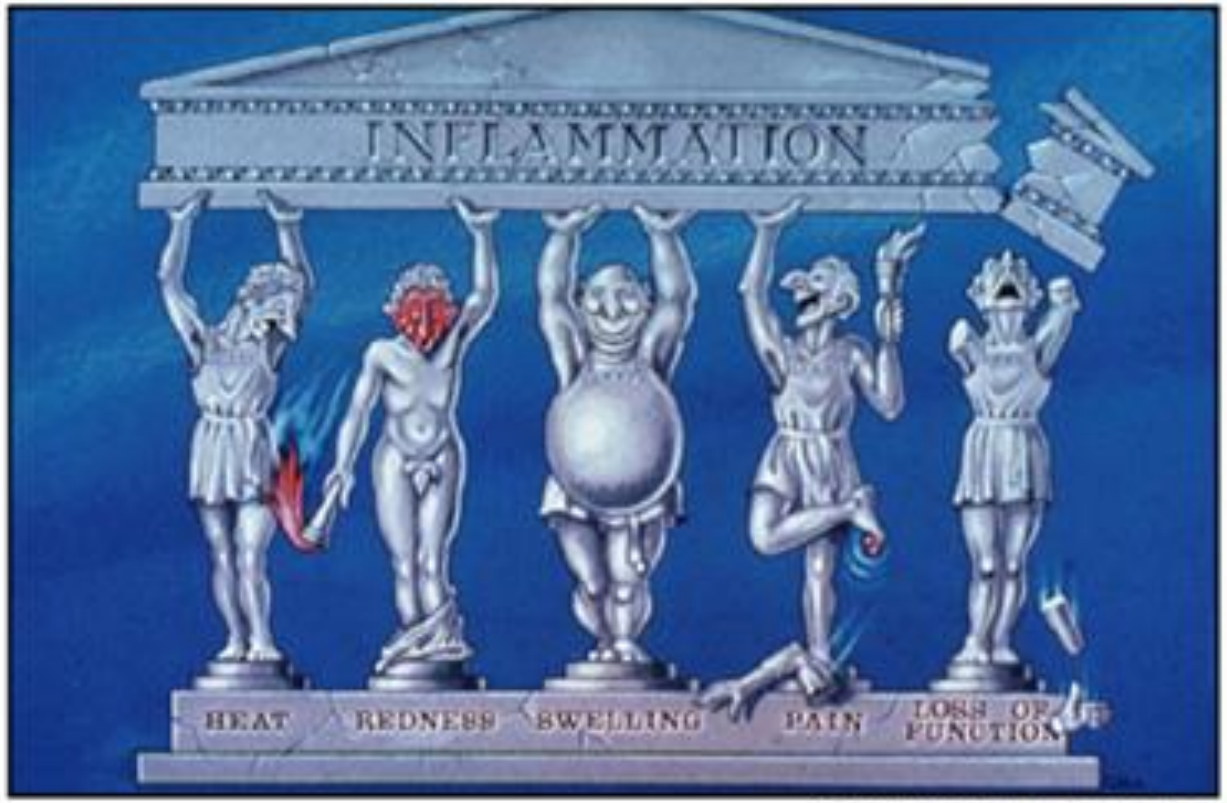
Autoimmune Disorder	Prevalence of Epilepsy in Children	OR (95% CI)[1]	Seizure Types
SLE	7%-40%	21.6 (11.0-42.7)	GTC, partial, and M
APS	3.2%-8.6%	9.0 (7.7-10.5)	Partial
RA	1%-1.7%	3.1 (1.4-7.0)	GTC and partial
SS	1%-10%	4.3 (3.2-5.6)	GTC, CP, and EPC
BD	2%-16%		GTC
IBD	3%-6%	8.4 (3.7-19.0)	GTC and CP
Celiac disease	1%-5.7%	16.7 (9.9-28.2)	Any type
WG	3%		GTC, CP, and M
Sarcoidosis	38% of pediatric neurosarcoidosis[49]		GTC, partial, and M
DM	1%-2%	3.9 (2.5-6.1)	
MG	1.7%	4.9	
HT	2.4% (66% in encephalopathy)	6.8 (3.5-13.3)	Any type, and EPC
GD	1.7%	4.7 (1.2-19.1)	GTC

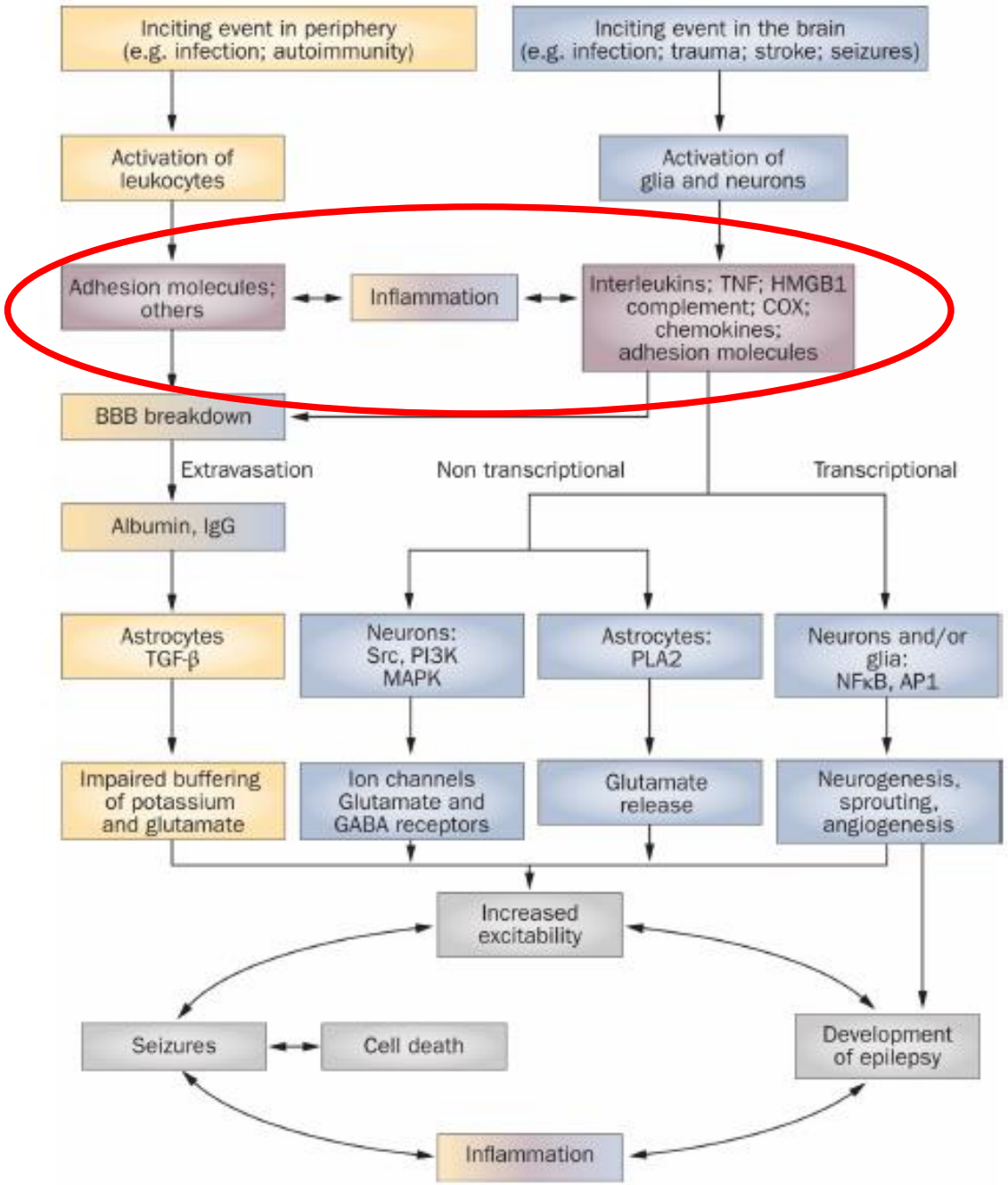
Modified from Ong et al[1], Devinsky et al[2], and Baumann and Robertson[49]

APS, Antiphospholipid syndrome; BD, Behçet's Disease; CP, complex partial; EPC, epilepsia partialis continua; DM, Type 1 diabetes mellitus; GD, Graves disease; GTC, generalized tonic-clonic; HT, Hashimoto thyroiditis; IBD, inflammatory bowel disease; M, myoclonic; MG, myasthenia gravis; OR, odds ratio; RA, Rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; SS, Sjögren's syndrome; WG, Wegener granulomatosis.

Valencia I, Sem in Ped Neurol, 2014

Neuro-inflammology for dummies





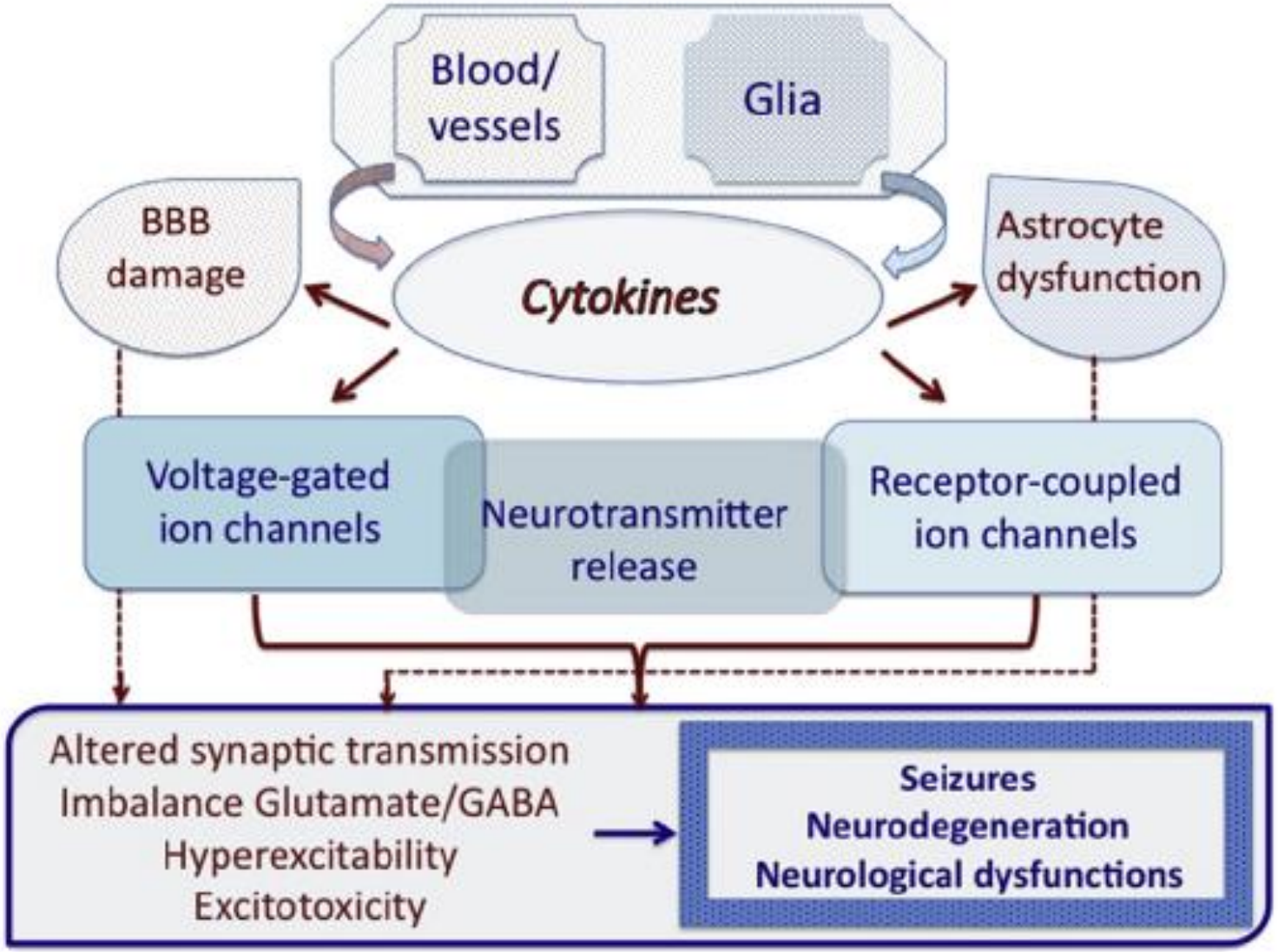
Inflammation ⟺ Epilepsy

Innate and adaptive immunology

Primary in the brain or systemic via “broken” BBB

Cytokines key players

Vezzani et al, 2011



A. Vezzani, B. Viviani / Neuropharmacology 96 (2015) 70–82

Cytokines : Influence/change/modulate receptor excitability

Cytokine	VGC	Signalling	Functional readout	ROC	Signalling	Functional readout
IL-1β/IL-1R1	VGSCs – Nav (Trigeminal neurons)	PKC/G-protein	[a]Increased Na^+ currents Hyperalgesia	NMDAR-NR2B (Hippocampal cultures)	[c]Sphingomyelinase/Src K	Increased Ca^{2+} influx Hyperexcitability/ Excitotoxicity Increased seizure susceptibility
	α_1 subunit (Cortical neurons)	PKC	Reduced Na^+ currents Neuroprotection	GABA-A R *β2/β 3 subunits* (Hippocampal cultures)	PI3K/Akt	Increased GABA current (*Xenopus laevis* oocytes)
	VGCCs – Cav L- and N-type (Hippocampal and cortical cultures)	PKC/G-protein	Reduced Ca^{2+} influx Reduced Ca^{2+} currents Neuroprotection	*α5 subunit* (Hippocampal slices)	p38-MAPK	Increased tonic GABA current
	VGKC – Kv (Trigeminal ganglion neurons – retinal ganglion cells)	n.d.	Reduced K^+ currents Neuroprotection Increased excitability Hyperalgesia			
TNFR1(p55)	[e]VGSCs – Nav 1.3	[b]p38-MAPK	Enhanced TTX-R and TTX-S Na^+ currents Pain facilitation	[d]AMPAR-GLUR2 (Hippocampal pyramidal cells)	PI3K/Akt	Increased Ca^{2+} influx Hyperexcitability/ Excitotoxicity
	Nav1.7; Nav1.8 (*sTNF-alfa* in DRG)			AMPAR-GLUR1/GLUR2 (GABA neurons in striatum)	PP1	Reduction of glutamatergic drive
	VGCCs – Cav (DRG)	n.d.	Decreased Ca^{2+} currents	[e]AMPAR-GLUR1 [e]NMDAR-NR1 (Hippocampus)	n.d.	Increased seizure susceptibility
	N-Type (Superior mesenteric ganglia *sTNF-alfa*)	NFκB	Decreased Ca^{2+} currents	GABA-A R *β2/β 3 subunits* (Hippocampal slices)	n.d.	Decreased inhibitory synaptic strength
TNFR2 (p75)	[e]VGSCs – Nav1.7; Nav1.8 (*mTNF-α* in DRG)	n.d.	Enhanced TTX-R and TTX-S Na^+ currents Pain facilitation	[e]AMPAR-GLUR2/GLUR3 [e]KA-GLUR6/7 [e]NMDAR-NR2 (Hippocampus)	n.d.	[e]Decreased response to glutamate [e]Decreased seizures
	[e]VGCCs – Cav3.2 (*mTNF-α* in DRG)	n.d.	Increased Cav3.2 expression			
IL-6 (gp130)	VGSCs – Nav1.7 (Trigeminal ganglia)	ERK1	Increased number of spikes; Decreased latency to first AP Hyperexcitability	mGLUR2/3	STAT3	Alterations in presynaptic glutamate release and changes in synaptic network activity
	α_1 subunit (spinal cord neurons)	n.d.	Reduced Na^+ currents Neuroprotection	AMPAR-GLUR2 (Hippocampal cultures)	n.d.	Reduced Ca^{2+} influx
	VGCCs – Cav L-Type (CGC)	n.d.	Reduced Ca^{2+} currents Neuroprotection	NMDAR-NR1 GABA-A R (Cerebellar granule neurons)	PI3K-Akt	Decreased GABA current

Mechanisms of Epileptogenesis in Pediatric Epileptic Syndromes: Rasmussen Encephalitis, Infantile Spasms, and Febrile Infection-related Epilepsy Syndrome (FIRES)

Carlos A. Pardo · Rima Nabbout · Aristea S. Galanopoulou

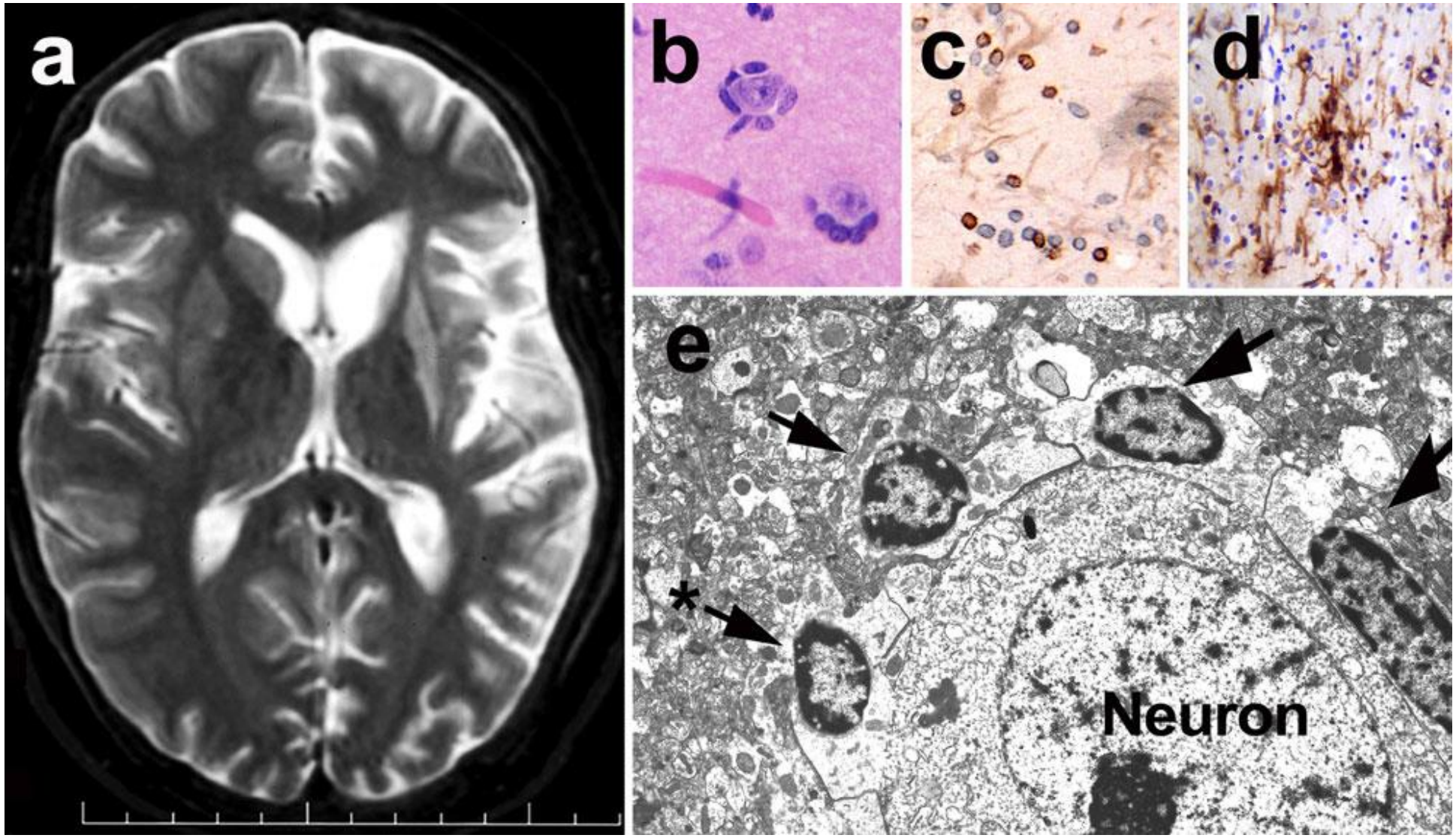
Trying to explain what we see in clinic

Table 1 Mechanisms associated with epileptogenesis in pediatric epileptic syndromes

Mechanisms/disorder	Adaptive immunity	Innate immunity	Genetic	Infection	Other/metabolic
Rasmussen encephalitis	$CD8^+$ T cell cytotoxicity against neurons and glia Suspected autoantibodies	Microglial and astroglial activation	Unknown	Suspected	Unknown
Infantile spasms	Disarrangements of T cell populations and increased cytokines in blood and cerebrospinal fluid Few cases with autoantibodies	Suspected	Several known gene mutations	Few cases described	Structural, metabolic
Febrile infection-related epilepsy syndrome	Suspected, inconclusive evidence	Suspected	Suspected	Suspected	Metabolic (suspected, inconclusive evidence)

Neurotherapeutics, 2014

Rasmussen syndrome

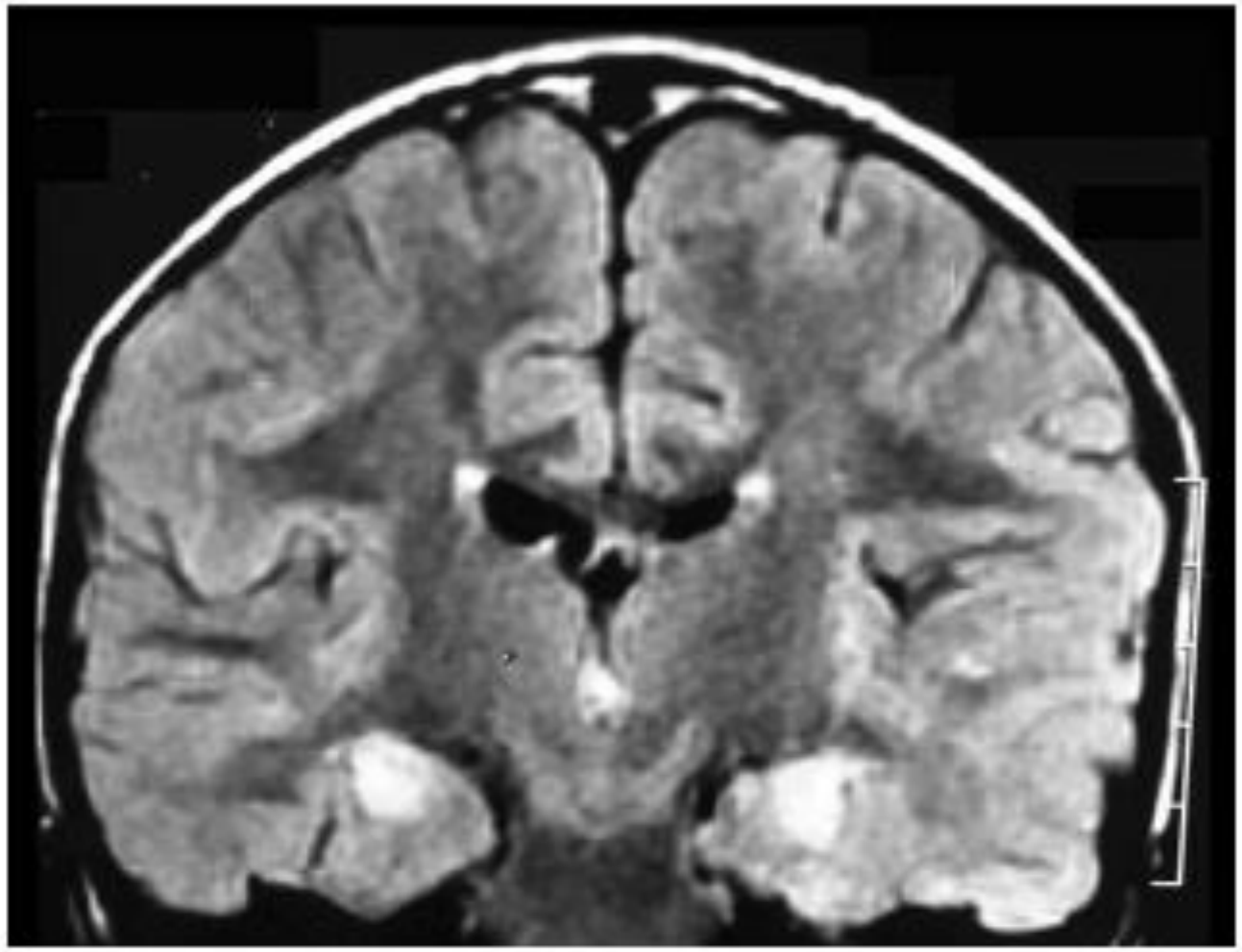


Microglial activation

T lymphocytes around neuron

FIRES

3 weeks after status epilepticus in a 3.5 year old boy



How specific is this finding ?

Infantile spasms as a model

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics

Working Group: *Jo M. Wilmshurst, †William D. Gaillard, ‡Kollencheri Puthenveettil Vinayan, §Tammy N. Tsuchida, ¶Perrine Plouin, #Patrick Van Bogaert, **Jaime Carrizosa, ††Maurizio Elia, ‡‡§§Dana Craiu, ¶¶Nebojsa J. Jovic, ##Doug Nordli, ***Deborah Hirtz, †††‡‡‡Virginia Wong, §§§Tracy Glauser, ¶¶¶###Eli M. Mizrahi, and ****J. Helen Cross

Epilepsia, 56(8):1185–1197, 2015
doi: 10.1111/epi.13057

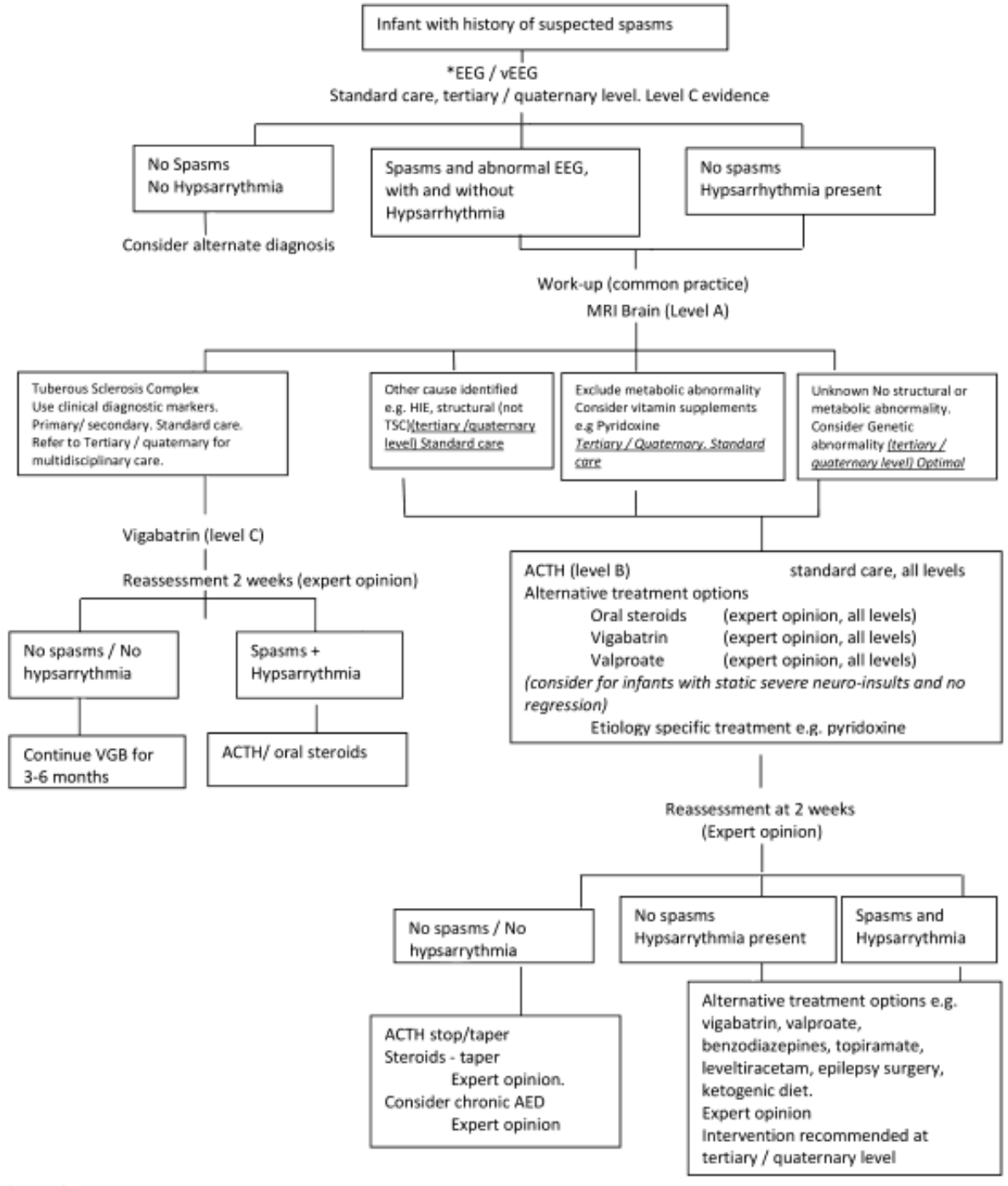
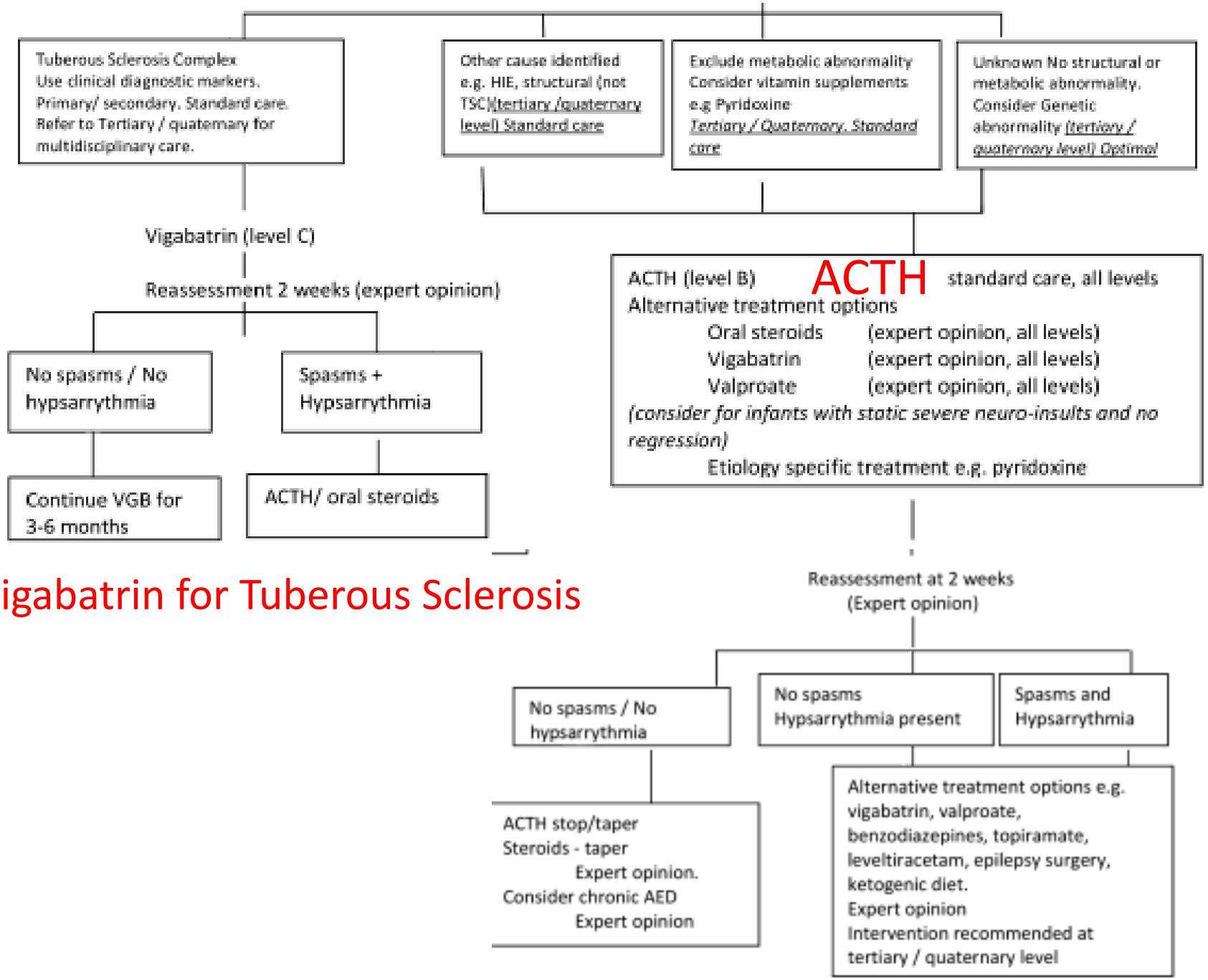

Infant with history of suspected spasms
*EEG / vEEG
Standard care, tertiary / quaternary level. Level C evidence
No Spasms
No Hypsarrythmia
Consider alternate diagnosis
Spasms and abnormal EEG, with and without Hypsarrhythmia
No spasms
Hypsarrhythmia present
Work-up (common practice)
MRI Brain (Level A)
Tuberous Sclerosis Complex
Use clinical diagnostic markers. Primary/ secondary. Standard care. Refer to Tertiary / quaternary for multidisciplinary care.
Other cause identified e.g. HIE, structural (not TSC)(tertiary /quaternary level) Standard care
Exclude metabolic abnormality Consider vitamin supplements e.g Pyridoxine Tertiary / Quaternary. Standard care
Unknown No structural or metabolic abnormality. Consider Genetic abnormality (tertiary / quaternary level) Optimal
Vigabatrin (level C)
Reassessment 2 weeks (expert opinion)
No spasms / No hypsarrythmia
Continue VGB for 3-6 months
Spasms + Hypsarrythmia
ACTH/ oral steroids
ACTH (level B) standard care, all levels
Alternative treatment options
Oral steroids (expert opinion, all levels)
Vigabatrin (expert opinion, all levels)
Valproate (expert opinion, all levels)
(consider for infants with static severe neuro-insults and no regression)
Etiology specific treatment e.g. pyridoxine
Reassessment at 2 weeks
(Expert opinion)
No spasms / No hypsarrythmia
ACTH stop/taper
Steroids - taper
Expert opinion.
Consider chronic AED
Expert opinion
No spasms
Hypsarrythmia present
Spasms and Hypsarrythmia
Alternative treatment options e.g. vigabatrin, valproate, benzodiazepines, topiramate, leveltiracetam, epilepsy surgery, ketogenic diet.
Expert opinion
Intervention recommended at tertiary / quaternary level

Figure 2.



Vigabatrin for Tuberous Sclerosis

Why would TS be different ?

See CRH final common pathway

[Intervention Review]

Treatment of infantile spasms

Eleanor C Hancock[1], John P Osborne[2], Stuart W Edwards[3]

[1]c/o Cochrane Epilepsy Group, University of Liverpool, Liverpool, UK. [2]The Children's Centre, Royal United Hospital, Bath, UK. [3]The Children's Centre, International Collaborative Infantile Spasms Study (ICISS), Bath, UK

Contact address: Eleanor C Hancock, c/o Cochrane Epilepsy Group, University of Liverpool, Room 2.28, Clinical Sciences Centre, University Hospital Aintree, Lower Lane, Liverpool, L9 7LJ, UK. ellie.clayden@icloud.com.

Editorial group: Cochrane Epilepsy Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2014.
Review content assessed as up-to-date: 1 May 2013.

Citation: Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD001770. DOI: 10.1002/14651858.CD001770.pub3.

Analysis 9.1. Comparison 9 Vigabatrin versus hormonal treatment, Outcome 1 Cessation of spasms.

Review: Treatment of infantile spasms

Comparison: 9 Vigabatrin versus hormonal treatment

Outcome: 1 Cessation of spasms

Non tuberous sclerosis

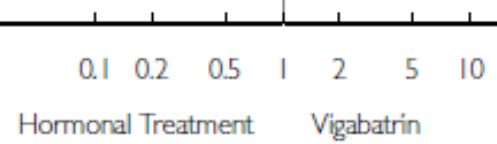
Study or subgroup	Vigabatrin n/N	Hormonal treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Vigevano 1997	11/23	14/19		29.1 %	0.35 [0.10, 1.19]
Lux 2004	28/52	40/55		70.9 %	0.45 [0.20, 0.98]
Askalan 2003	6/6	3/3			Not estimable
Total (95% CI)	**81**	**77**		**100.0 %**	**0.42 [0.21, 0.80]**

Total events: 45 (Vigabatrin), 57 (Hormonal treatment)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 2.61 (P = 0.0092)

Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9 Vigabatrin versus hormonal treatment, Outcome 2 Resolution of EEG.

Review: Treatment of infantile spasms

Comparison: 9 Vigabatrin versus hormonal treatment

Outcome: 2 Resolution of EEG

Non tuberous sclerosis

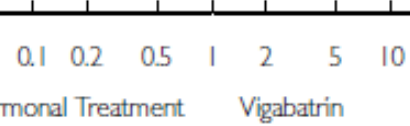
Study or subgroup	Vigabatrin n/N	Hormonal treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Askalan 2003	6/6	3/3			Not estimable
Lux 2004	20/28	26/32		63.8 %	0.58 [0.18, 1.91]
Vigevano 1997	4/11	11/14		36.2 %	0.18 [0.04, 0.90]
Total (95% CI)	**45**	**49**		**100.0 %**	**0.38 [0.15, 0.99]**

Total events: 30 (Vigabatrin), 40 (Hormonal treatment)

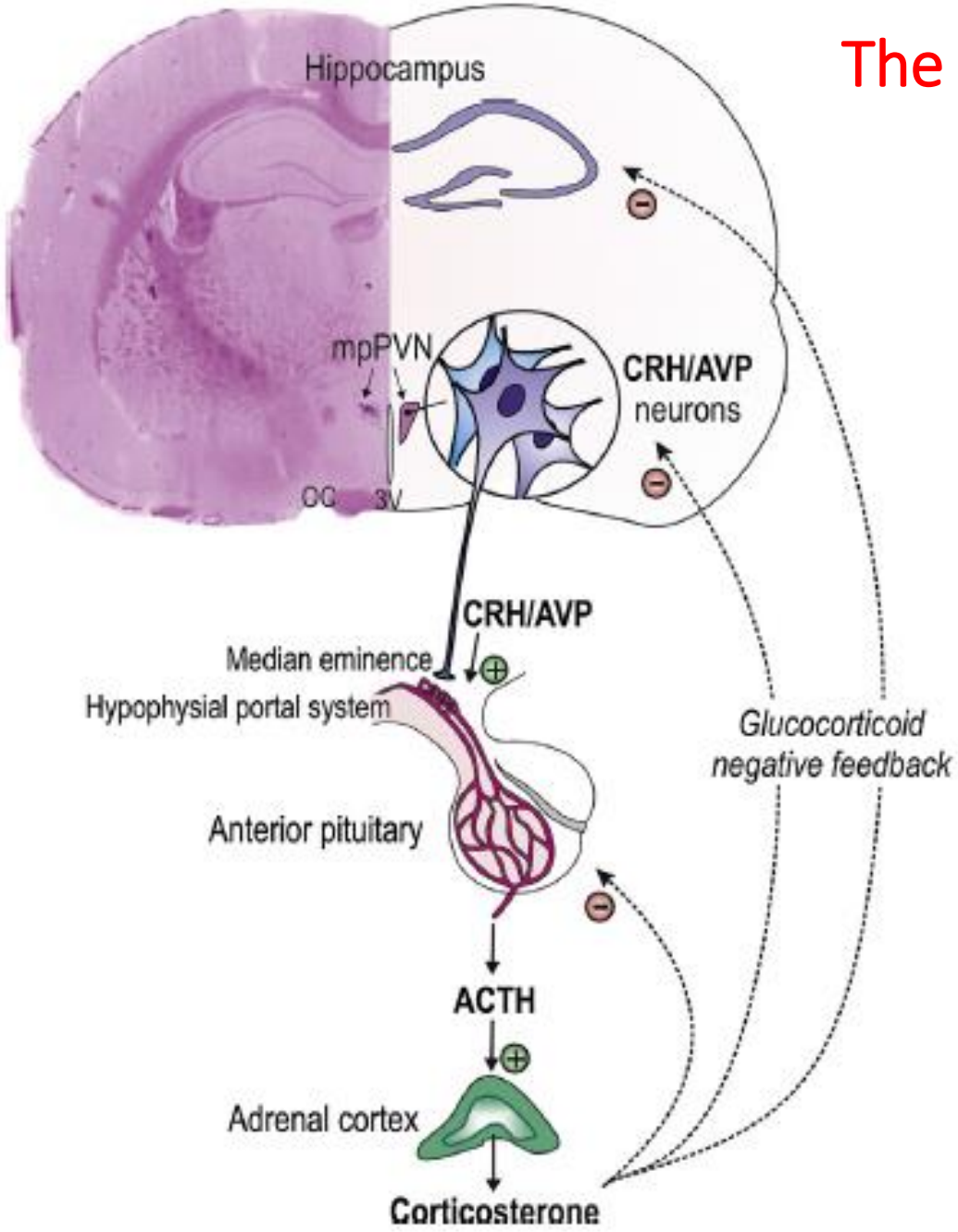
Heterogeneity: $Chi^2 = 1.30$, df = 1 (P = 0.25); $I^2 = 23\%$

Test for overall effect: Z = 1.97 (P = 0.049)

Test for subgroup differences: Not applicable



The hypothalamo-pituitary-adrenal axis (HPA)



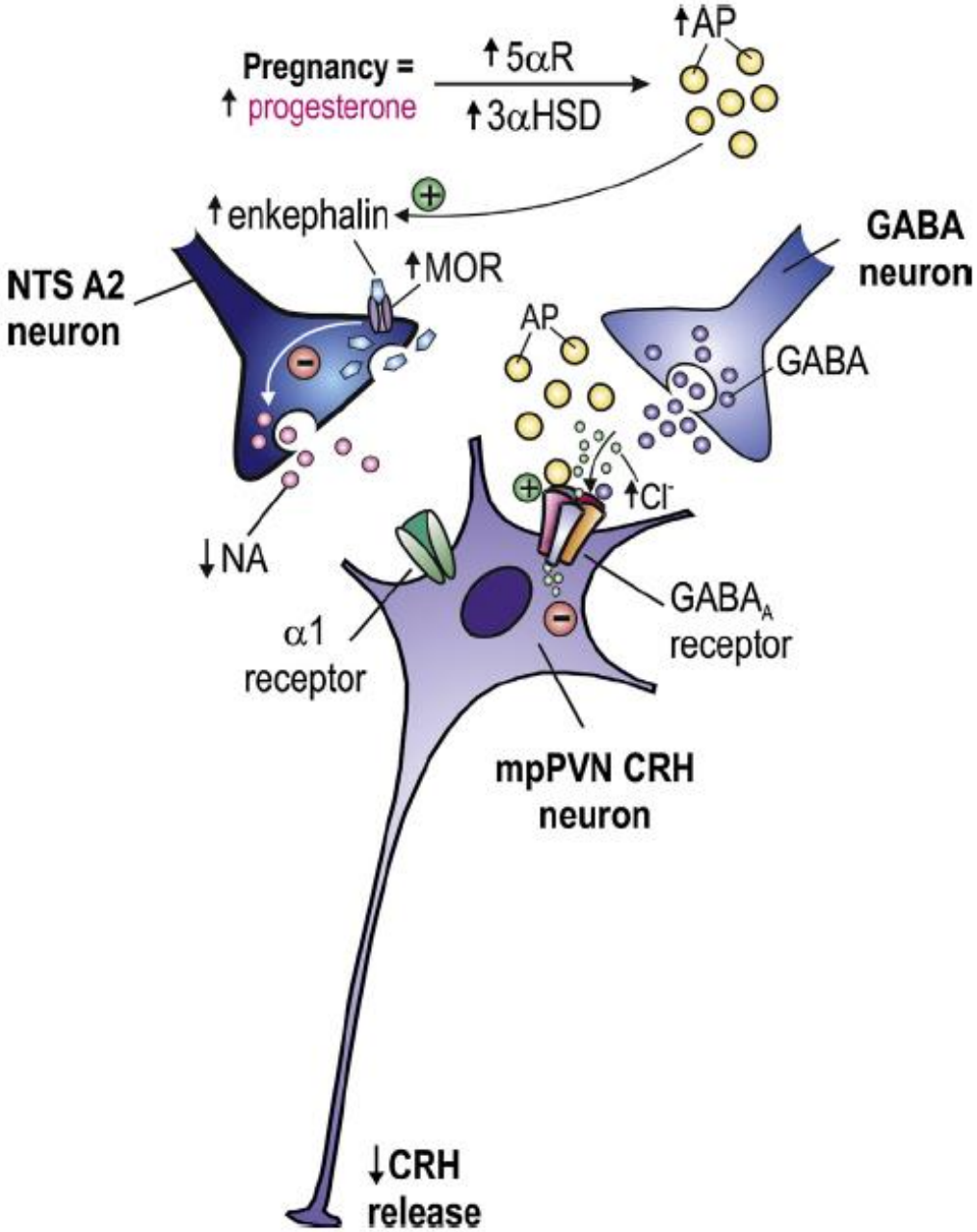
"Stress" :

Corticotropin releasing hormone CRH

ACTH

Adrenal cortex glucocorticoids (cortisol)

Brunton PJ, J Steroid Biochemistry and Molecular Biology, 2015



Modulation of CRH releasing neuron

- Noradrenergic A2 neurons (brainstem): excitatory
- Allopregnanolone / encephalin can stimulate opoid receptor MOR
- MOR inhibits release NA

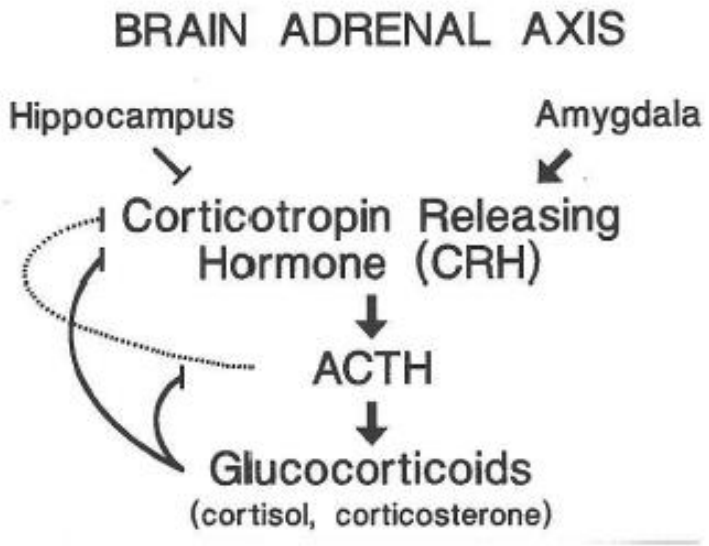
- Inhibitory GABA neuron

Allopregnalolone : neuro- steroid

- direct action on steroid receptors
- modulation of GABA-A receptors

Pathophysiology of Massive Infantile Spasms: Perspective on the Putative Role of the Brain Adrenal Axis

Tallie Z. Baram, MD, PhD
Department of Neurology, University of Southern California, and Division of Neurology, Childrens Hospital Los Angeles, Los Angeles, CA.



CRH injection in rodents : potent convulsant

CHR-R1 receptor in amygdala hippocampus

Time specific (young animals more prone than adult animals)

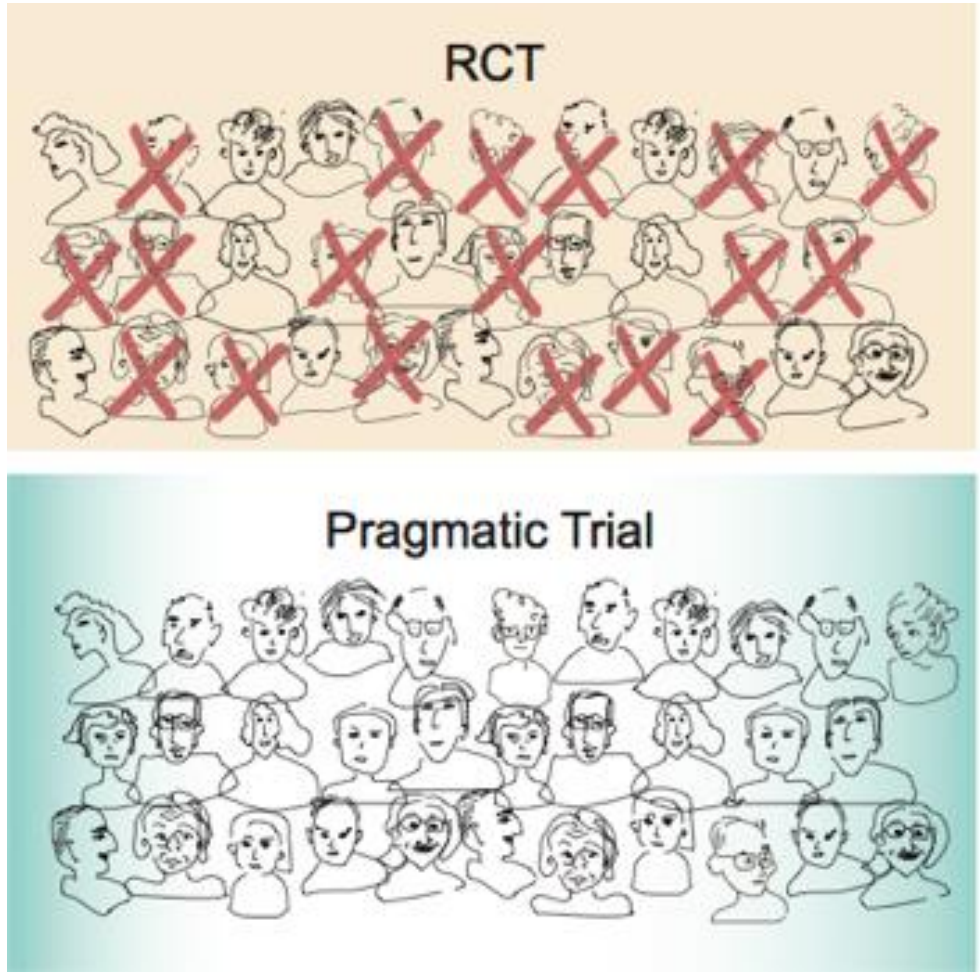
R1 receptors disappear

ACTH

-effect on melanocortin (MCR) Type 4 receptor in amygdala: Stops CRH release
-direct effect on steroid receptors (steroid dependent activity)
-indirect effect on adenenosine (second messenger)
-direct anticonvulsant effect (fragments ACTH)

(gluco)steroids

ACTH / Steroids in other epilepsies



Cfr RESCUE study

Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases

*[!]Bart van den Munckhof, *[!]Violet van Dee, †Liora Sagi, ‡Roberto H. Caraballo, §Pierangelo Veggiotti, ¶Elina Liukkonen, #**Tobias Loddenkemper, **Iván Sánchez Fernández, ††Marga Buzatu, ‡‡§§¶¶##***Christine Bulteau, *Kees P. J. Braun, and *Floor E. Jansen

Treatment	OR (95% CI) Univariate (complete case)	OR (95% CI) Univariate (MI)	OR (95% CI) Multivariate (MI)
AED	Reference	Reference	Reference
Benzodiazepines	**2.2 (1.5–3.2)***	**2.2 (2.0–2.5)***	**2.1 (1.4–3.1)***
Steroids	**4.4 (2.9–6.7)***	**4.4 (3.9–5.0)***	**4.2 (2.7–6.5)***
Surgery	**9.8 (4.1–23.1)***	**9.8 (7.5–12.6)***	**8.6 (3.5–21.4)***
Other	1.2 (0.69–2.1)	**1.2 (1.0–1.4)***	1.1 (0.6–2.0)
Patient characteristics			
Male gender	1.2 (0.9–1.6)	1.2 (0.9–1.5)	**1.4 (1.0–1.8)***
Age at diagnosis	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Interval diagnosis—treatment	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Febrile seizures	1.2 (0.7–2.1)	1.3 (0.7–2.3)	1.4 (0.8–2.6)
Abnormal development before ESES onset	**0.6 (0.5–0.9)***	**0.6 (0.5–0.8)***	0.6 (0.4–0.8)*
CT/MRI abnormalities	0.8 (0.6–1.1)	0.8 (0.6–1.1)	1.0 (0.7–1.4)
CT/MRI abnormalities in nonsurgically treated patients	0.7 (0.5–1.0)*	0.7 (0.5–1.0)	1.0 (0.7–1.4)
Number of previous treatments	1.2 (1.1–1.4)*	1.1 (0.9–1.3)	1.1 (0.9–1.0)

Improvement :

Cognitive and /or EEG improvement

Epilepsia, 2015

Can ACTH therapy improve the long-term outcome of drug-resistant frontal lobe epilepsy?

Giuseppe Gobbi [1], Giulia Loiacono [2], Antonella Boni [1], Lucia Marangio [3], Alberto Verrotti [4]

[1] Child Neurology Unit, IRCCS (Istituto delle Scienze Neurologiche di Bologna), Bellaria Hospital, Bologna
[2] Department of Paediatrics, University of Chieti, Chieti
[3] Department of Paediatrics, Arcispedale S. Anna-University of Ferrara, Ferrara
[4] Department of Paediatrics, University of Perugia, Perugia, Italy

Epileptic Disorders 2014

Patient	Sex	Age at onset of epilepsy (years)	Epilepsy duration (years)	Follow-up (years)	Seizure type	Age at start of ACTH	Short-term outcome	Medium-term outcome	Long-term outcome
1	M	12	6.2	14	Atypical absences, tonic versive	14 years, 8 months	Effective	Excellent	Excellent
2	M	11	5.8	11	Atypical absences, tonic versive, drop attacks	15 years, 9 months	Effective	Good	Excellent
3	F	4	4.2	6	Tonic, partial complex	4 years, 11 months	Effective	Excellent	Excellent
4	M	11	8.3	16	Atypical absences, tonic versive	17 years	Effective	Good	Excellent
5	M	3.5	2.6	5.5	Atypical absences, tonic versive, generalised tonic-clonic	4 years	Ineffective	Ineffective	Poor
6	M	4	5.6	11	Atypical absences, tonic versive, drop attacks	4 years, 6 months	Effective	Excellent	Excellent

The ACTH dose used was 0.01 mg/kg/day *i.m.* for 2 weeks in all patients, followed by tapering for 6 weeks,

Intravenous Methylprednisolone for Intractable Childhood Epilepsy

Kholoud H. Almaabdi MBBS, Rawan O. Alshehri MBBS, Areej A. Althubiti MBBS, Zainab H. Alsharef MBBS, Sara N. Mulla MBBS, Dareen S. Alshaer MBBS, Nouf S. Alfaidi MBBS, Mohammed M. Jan MBChB FRCPC *

Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Methylprednisolone :

- Inhibits cytokine (prostaglandins)
- Inhibits T cells
- Decreases extravasation of immune cells into CNS
- Inhibits CRH release

Methodology

IV Methylprednisolone 15 mg/kg/day for 3 days
Followed by
Oral prednisolone 1 mg/kg for 1week
Then weaned over 2-8 weeks

Follow up 6 -24 months

Pediatric Neuroloy 2014

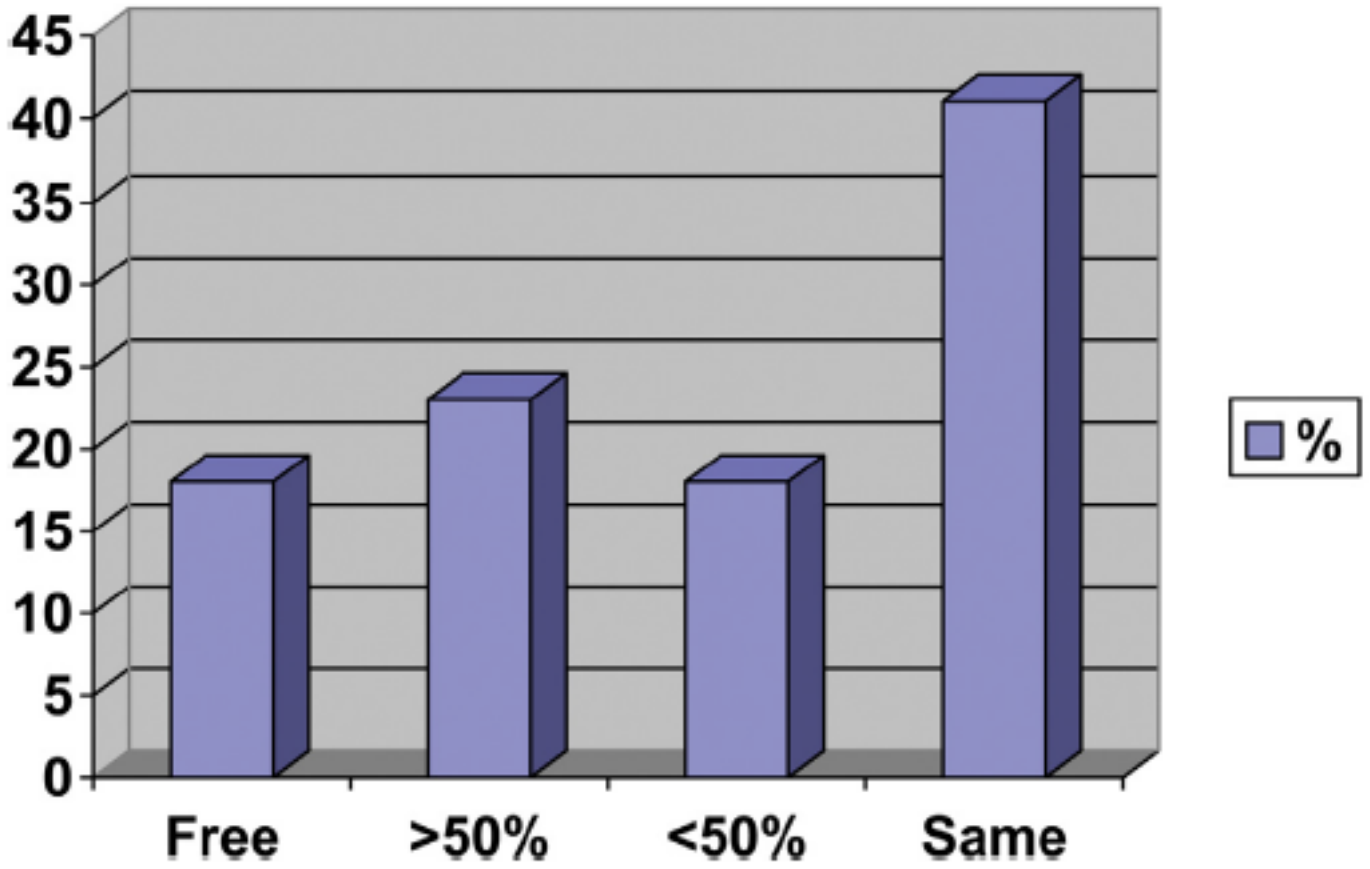


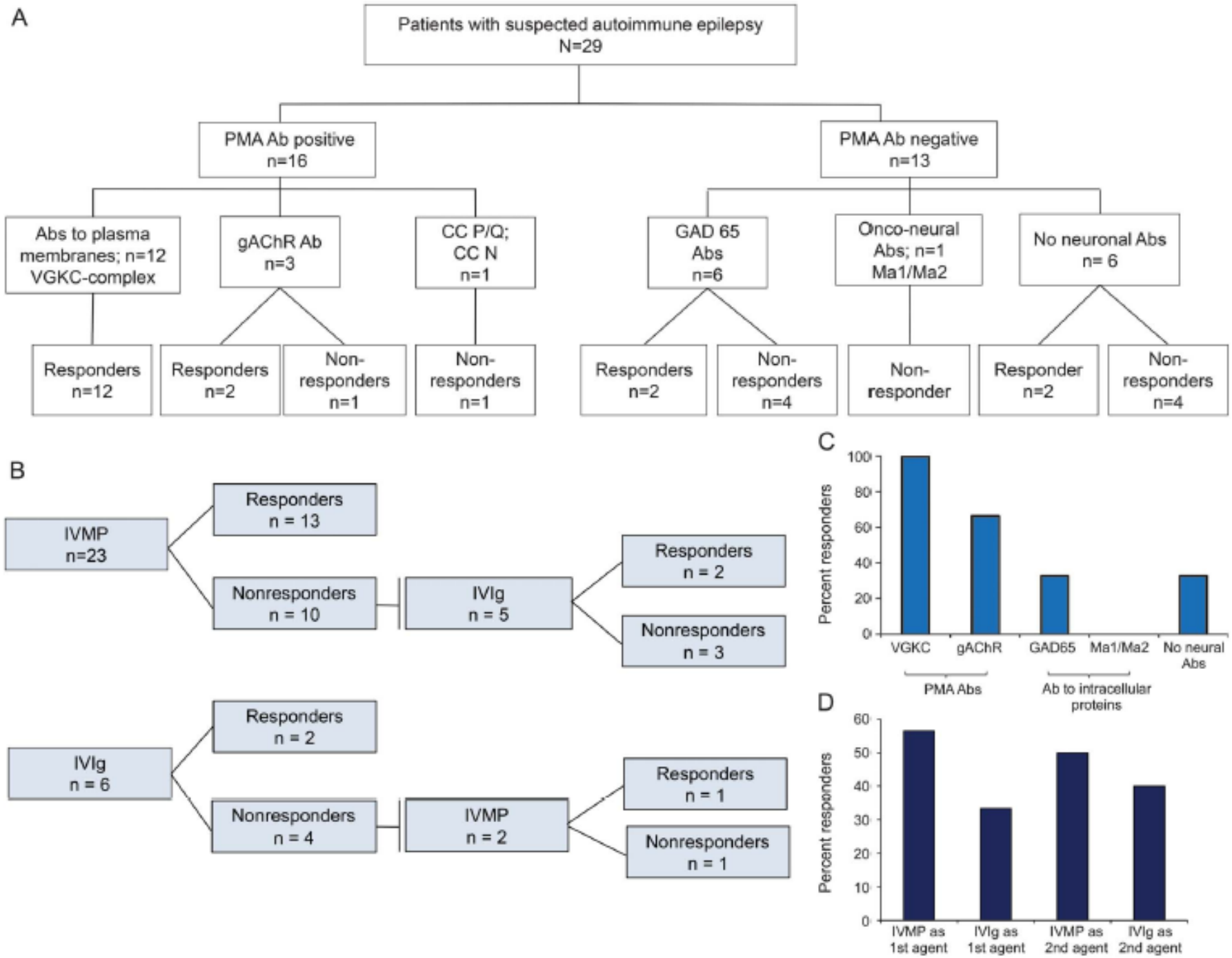
FIGURE.
Seizure outcome at 6 months after the intravenous pulse of methylprednisolone shown in percentages of children achieving complete seizure control, >50% seizure reduction, <50% seizure reduction, or no change. (The color version of this figure is available in the online edition)

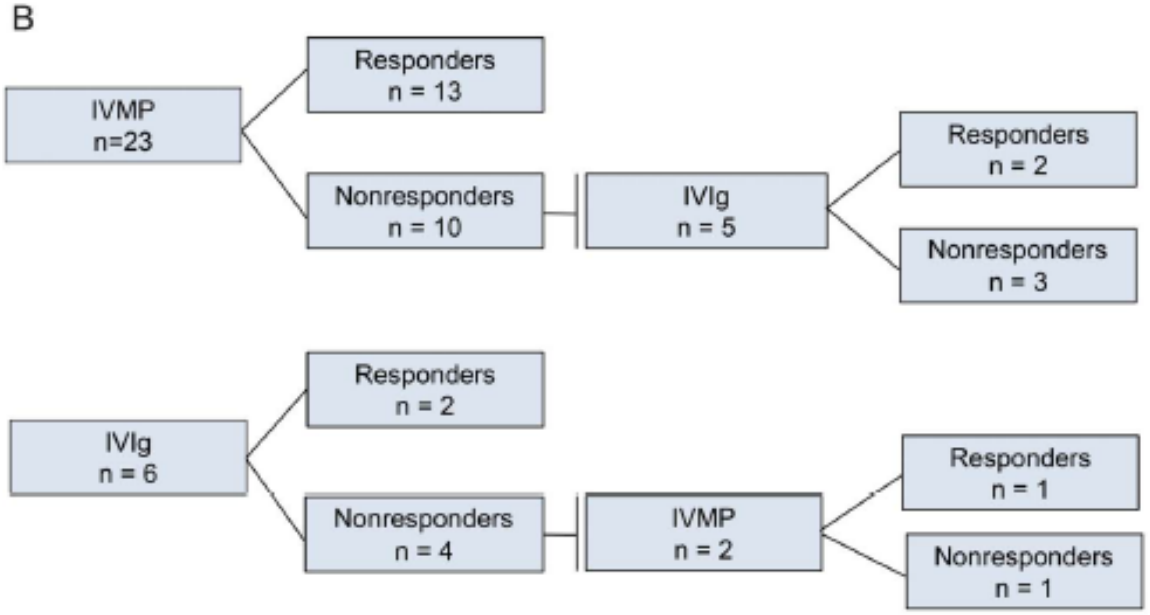
45 % responders

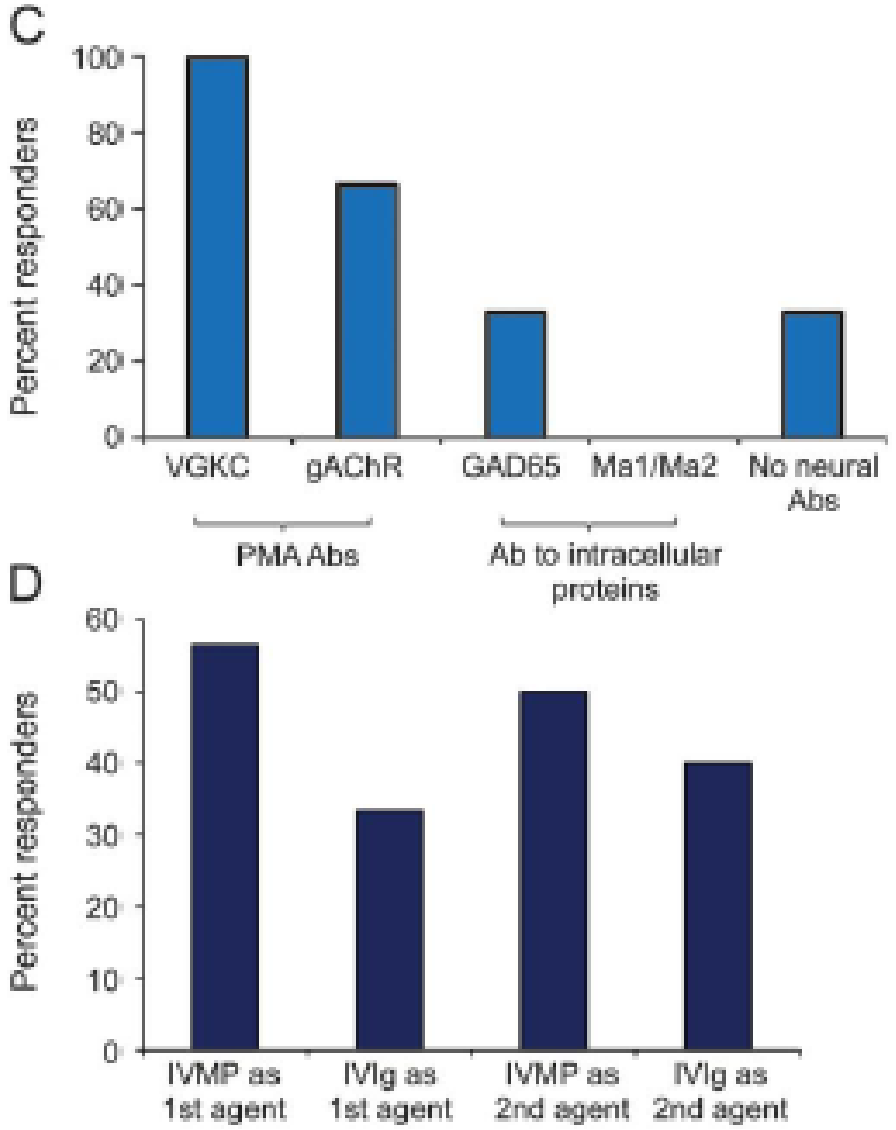
Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy

Figure 1 Clinical features suggestive of autoimmune epilepsy

- Acute to subacute onset (maximal seizure frequency ≤ 3 months)
- Multiple seizure types or faciobrachial dystonic seizures
- AED resistance
- Personal or family history (1st degree relative) of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation
  - CSF (elevated protein, pleocytosis, oligoclonal bands, + CSF index)
  - MRI (mesial temporal or parenchymal T2 hyperintensity)
  - Hypermetabolism on functional imaging (PET)
- Detection of neural autoantibody


A
Patients with suspected autoimmune epilepsy
N=29
PMA Ab positive
n=16
PMA Ab negative
n=13
Abs to plasma membranes; n=12
VGKC-complex
gAChR Ab
n=3
CC P/Q;
CC N
n=1
GAD 65
Abs
n=6
Onco-neural
Abs; n=1
Ma1/Ma2
No neuronal Abs
n= 6
Responders
n=12
Responders
n=2
Non-
responders
n=1
Non-
responders
n=1
Responders
n=2
Non-
responders
n=4
Non-
responder
Responder
n=2
Non-
responders
n=4
B
IVMP
n=23
Responders
n = 13
Nonresponders
n = 10
IVIg
n = 5
Responders
n = 2
Nonresponders
n = 3
IVIg
n = 6
Responders
n = 2
Nonresponders
n = 4
IVMP
n = 2
Responders
n = 1
Nonresponders
n = 1
C
Percent responders
100
80
60
40
20
0
VGKC
gAChR
GAD65
Ma1/Ma2
No neural Abs
PMA Abs
Ab to intracellular proteins
D
Percent responders
60
50
40
30
20
10
0
IVMP as 1st agent
IVIg as 1st agent
IVMP as 2nd agent
IVIg as 2nd agent


B
IVMP
n=23
Responders
n = 13
Nonresponders
n = 10
IVIg
n = 5
Responders
n = 2
Nonresponders
n = 3
IVIg
n = 6
Responders
n = 2
Nonresponders
n = 4
IVMP
n = 2
Responders
n = 1
Nonresponders
n = 1


C
Percent responders
100
80
60
40
20
0
VGKC
gAChR
GAD65
Ma1/Ma2
No neural Abs
PMA Abs
Ab to intracellular proteins
D
Percent responders
60
50
40
30
20
10
0
IVMP as 1st agent
IVIg as 1st agent
IVMP as 2nd agent
IVIg as 2nd agent

Efficacy and Tolerability of Methylprednisolone Pulse Therapy in Childhood Epilepsies Other Than Infantile Spasms

Thomas Bast[1,*] Sarah Richter[2,*] Friedrich Ebinger[3] Dietz Rating[§] Adelheid Wiemer-Kruel[1]
Susanne Schubert-Bast[4]

Methodology

Fixed :
weekly MPR pulses 20mg/kg/day for 3 days
4days interval
4 cycles

Adjustable :
Good effect : continu MPR every 2 weeks
Later : every 3 or 4 weeks
Relapse : intensification

Neuropediatrics 2014

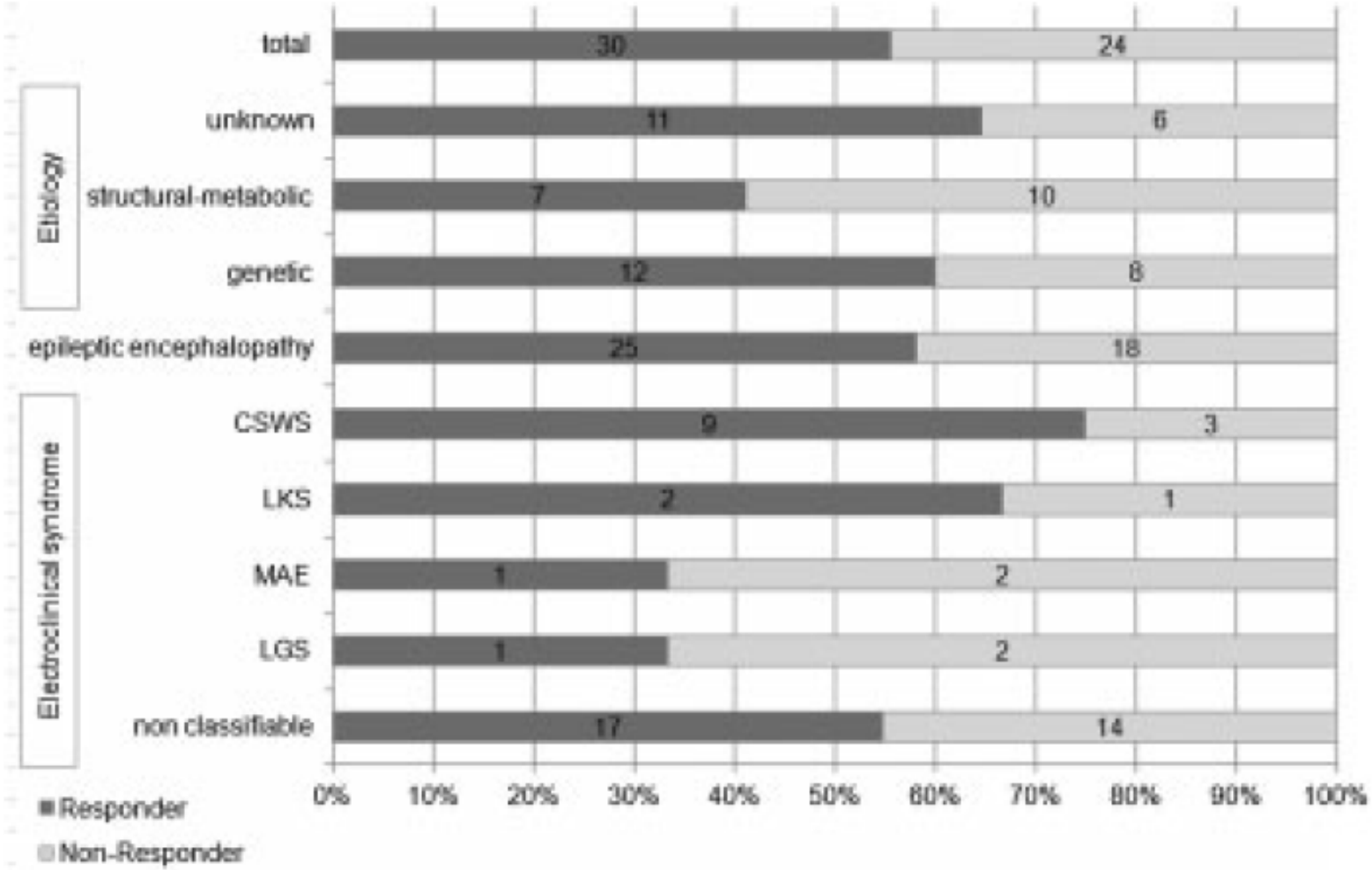
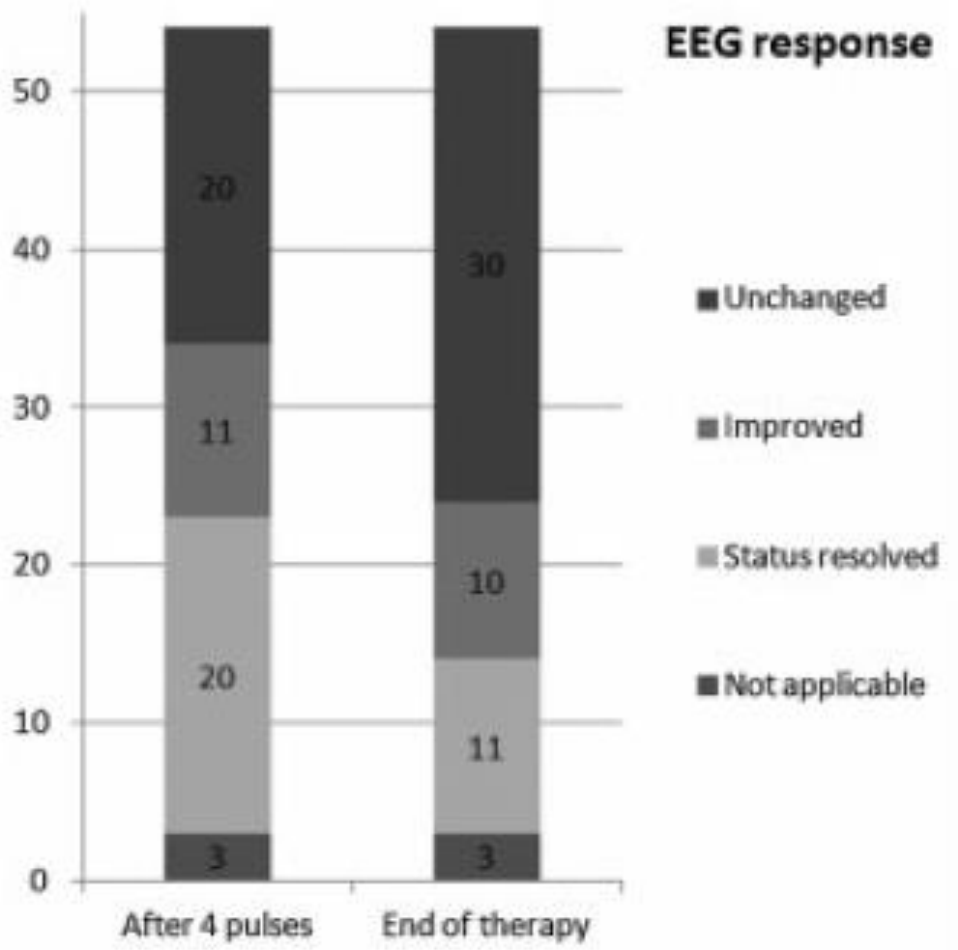
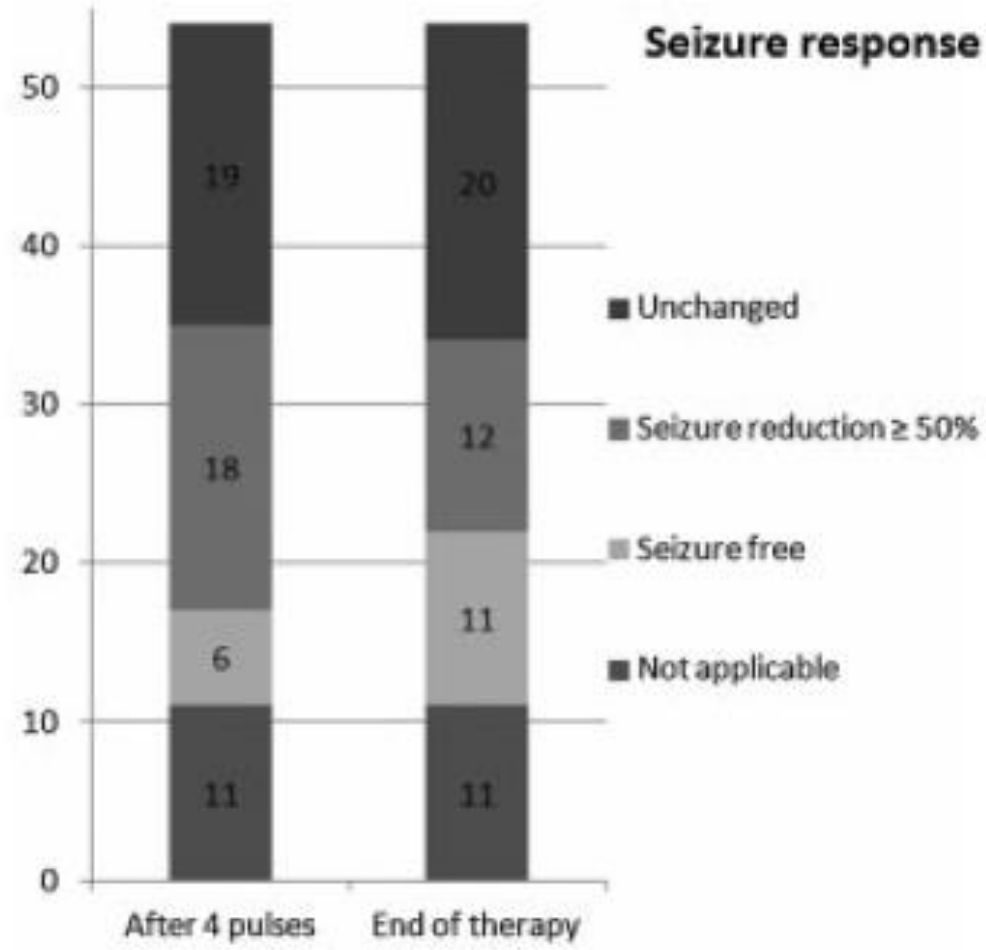


Fig. 2 Response after four methylprednisolone pulses. CSWS, continuous spike-waves in slow sleep; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; MAE, myoclonic-astatic epilepsy.


EEG response
50
40
30
20
10
0
20
11
20
3
30
10
11
3
After 4 pulses
End of therapy
Unchanged
Improved
Status resolved
Not applicable


Seizure response
50
40
30
20
10
0
19
18
6
11
20
12
11
11
After 4 pulses
End of therapy
Unchanged
Seizure reduction ≥ 50%
Seizure free
Not applicable

Original Article

Effectiveness of a hybrid corticosteroid treatment regimen on refractory childhood seizures and a review of other corticosteroid treatments

*Dewi P. Bakker, Coriene E. Catsman-Berrevoets, Rinze F. Neuteboom**

Erasmus University Hospital-Sophia Children's Hospital, The Netherlands

Methodology

Refractory epilepsy, no WEST, no Landau Kleffner

IV methylprednisolone 20/KG/day for 3 days
12 weeks oral prednisolone (0,5 mg/kg/day alternate days)
Taper phase

Eur J Paed Neurol, 2015

Label	Author	Medication regimen	Number of patients	Treatment period (weeks)	Epileptic syndromes	Good response	Seizure free	Seizure free after therapy
1	Charuvanij[22]	ACTH, 5 w mean dosage 50 IU/d (15–100 IU/d)	21	5	LGS 18 (86%), UCF 3 (14%)		6 (29%)	2 (10%)
2	Kramer[23]	ACTH 2 w 40–100 IU/d or 110 IU/M^2	12	2	FOC 2 (17%), GEN 2 (17%), ME 8 (66%)	11 (92%)		
3	Oguni[25]	ACTH	22		MAE 22 (100%)	13 (59%)	8 (36%)	
4	Okumura[17]	ACTH 0.01–0.015 mg/kg/d (1–1.5 IU/kg/d)	14	2–4	FLE 1 (7%), GEN 13 (93%)	14 (100%)	12 (86%)	5 (36%)
5	O'Regan[24]	ACTH, 2 w 0.5 mg/d (50 IU/d), if successful continued	10	2 or more	Unclassified 2 (20%), LGS 7 (70%), SMEI 1 (10%)	5 (50%)	4 (40%)	
6	Snead[26]	ACTH, 3 w 150 IU/M^2/d, until 8 w taper	18	8	Unclassified 18 (100%)		12 (67%)	6 (33%)
7	Yamatogi[19]	ACTH 1–8 w 0.25–0.75 mg/d (=10–30 IU)	45	1–8	LGS 45 (100%)	28 (62%)	23 (51%)	13 (29%)
A	Bast[4]	Methylprednisolone, 3 d 20 mg/kg/d once a week	37	4 or more	LGS 3 (8%), MAE 3 (8%) UCF 31 (84%)	11 (30%)	4 (11%)	
B	Grosso[30]	Deflazacort, 0.75 mg/kg/d	16	24	FOC 6 (38%), GEN 7 (44%), LGS 3 (19%)	6 (38%)	0 (0%)	
C	Grosso[30]	Hydrocortisone, 4 w 10 mg/kg/d, 4 w 5 mg/kg/d, 4 w 2.5 mg/kg/d, 4 w 1 mg/kg/d, 8 w 1 mg/kg alternate day	13	24	FOC 5 (38%), GEN 6 (46%), LGS 2 (15%)	5 (38%)	1 (8%)	0 (0%)
D	Kramer[23]	Methylprednisolone 2–3 d 10–30 mg/kg/d, prednisone 4 w 2 mg/kg/d	10	4	GEN 5 (50%), FOC 2 (20%), ME 3 (30%)	3 (30%)		
E	Kramer[23]	Prednisone 4 w 2–2.5 mg/kg/d	13	4	FOC 2 (15%), GEN 4 (31%), LGS 2 (15%), MAE 3 (23%), ME 2(15%)	5 (38%)		
F	Sevilla[28]	Methylprednisolone, 5 d 15 mg/kg/d once a month	12	12	FOC 6 (50%), GEN 6 (50%)	10 (83%)	2 (17%)	1 (8%)
G	Sinclair[18]	Prednisone, 6 w 1 mg/kg/d, 6 w taper alternate day	26	8	ABS 7 (27%), LGS 10 (39%), ME 3 (12%), SMEI 6 (23%)	21 (81%)	16 (62%)	12 (46%)
H	Snead[26]	Prednisone, 4 w 3 mg/kg/d, 8 w 3 mg/kg alternate day, 4 w taper	16	16	Unclassified 16 (100%)	0 (0%)	0 (0%)	
I	Verhelst[29]	Dexamethasone, 3 d 0.5 mg/kg/d once a month	6	12	Unclassified 6 (100%)	1 (17%)	0 (0%)	
J	Verhelst[29]	Hydrocortisone, 20 mg/kg/d	5	24	Unclassified 4 (80%), LGS 1(20%)		4 (80%)	1 (20%)
K	You[27]	Prednisolone, 6 w 2 mg/kg/d, 2 w taper	38	8	GEN 2 (5%), LGS 32 (84%), MAE 4 (11%)	30 (79%)	24 (63%)	6 (16%)
L	**Our patients**	**Methylprednisolone 3 d 20 mg/kg, prednisolone 12 w 0.5 mg/kg/d alternate day**	**21**	**12**	**Unclassified 14 (64%), FOC 1 (5%), MAE 4 (18%), ME 1 (5%), PAN 1 (5%)**	**9 (43%)**	**6 (29%)**	**1 (5%)**

Abbreviations: IU international units; d, day; w, week; m, month; ABS atypical absence epilepsy; CSWS; generalized epilepsy with continuous spike-wave during sleep; FLE frontal lobe epilepsy; FOC epilepsy with focal seizures; GEN epilepsy with generalized seizures; LGS, Lennox–Gastaut syndrome; MAE myoclonic atonic epilepsy; ME, myoclonic epilepsy; PAN, panayiotopoulos epilepsy; SMEI severe myoclonic epilepsy of infancy.

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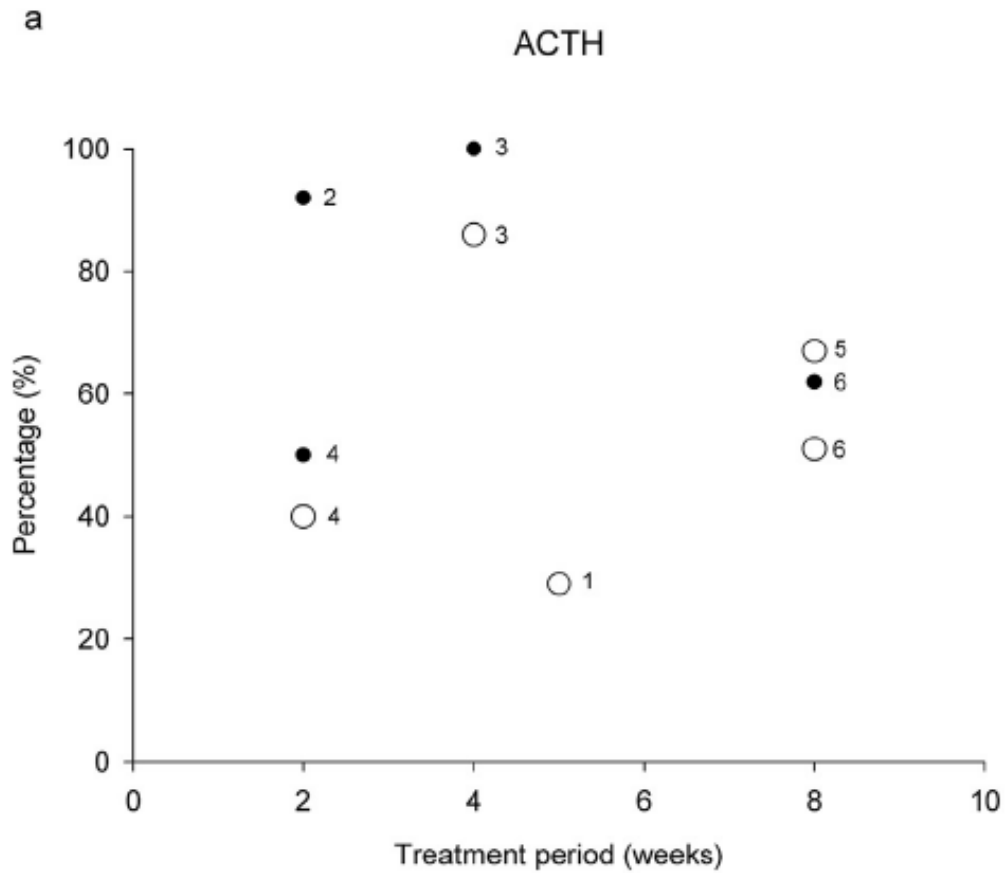

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D	Kramer[23]	Methylprednisolone 2–3 d 10–30 mg/kg/d, prednisone 4 w 2 mg/kg/d	10	4	GEN 5 (50%), FOC 2 (20%), ME 3 (30%)	3 (30%)		
E	Kramer[23]	Prednisone 4 w 2–2.5 mg/kg/d	13	4	FOC 2 (15%), GEN 4 (31%), LGS 2 (15%), MAE 3 (23%), ME 2(15%)	5 (38%)		
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I	Verhelst[29]	Dexamethasone, 3 d 0.5 mg/kg/d once a month	6	12	Unclassified 6 (100%)	1 (17%)	0 (0%)	
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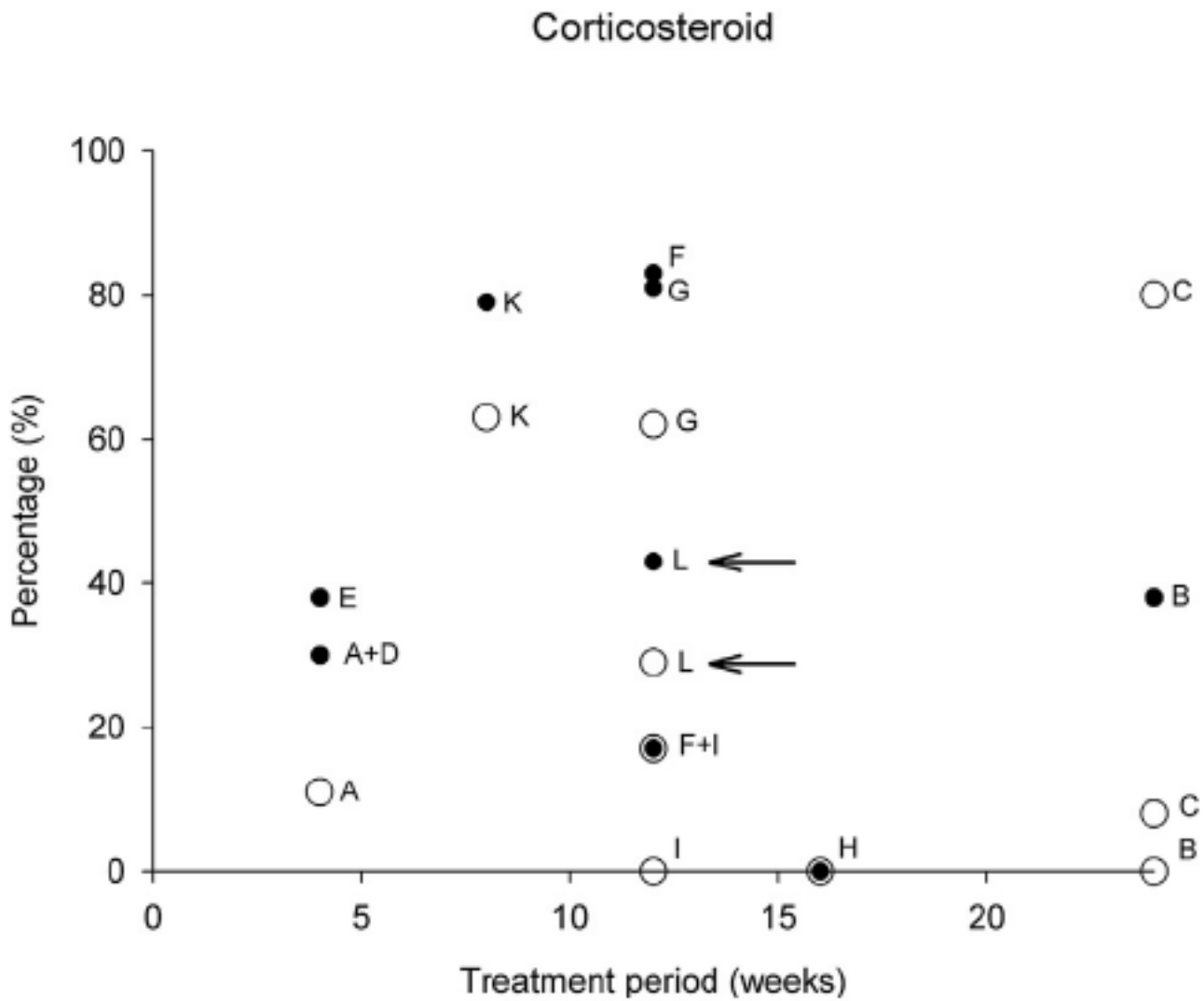
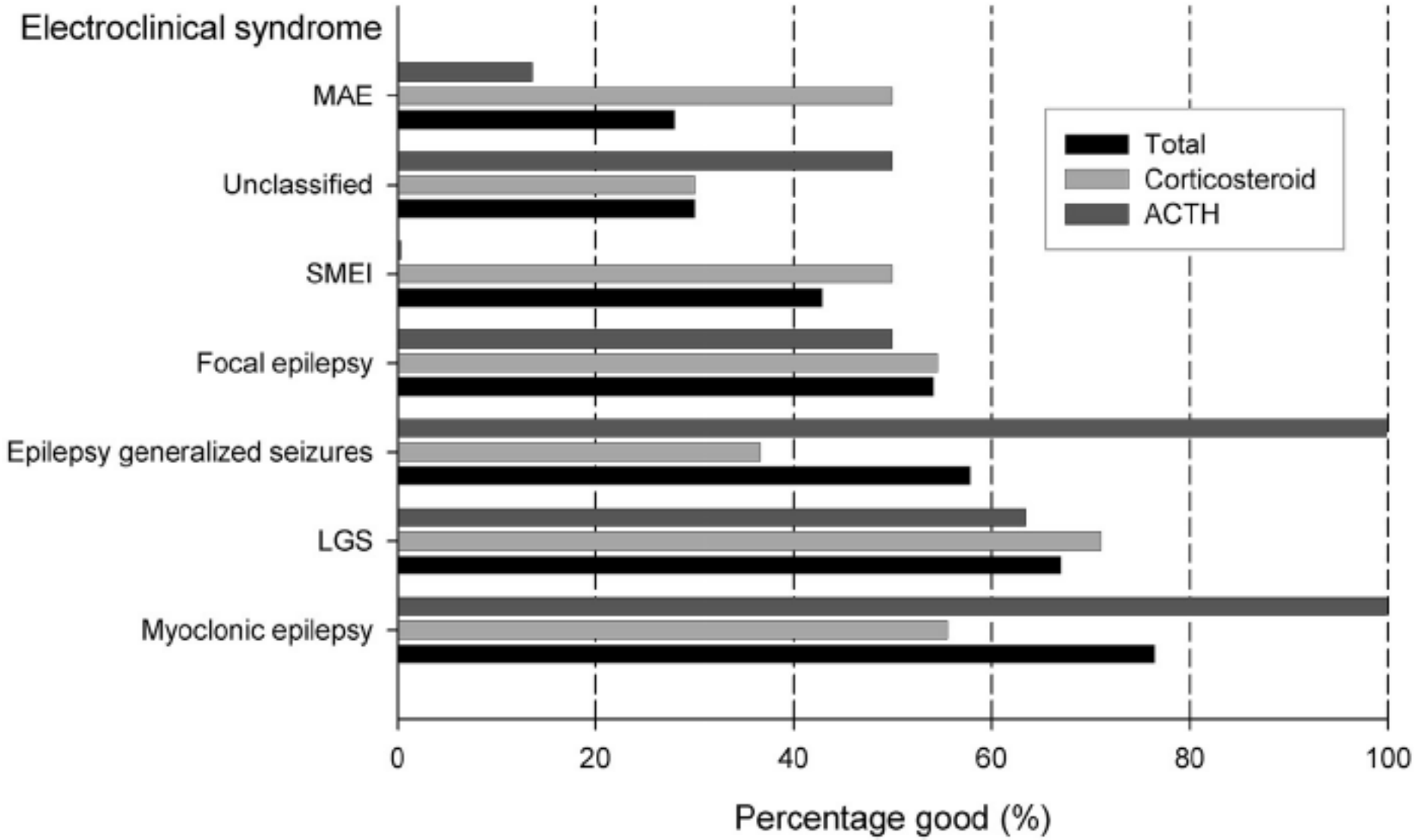
L	**Our patients**	**Methylprednisolone 3 d 20 mg/kg, prednisolone 12 w 0.5 mg/kg/d alternate day**	**21**	**12**	**Unclassified 14 (64%), FOC 1 (5%), MAE 4 (18%), ME 1 (5%), PAN 1 (5%)**	**9 (43%)**	**6 (29%)**	**1 (5%)**

Abbreviations: IU international units; d, day; w, week; m, month; ABS atypical absence epilepsy; CSWS; generalized epilepsy with continuous spike-wave during sleep; FLE frontal lobe epilepsy; FOC epilepsy with focal seizures; GEN epilepsy with generalized seizures; LGS, Lennox–Gastaut syndrome; MAE myoclonic atonic epilepsy; ME, myoclonic epilepsy; PAN, panayiotopoulos epilepsy; SMEI severe myoclonic epilepsy of infancy.


Corticosteroid
Percentage (%)
100
80
60
40
20
0
0
5
10
15
20
Treatment period (weeks)
K
K
F
G
G
C
L
L
E
A+D
B
F+I
A
C
B
I
H


Electroclinical syndrome
MAE
Unclassified
SMEI
Focal epilepsy
Epilepsy generalized seizures
LGS
Myoclonic epilepsy
Total
Corticosteroid
ACTH
0
20
40
60
80
100
Percentage good (%)

[Intervention Review]

Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms

Vishal Mehta[1], Colin D Ferrie[2], J Helen Cross[3,4], Gayatri Vadlamani[2]

[1]Department of Paediatrics, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK. [2]Department of Paediatric Neurology, Leeds General Infirmary, Leeds, UK. [3]UCL Institute of Child Health, London, UK. [4]The Neville Childhood Epilepsy Centre, Lingfield, UK

Contact address: Gayatri Vadlamani, Department of Paediatric Neurology, Leeds General Infirmary, Clarendon Wing, Belmont Grove, Leeds, LS2 9NS, UK. gayatri.vadlamani@nhs.net. nagayatri@googlemail.com.

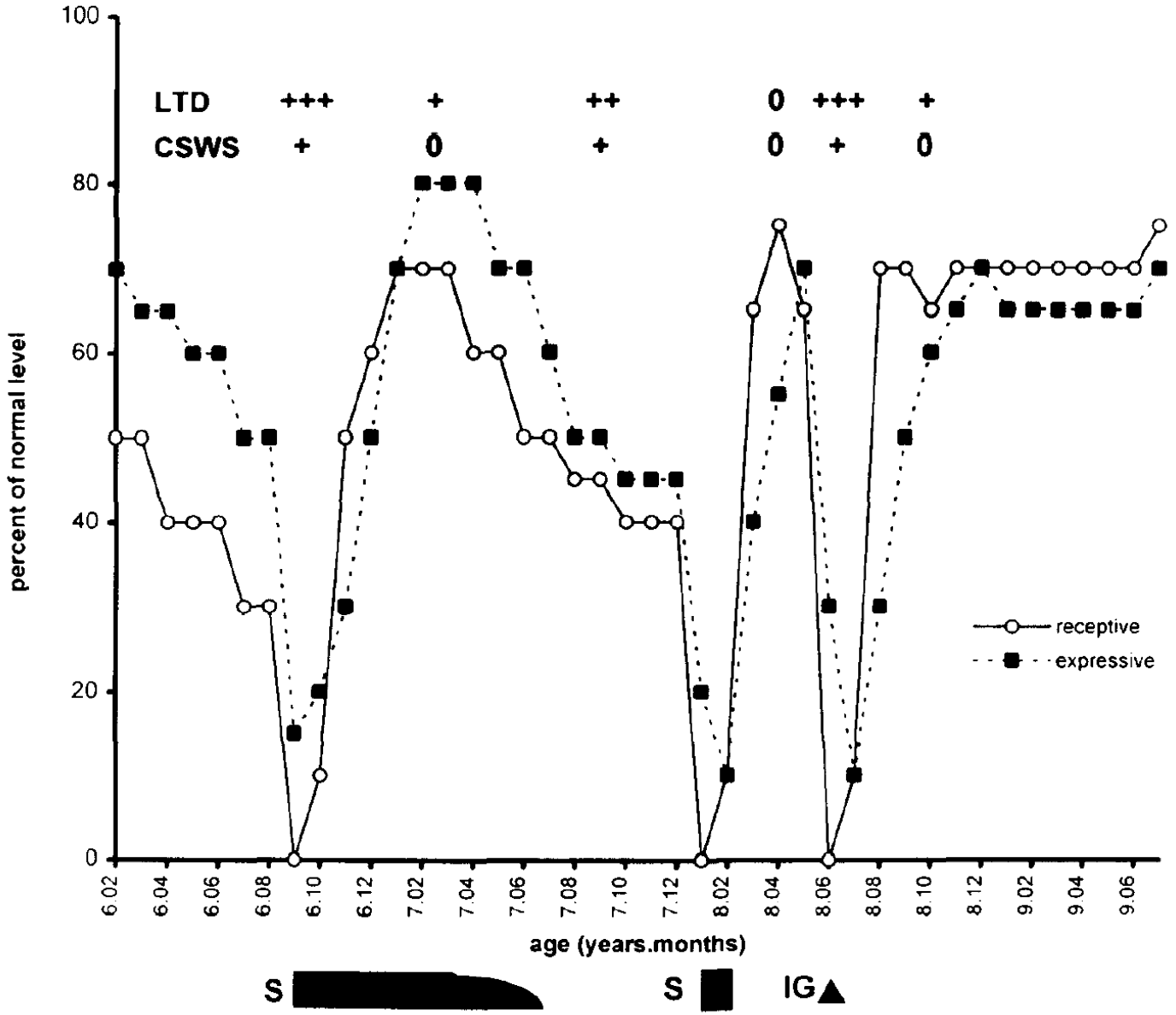
Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2015.
Review content assessed as up-to-date: 1 August 2014.

Citation: Mehta V, Ferrie CD, Cross JH, Vadlamani G. Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD005222. DOI: 10.1002/14651858.CD005222.pub3.

What about IVIG ?

Successful Use of Intravenous Immunoglobulins in Landau-Kleffner Syndrome

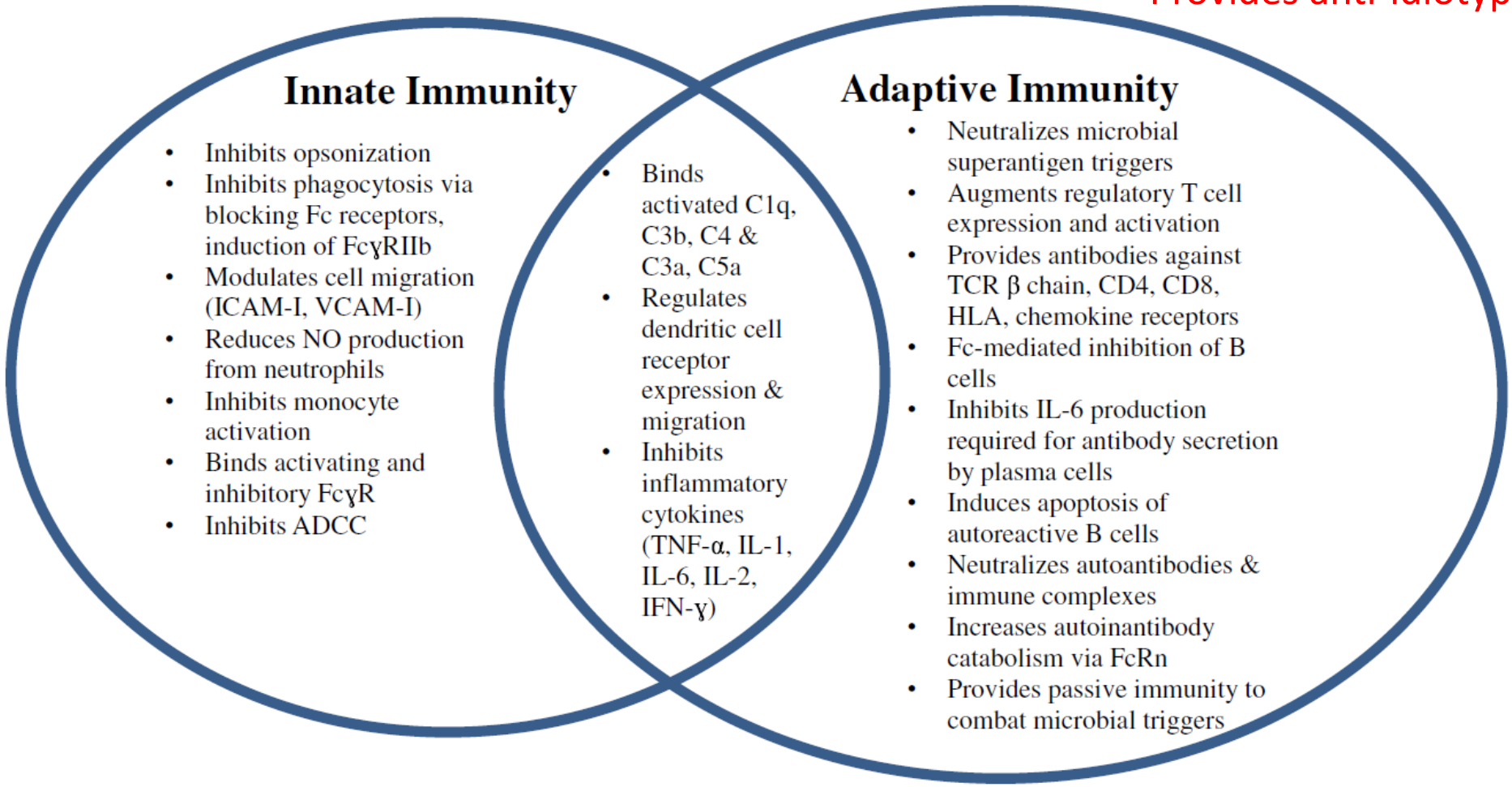
Lieven G. Lagae, MD, PhD*,
Jon Silberstein, MD*,
Phillippe L. Gillis, MD†, and
Paul J. Casaer, MD, PhD*



Lagae L et al ,Paediatric Neurology, 1996

Intravenous Immunoglobulins in refractory epilepsy

- Inhibits inflammatory cytokines
- Increases NK cell activity
- Provides anti-idiotypic antibodies



Wong and White, Clin REV Allerg Immunol, 2015

Reference, Study Type	No. Patients	Ages	Type(s) of Seizures	Epilepsy Syndrome(s)	Follow-up Period	Outcome
Ariizumi et al., 1987, open-label study[51]	11	3-12 months	Not specified	WS	3-6 months	7 (63.6%) seizure free, 1 (9%) mild improvement, and 3 (27.2%) no response
Van Engelen et al., 1994[36]	15	1.0-6.0 years	Infantile spasms, axial tonic, atypical absences, atonic	WS, LGS	3 months	Reduction in clinical seizures by 70%
Van Rijckevorsel-Harmant et al., 1994, double-blind trial[23]	(n = 61) 43 on IVIG; 18 on placebo	2-46.7 years	Partial, generalized	WS, LGS, LRE	6 months	No significant change in seizure frequency from treatment. In patients with partial epilepsy, a 50% reduction in seizure frequency was seen in 19 (44.2%) patients in the treatment group versus 2 (11.1%) patients in the placebo group
Turkay et al., 1996, open-label study[52]	6	5-13 years	Not available	Multiple	Not specified	Marked improvement in 4 (66.6%) and partial in 2 (33.3%)
Illum et al., 1998, single-blind trial[53]	10	4-14 years	Not specified	LGS	0.5 months	2 (20%) children seizures reduced 42%-100% with improvement of the intellectual function
Fayad et al., 1997[54]	11	2.5-8 years	Response of aphasia and not of seizures studied	LKS	5-72 months	Only 2 (18.1%) of the 11 patients had sustained and marked improvements
Espinosa-Zacarias et al., 2002, open-label study[55]	5	Not detailed	Not specified	WS, LGS	14 months	Satisfactory response was seen with IVIG add-on therapy in 5 (100%) patients with WS and LGS
Bingel et al., 2003, open-label study[56]	5	4.5-11.5 years	Infantile spasms, partial-onset tonic generalized myoclonic, myoclonic, tonic, atypical generalized, absence, juvenile spasms, absence, complex partial	LGS	12 months	4 (80%) patients had >50% to 92% seizure reduction
Billiau et al., 2007, open-label study[29]	13	1.6-25.8 years	Infantile spasms, focal, tonic-clonic, myoclonic, atypical and typical absence, clonic and tonic	WS, LGS, SFE	3-6 weeks	Four (30.7%) patients had seizure frequency reduced by 50% patients and by 25% to 50% in another 3 (23%) patients
Kramer et al., 2009, open-label[57]	9	Not clearly indicated	Did not study clinical seizures	ESES	1 months	Three of 9 (33%) had a >75% decrease in spike wave index, or >75% improvement of encephalopathy
Mikati et al., 2010, open-label study[30]	37	2-20 years	Partial, generalized	WS, LGS, LRE	15 (1-56) months	43% had a >50% decrease in seizure frequency, and 15% became seizure-free
Bello-Espinosa et al., current study	27	3-17 years		WS, LGS, SFE, SMFE, SGE, MAE, DS, CSWS	38 (9-101) months	In 19 (70.4%) patients, there was greater than 50% reduction in seizures. Eight (29.6%) had mild or no response to the continuous use of IVIG

Intravenous Immunoglobulins in refractory epilepsy

- Inhibits inflammatory cytokines
- Increases NK cell activity
- Provides anti-idiotypic antibodies

12 studies

1 RCT
5-37 patients

Variable methodology (dose, cycles, duration, follow up)

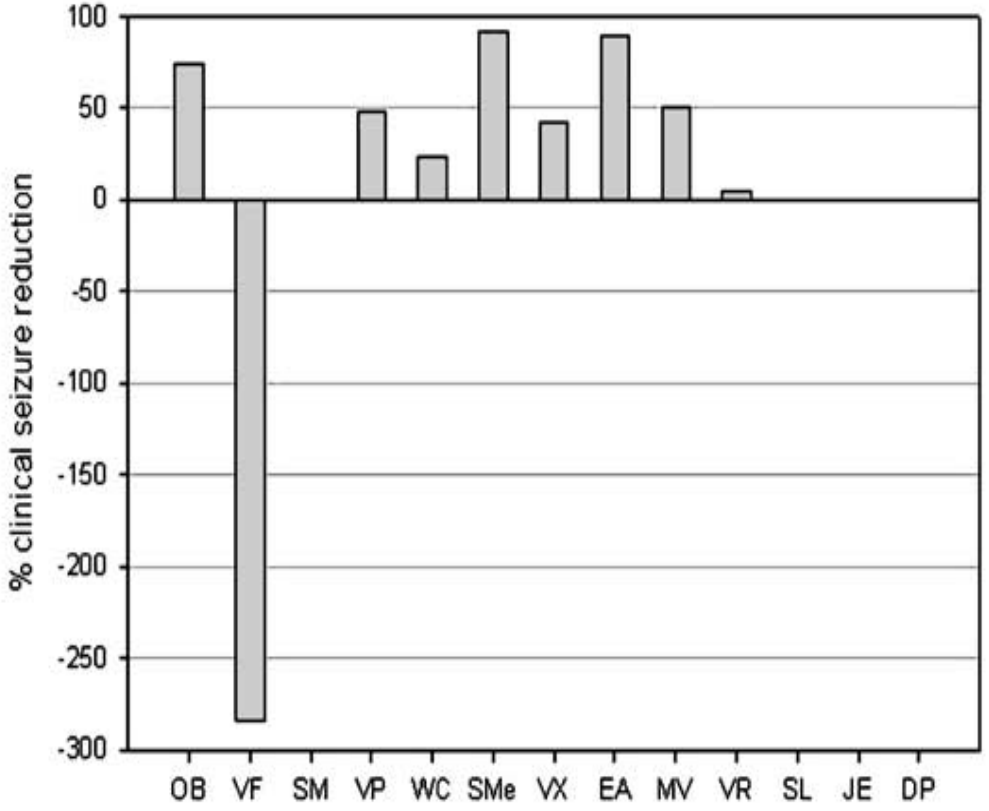
“Responders” : variable 0 - 66%

Bello-Espinova et al, Paed Neurol, 2015

Intravenous Immunoglobulins in Refractory Childhood-onset Epilepsy: Effects on Seizure Frequency, EEG Activity, and Cerebrospinal Fluid Cytokine Profile

*†An D. Billiau, ‡Peter Witters, ‡Berten Ceulemans, §Ahmad Kasran, †Carine Wouters, and ‡Lieven Lagae

Seizure frequency



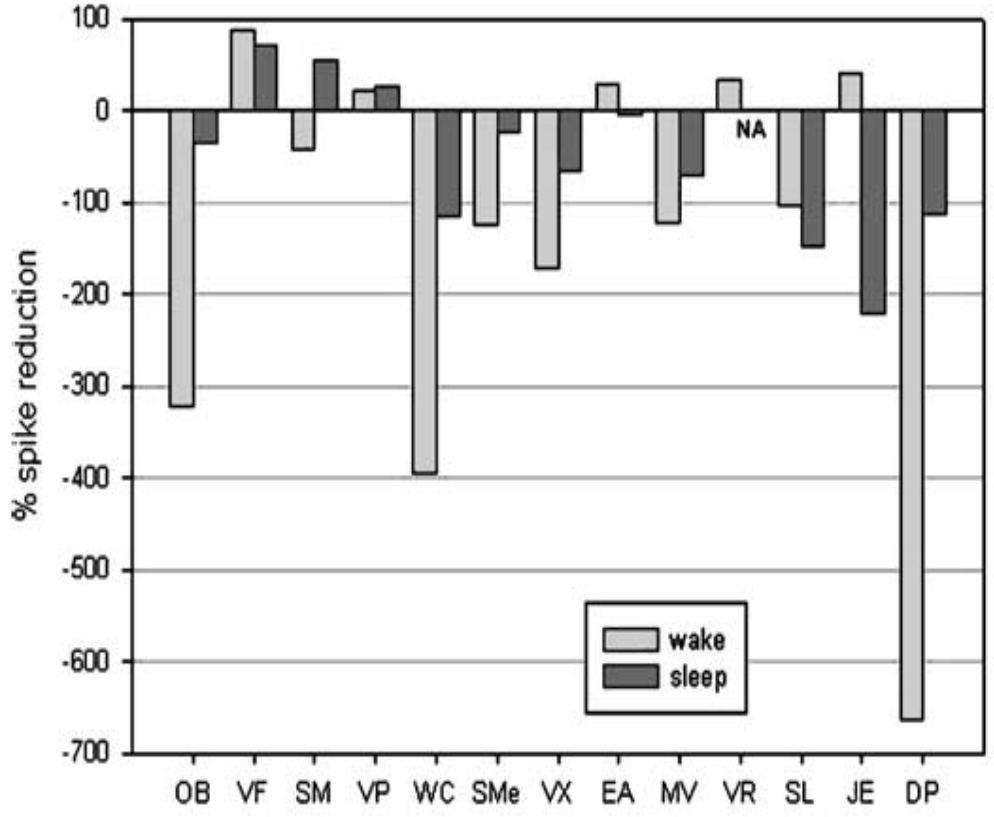
4/13 > 50% decrease

7/13 > 25% decrease

No relationship with duration or etiology

Epilepsia 2007

Effect on EEG



CSF cytokines

TABLE 3. *Cytokine levels in CSF and plasma before and after IVIG treatment*

	CSF (median (range)) (pg/ml)		Plasma (median (range)) (pg/ml)	
	Before	After	Before	After
IL-8	12.8 (6.3–46.6)[a]	15.2 (6.8–49.9)[a]	0 (0–6.8)	1.55 (0–11.8)
IL-6	1.8 (1–2.5)[a]	2 (0–4.2)[NS]	1.1 (0–3.8)	1.9 (0–14.2)
IL-10	0 (0–2.1)	0 (0–1.9)	0 (0–2.3)	0 (0–6)
IL-12	0 (0–7.1)	0 (0–2.9)	0 (0–4.6)	0 (0–4.5)

[a]$p < 0.05$.

IL-6 and IL-8 detectable in all patients, and higher in CSF than in serum : local production

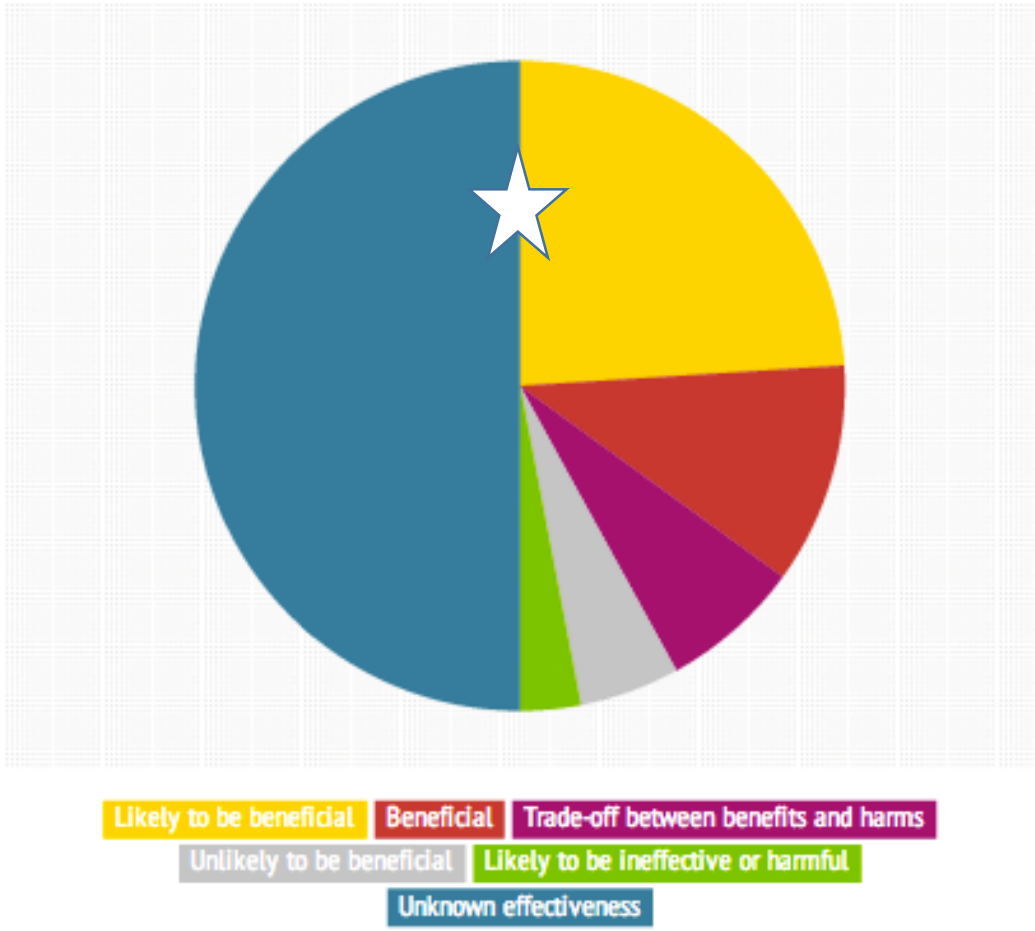
Pretreatment IL-8 correlated inversely with clinical improvement after IVIG

“conclusions”

- No hard data to support widespread use of steroids in epilepsy, except infantile spasms and ESES/CSWSS (?)
  Because of : poor methodology and outcome parameter definitions

- Not specific / not targeted enough : ***‘like a bull in a china shop’***
  Better understanding immunological processes needed

Effectiveness of medical treatments



Effectiveness of 3,000 treatments as studied in randomized trials, as collected by Clinical Effectiveness. This does NOT indicate how often treatments are used.

British Medical Journal