Epilepsi, inflammation och behandling
SNPF januari 2016
Per Åmark

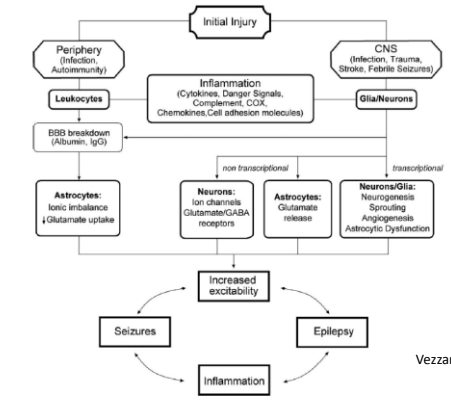
Inflammation: Cause and consequence of seizures?

Activation of cytokines, interleukines, complement and prostaglandins leads to a proconvulsive process and also modify voltage-gated and ligand-gated ion channels and increase extracellular glutamate concentrations.

Seizures by themselves may contribute to pro-exitatory and pro-convulsive inflammatory responses (i e via interleukins) and thus promote further seizures.

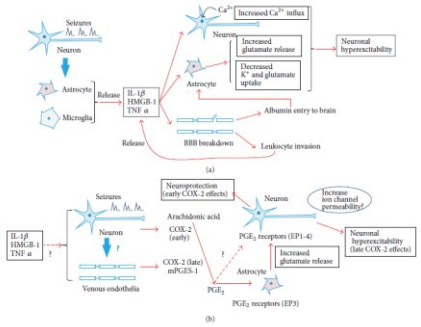
A process finally causing progressive cognitive/behavioural decline?

Balosso 2008, Stellwagen 2005, Galic2008, Vezzani 2008, Nabbout 2012, Libizzi 2012



Vezzani 2014

Figure 1. Pathophysiological cascade of events leading from inflammation to epilepsy. See Conclusion section for explanation.



Shimada T 2014

Figure 1: Proposed inflammatory mechanisms in epileptogenesis. (a) Epileptic seizures induce the release of cytokines from glial cells, thereby (1) increasing the influx of neuronal calcium; (2) enhancing extraneuronal glutamate concentration; (3) decreasing K^+ and glutamate uptake by glia; and (4) impairing the BBB. BBB breakdown leads to albumin entry and leucocyte invasion into the brain, resulting in a further release of inflammatory cytokines. Such inflammatory responses cause an induction of neuronal hyperexcitability, reoccurrence of seizures, and finally the development of refractory epilepsy. (b) Seizures induce COX-2 in neurons (early phase) and vascular endothelial cells (late phase) and mPGES-1 in endothelial cells. These inducible PG synthases cooperate to produce PGE_2, most likely in endothelial cells. Endothelial PGE_2 might cause neuronal hyperexcitability by enhancing glutamate release from astrocytes via the glial EP3 receptor, whereas neuronal PGs may protect neurons against seizures.

Cytokines may be activated by febrile sezures, detected in blood but usually not in CSF. Genetic polymorphism may explain variation in suscepitibility to experience febrile seizures. Also, induced inflammatory effects may start long-standing inflammatory processes leading to later epilepsy, i e temporal lobe epilepsy.

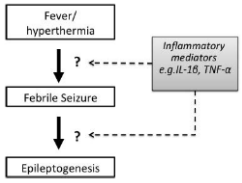


FIGURE 1. The possible role of inflammatory mediators in the progression from fever to FS to epileptogenesis. Inflammatory mediators such as IL-1 and TNF are potent pyrogens, and there is evidence for their involvement in seizure generation. In addition, they are present following FS, raising the possibility that they may influence epileptogenesis. However, the precise role of inflammatory mediators remains to be clarified.

Choy Mankin 2014

Acta Neuropathol

Table 3 Spectrum of antibody-associated epileptic encephalitides

Antibody—target	Epitopes	Clinics	Neuropathology
Intracellular	GAD65, AMP	VAR. (NPE)	CD8-positive T-cells and neuronal cell loss preferentially in hippocampus
Intranuclear	Hu, Yo, Ma2	PE	CD8-positive T-cells attacking neurons
Voltage-gated potassium channel complex (VGKC)	LGI1 Caspr2	NPE (PE)	CD8-positive T-cells attacking neurons, severe cell loss preferentially in hippocampus
Glutamate receptors	NMDA R1	NPE (PE)	Few T-cells, only mild neuronal cell loss

Most of these antibody-associated encephalitides can occur with or without an underlying neoplasm

GAD glutamic acid decarboxylase, *AMP* amphiphysin, *VAR* variable, *NPE* non-paraneoplastic encephalitis, *PE* paraneoplastic encephalitis, *LGI1* leucine-rich glia-inactivated 1, *Caspr2* contactin-associated protein-like 2, *NMDA N*-methyl-D-aspartate

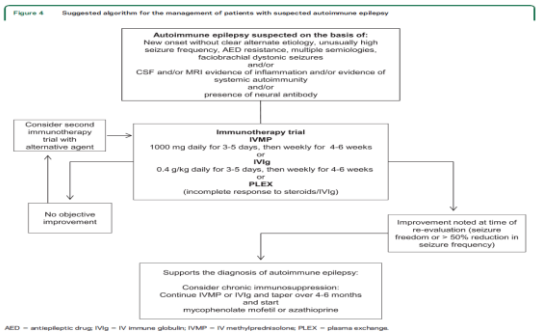
New onset epilepsy and immune-mediated disorders with seizures may be caused by specific immunopathology with antibodies against intracellular targets (GAD) or cell-surface proteins such as NMDA receptors or VGKC channels. These processes may further induce an inflammatory brain process leading to chronic 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

AED = antiepileptic drug.

Toledano 2014,Vezzani 2011, Vincent 2010



Toledano 2014

Children suggested: IVMP20-30mg/kgxIII. Prednisolone 2-3 mg/kg 4w, slowly tapered over 2-several months depending on response. Rituximab and/or cyclophosphamide in unresponsive cases.

Table III: Immunotherapy for autoimmune epilepsy in children–recommended regimen

	Treatment and suggested regimen	Comments
(a) *Acute treatment*		
First line	Pulse intravenous methyl prednisolone (30mg/kg/d for 3–5d, maximum 1g/d)[60,70,80]	This can be repeated weekly for 4–6wks[70,80] and is often followed by oral prednisolone (given over weeks to months): see maintenance treatment
	Adjunctive IVIG (2g/kg given in two doses over 2d or 0.4g/kg/d for 5d)[60,69,81]	This treatment (IVIG) can be given as a one-off, or continued monthly for 3mo or longer depending on the syndrome and response
	Plasma exchange can be used as an alternative for IVIG (five to seven exchanges of 50ml/kg on alternate days)[60,81]	Patients who are steroid resistant may instead respond to IVIG or plasma exchange
Second line	Rituximab (375mg/m^2 weekly, four doses, or other regimens)[60,71]	Reserved for severe refractory cases with partial or no response to first-line agents
	Cyclophosphamide (750mg/m^2)[69,82]	Usually given as monthly pulses for 3–6mo, or until clinical recovery is achieved. Indications as for rituximab
(b) *Maintenance therapy*		
	Oral prednisolone (1–2mg/kg/d tapering over a few weeks–months)[81]	
	Monthly IVIG (0.4–1.0g/kg for 1d)	
	Mycophenolate mofetil (600mg/m^2 orally twice daily; maximum 2g/d)[83] or azathioprine (1–3mg/kg orally once a day) (steroid sparing agents)[69]	For steroid dependence, or relapsing course in steroid-responsive patients
	Maintenance rituximab or cyclophosphamide	In severe cases with high risk of relapse

IVIG, intravenous immunoglobulin.

Suleiman 2014

Autoimmun encephalitis and seizures

In a cohort of suspected autoimmune encephalitis (n=3973), 24% had seizures and 42% of these had neuronal antibodies.

If seizures were SE, 30% had autoimmune SE.

Davis R unpubl

Inflammation: With or without infection?

Idiopathic/symptomatic HHS (Hemiconvulsion-hemiplegia syndrome)

FIRES (Fever induced refractory epileptic encephalopathy in school-aged children)

NORSE (New onset refracory status epilepticus)

AEIMSE (Acute encephalopathy with inflammation mediated status epilepticus)

Rasmussen`s syndrome

Nabbout 2011

Inflammation: With or without infection?

Fever often included, Seizures induced by fever?

Brain maturation (age) related to syndrome

Acute phase followed by chronic phase including resistant epilepsy and cognitive/behavioural decline

Age/development related to clinical presentation

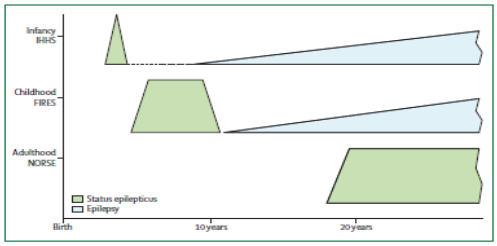


Figure 3: **Different courses of acute encephalopathy with inflammation-mediated status epilepticus according to age of onset**
IHHS=idiopathic hemiconvulsion-hemiplegia syndrome. FIRES=fever-induced refractory epileptic encephalopathy in school-aged children. NORSE=new-onset refractory status epilepticus.

Nabbout 2011

Immunotherapy and epilepsy syndromes

LKS/CSWS

IS/West

LGS

Rasmussen

Refractory SE

Landau-Kleffner

2-8 y

Verbal-auditory agnosia

Behavioural-cognitive problems

Seizures, often nocturnal, variation in type and semiology

Etiology unknown

Probably an epileptic focal abnormality affecting speech areas

CSWS, ESES, LKS

- Usually clinical seizures
- EEG shows dramatic increase of epileptic abnormalities during sleep sometimes to the degree of continous (CSWS, ESES)
- Language, cognitive, behavioural problems
- Treatment aims: Sz reduction, behavioural improvement, EEG improvement?
- Treatment success better if started within 12-18 m

Landau-Kleffner syndrome (LKS) Treatment options

- *Probable effect:*
- Valproate, Ethosuximide, sulthiame, *levetiracetam, bensodiazepines* (CLB,CLN,LZP)
- *Possible effect:*
- Topiramate, vigabatrin, felbamate, ketogenic diet
- *No effect:*
- Phenytoin,
- phenobarbital, carbamazepine

Corticosteroids and/or IVIg

LKS

IVIg very little experience, 2/11 pts long-standing positive effects (Mikati 2002,2005)

Corticosteroids tried in a number of small patient series, case reports.

No controlled studies found.

ACTH/Methylpred/Pred have been used.

Protocols often suggest Prednisolone 2-3 mg/kg/d 1-2 m, slowly tapered over several months, sometimes repeated pulses or alternate-day treatment to reduce side effects.

CSWS/ESES

Studies are retrospective, case reports, expert opinions.

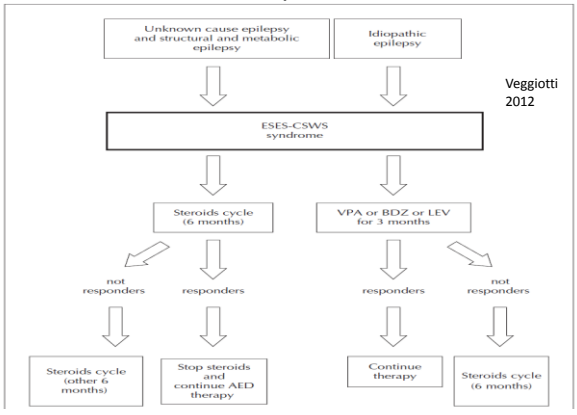
44 pts retrospectively studied given hydrocortisone 5mg/kg slowly tapered over 21 months. 34/44 positive respone 3 m, 14/34 relapsed.

High IQ, short disease duration = better outcome. (Buzatu 2009)

17 pts different protocols (ACTH,Methylpred, pred). 11/17 pos effects but relapses/side effects caused recommendation to give only short term steroids (Kramer 2008)

IVIg 9 pts, 3/9 positive effects (Kramer 2008)

CSWS/ESES



Veggiotti 2012

CSWS/ESES

Steroids or surgery most effective treatment options.

Benzodiazepins possible alternative

Other AEDs less effective.

RESCUE trial to compare Methylprednisolone/prednisolone vs clobazam

IS/West syndrome, therapy

ACTH Efficacy shown in several studies (Sorel Acta Neurol Belg 1958;58:130-41, Hrachovy J Pediatr 1983,103:641-45,and J Ped1994;124:803,Baram Pediatrics1996;97:375, Snead Neurology 1983;33:966-70,Vigevano Epilepsia1997;38:1270,Lux Lancet 2004;364:1773 and 2005 Lancet Neurol 4:712). ACTH short-time treatment, better than oral steroids, side effects no limitation (Mackay Neurology 2004;62:1668)

Insufficient data to recommend dosage and duration

Prednisone less effective as compared to ACTH. One study found no difference (Lombroso Epilepsia 1983;24:135-58 , Hrachovy J Pediatr 1983,103:641-45 Baram Pediatrics1996;97:375,Lux Lancet 2004;364:1773).

IS/West syndrome, therapy

VGB efficacious. Best results when TSC(90-100%). Probably TSC cases respond to lower doses (Aicardi Epilepsia1996;37:638 Vigevano Epilepsia1997;38:1270,Cosette Neurology 1999;52:1691, Appleton Epilepsia 1999;40:1627) Effective within14days. Duration of treatment not known, usually 3-6 months

Long term prognosis: Lack of sufficient data to recommend treatment (Mackay 2004). Slightly better for ACTH than VGB idiopathic cases(Lux Lancet 2004;364:1773and 2005 Lancet Neurol 4:712)

Lack of data to conclude early treatment to improve long-term outcome

IS/West syndrome,therapy

Pyridoxine 5/17, 3/13 and 3/3 patients respectively responded to(20-50) 100-300mg/kg/d (Pietz Epilepsia 1993;34:757-63,Ito Ped Neurol 1991;7:91-96, Blennow Neuropediatrics 1986;17:7-10). Not significantly better than placebo/spontaneous remission(Mackay2004).

VPA Not studied as initial therapy. 65%-73% sz control in one study (Siemes Epilepsia 1988;29:553,FisherEpilepsia1992:33;165) Widely used but not for initial therapy (Pavone Dev Med Child Neurol 1981;23:454).

IS/West syndrome, therapy

Nitrazepam effective(30%-54%) and Clonazepam less efficacious (Farell Epilepsia 1986;27:s45-51,ChamberlainJ Child Neurol1996;11:31)

TPM 11 cases of refractory IS given up to 24mg/kg, 5 spasm free, 9 had >50% reduction (Glauser Epielpsia 1998;39:1324-28). 3-5mg/kg/d given to 544 children, initially or additional, following 20 w. observation, 44% sz free (Zou et al 2008).

Ketogenic diet Retrospective data small number of patients, 8/13 responded first line treatment (Kossoff Epilepsia 2008) Used sometimes for idopathic cases first line, others later alternative.

Therapy	Percentage Spasm-Free
Corticosteroids	
ACTH	54%–87%
High-dose oral steroids	67%–76%
Low-dose oral steroids	29%–39%
Vigabatrin	16%–67%*
Ketogenic diet	62%
Valproate	72%–73%
Nitrazepam	30%–54%
Sulthiame	40%
Zonisamide	33%–36%
Topiramate	20%–30%
Pyridoxine	0%–29%

Kossoff 2009

- Vigabatrin is the first-choice treatment for infantile spasms caused by tuberous sclerosis.
- For other etiologies, adrenocorticotropic hormone (ACTH)/hormonal therapy seems to be more efficacious than vigabatrin in stopping spasms within 2 weeks.
- In infantile spasms of cryptogenic etiology, ACTH/hormonal treatment may be associated with better developmental outcome than vigabatrin.
- For symptomatic etiology other than tuberous sclerosis, long-term seizure prognosis and cognitive outcome seem to be similar regardless of whether treatment was started with vigabatrin or ACTH/hormonal therapy.
- All patients receiving vigabatrin should have regular visual field examinations every 3 months, as vigabatrin may cause permanent peripheral visual field constriction.
- Infants on vigabatrin may demonstrate transient hyperintensive MRI abnormalities in the central parts of the brain. Routine MRI follow-up of asymptomatic infants is not necessary.

Gaily 2012

Infantile spasms, evidence

Cochrane review: Hancock EC et al 2013

96 studies were reviewed. 18 were RCTs including 858 patients involving 12 therapies.

GENERAL CONCLUSIONS:

Hormonal therapies (prednisolone, tetracosactide, ACTH) resolves spasms faster and in more children than VGB.

Possibly hormonal therapy gives *better developmental outcome* in idiopathic cases. Generally *high doses* preferred over low doses.

Still much more studies are needed to conclude which strategies are the best, including different etiologies, adverse reactions and other characteristics.

LGS

- Prevalence:
- As much as 10% among those with seizures before 5 years, 1-4% of all children with epilepsy. Approximately 200-400 children in Sweden

Lennox-Gastaut syndrome

VPA (Covanis Epilepsia 1982;23:693-720)

BZD All types widely used as adjunctive therapy

LTG Efficacious in an enrichment study, 30 patients. (Eriksson Epilepsia;1998:39:495-501) and open add-on studies (Oller Epilepsia 1991;32:58, Timmings Eur Neurol 1992;32:305-7)

TPM Placebo-controlled, 98 patients, TPM better than placebo(Glauser Neurology 1997;48:1729) and reduced drop attacks (Glauser Epilepsia 2000;41:86-90)

FBM One study showed efficacy (The Felbamate...N Eng J Med 1993;328:29-33)

ESM Combined with VPA to decrease absences

RUF shown effective to treat drop attacks

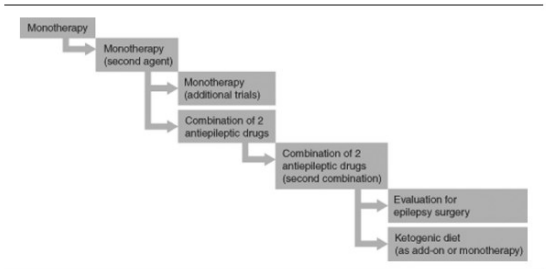


Figure 5. Overall treatment strategy for Lennox-Gastaut syndrome. Adapted from Wheless et al.[19]

LGS evidence

Cochrane report 2012 (Hancock EC, Cross HJ)

Found 9 RCTs with different therapies, different outcomes and different populations. No Immunomodulation included.

General conclusion is that we have very little evidence regarding choice of therapy.

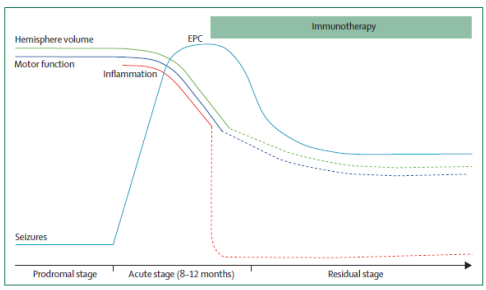


Figure 1: **Natural clinical course and expected effect of immunotherapy**
The natural clinical course of Rasmussen's encephalitis was characterised in the past century. The disease might have a preceding prodromal stage with infrequent seizures, and presents with an acute stage of drug-resistant epilepsy. The epilepsy is characterised by very frequent seizures of different semiologies in the same patient, often epilepsia partialis continua, with the emergence of a fluctuating then permanent hemiplegia (motor function) and concurrent progressive hemispheric volume loss on neuroimaging. With the advent of immunotherapy, the natural clinical course seems to be changing. The rate of motor function and hemispheric volume loss is slowed, and seizures decrease in frequency and plateau. Cognitive deterioration is not shown because it is more variable, although usually becomes manifest during the acute phase. EPC=epilepsia partialis continua.

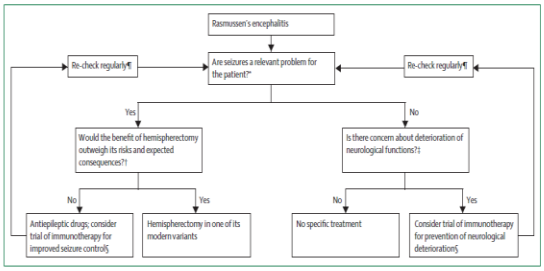


Figure 4: **Suggested therapeutic management of the patient with Rasmussen's encephalitis**
*A judgment or decision to be made by the patient, carers or parents, and the treating physician. †This is a matter of consideration, not an objective measure. ‡This will mainly apply to patients with short disease duration and preserved function of the affected hemisphere. §There is no evidence to support any special agent. ¶No formal recommendation regarding the intervals can be given, and will be affected by the needs of the patient. If the course is unsatisfactory, the patient will most probably return to the treating institution needing reassessment. Modified from Bien and Schramm,[9] by permission of Elsevier.

IVIg refractory epilepsy, evidence

Cochrane review Geng J et al 2011

8 studies were reviewed, one was a RCT. The others self controlled trials

No studies on monotherapy IVIg

One study compared three different doses of IVIg as add-on compared to placebo. 61 patiens 2-51 y different diagnoses.

No significant differences were noted.

(van Rijckevolsel 1994)

IVIg

Encouring results have been reported on LGS (Gross-Tsur 1993), West (Ariizumi 1987), therapy resistant epilepsy (i e Billiau 2007: 4/13 pts reduced sz frequency) and juvenile spasms (Bingel 2003)

Table 2 Studies reporting on IVIG treatment for LGS and/or WS.

Authors	Patient population	Outcome of IVIG treatment
Illum et al.[46]	LGS ($n=10$)	Reduction in seizures in 2 patients
Echenne et al.[47]	WS or LGS ($n=25$)	EEG response in 8 patients
Gross-Tsur et al.[48]	LGS ($n=8$)	Partial or complete remission in 6 patients
van Engelen et al.[49]	WS or LGS ($n=15$)	70% clinical and 40% EEG reduction in seizure frequency

Corticosteroids to childhood epilepsy (excluded spasms)

Cochrane review Gayatri N 2007

Only one RCT with 4 patients, 3 patients had a sz reduction 25-50%.

No patient had a reduction >50%. (Pentella 1982)

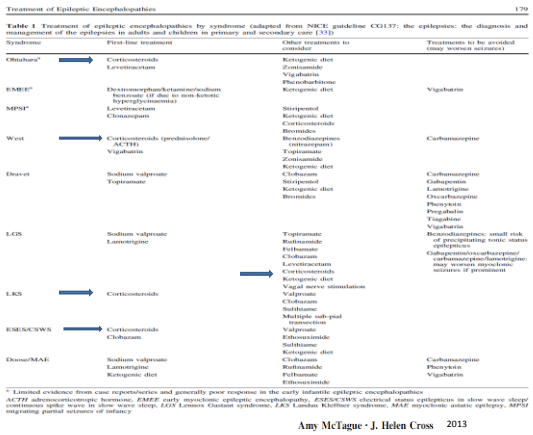
5/6 children (4-17y) with FLE responded to ACTH, remaining good results in some (Gobbi 2014)

Epileptic encephalopathies

Corticosteroid use is described for LGS, MAE and Othahara, mainly to influence on non-convulsive SE, periods of seizure escalation and cognitive decline.

I e in a study by You SJ et al 2008 retrospectively noted rewarding results of a short course, 8 w, with corticosteroids 40/51 had >50% sz reduction. >50% relapsed first 12 m. 20/32 LGS patients responded.

Verhelst et al reported (2005) retrospective results on 32 pts, 47% had a seizure reduction. Dose, duration and etiologies were different.



Treatment of Epileptic Encephalopathies 179

Table 1 Treatment of epileptic encephalopathies by syndrome (adapted from NICE guideline CG137: the epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [33])

Syndrome	First-line treatment	Other treatments to consider	Treatments to be avoided (may worsen seizures)
Ohtahara*	Corticosteroids Levetiracetam	Ketogenic diet Zonisamide Vigabatrin Phenobarbitone	
EMEE*	Dextromorphan/ketamine/sodium benzoate (if due to non-ketotic hyperglycinaemia)	Ketogenic diet	Vigabatrin
MPSI*	Levetiracetam Clonazepam	Stiripentol Ketogenic diet Corticosteroids Bromides	
West	Corticosteroids (prednisolone/ACTH) Vigabatrin	Benzodiazepines (nitrazepam) Topiramate Zonisamide Ketogenic diet	Carbamazepine
Dravet	Sodium valproate Topiramate	Clobazam Stiripentol Ketogenic diet Bromides	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
LGS	Sodium valproate Lamotrigine	Topiramate Rufinamide Felbamate Clobazam Levetiracetam Corticosteroids Ketogenic diet Vagal nerve stimulation	Benzodiazepines: small risk of precipitating tonic status epilepticus Gabapentin/oxcarbazepine/tiagabine/vigabatrin/lamotrigine: may worsen myoclonic seizures if prominent
LKS	Corticosteroids	Valproate Clobazam Sulthiame Multiple sub-pial transection	
ESES/CSWS	Corticosteroids Clobazam	Valproate Ethosuximide Sulthiame Ketogenic diet	
Doose/MAE	Sodium valproate Lamotrigine Ketogenic diet	Clobazam Rufinamide Felbamate Ethosuximide	Carbamazepine Phenytoin Vigabatrin

* Limited evidence from case reports/series and generally poor response in the early infantile epileptic encephalopathies

ACTH adrenocorticotropic hormone, *EMEE* early myoclonic epileptic encephalopathy, *ESES/CSWS* electrical status epilepticus in slow wave sleep/continuous spike wave in slow wave sleep, *LGS* Lennox Gastaut syndrome, *LKS* Landau Kleffner syndrome, *MAE* myoclonic astatic epilepsy, *MPSI* migrating partial seizures of infancy

Amy McTague · J. Helen Cross 2013

Further studies

Adequately powered multicenter randomised controlled studies

Use relevant clinical efficacy measures, considering differences between various syndromes and indications for immunotherapy.

Include QoL measures and cognitive effects.

Studies should be of sufficient duration to evaluate adverse events, long-term effects etc

Conclusions

Immunomodulation is used to treat a variety of pediatric epilepsy syndromes and seizures.

It is well established in cases with autoimmune origin and in some selected syndromes (i e West, LKS)

It is often used as add-on with little or no evidence regarding effectiveness, dosing, duration etc.

There is an increasing need for controlled trials to establish its place in treatment of childhood epilepsy

Evidence and Experience

Evidence for West syndrome.

Other syndromes: weak evidence.

Experience is widespread and the use of immunomodulation is part of treatment possibilities in selected cases without effect of other treament options.

If antibody mediated disease with epileptic seizures, immunomodulation is warranted.

Tack för uppmärksamheten