Epilepsy & CNS Inflammation in Children

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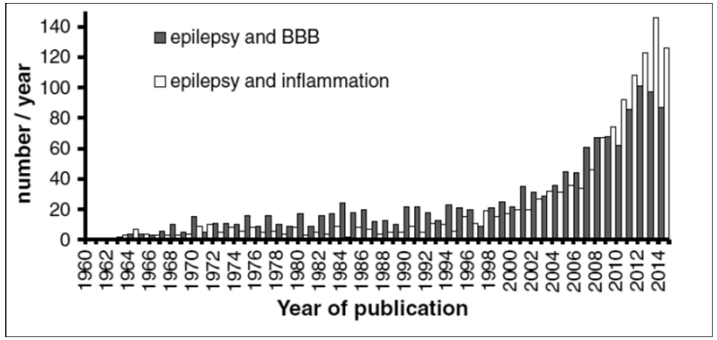
Epilepsy & CNS Inflammation

- Inflammation **<==>** Seizure & Epilepsy
- CNS infection; viral encephalitis
- Epilepsy with CNS inflammation/Autoimmune encephalitis
  - Rasmussen encephalitis
  - Anti-NMDA encephalitis (children)
  - Limbic encephalitis (Anti-VGKC)
  - Anti-GAD encephalopathy
  - Febrile-Infection Related Epilepsy Syndrome (FIRES)

Pubmed search for the number of yearly publications related to "epilepsy and blood–brain barrier" and "epilepsy and inflammation"



Gorter J. Epilepsy & Behavior 2015; 49:13–16

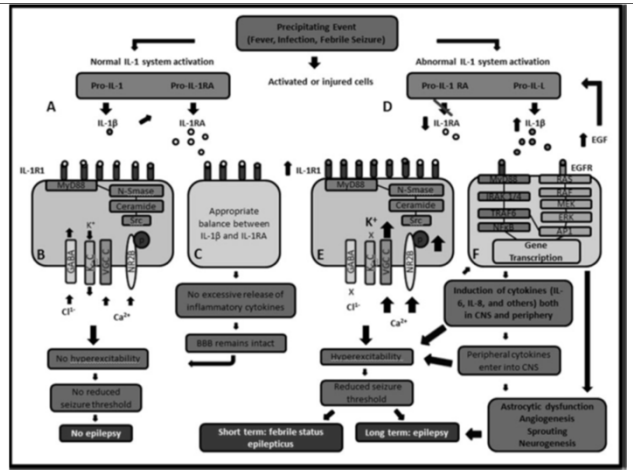
Brain Inflammation in Structural Focal Epilepsy and Status Epilepticus

- Inflammation in focal epilepsy documented in surgical samples (FCD, TSC, HS) from patients with refractory epilepsy
- Microglial activation and increased IL-1ß (proconvulsant)
- *Toll-like receptor 2/4, Receptors for advanced glycation end products (RAGE), High-mobility group box (HMGB)*
- Inflammation activation after prolonged seizures in the immature brain (IL-1ß, IL-6, IL-8, TNFα, IL1-RA*)

*IL1-RA= Interleukin-1 receptor antagonist

Dupuis N. CNS Neuroscience & Therapeutics 2015; 21: 141–151
Gallentine WB et al. (FEBSTAT) Epilepsia. 2017;58(6):1102-1111

Plasma Cytokines Associated with Febrile Status Epilepticus in Children: A Potential Biomarker for Acute Hippocampal Injury



Gallentine WB, et al. Epilepsia. 2017;58(6):1102-1111

Spectrum of Antibody-associated Epileptic Encephalitis

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

Vezzani A. Acta Neuropathol 2016;131:211–34

Epilepsia, 54(6):1036–1045, 2013
doi: 10.1111/epi.12142

FULL-LENGTH ORIGINAL RESEARCH

Autoimmune epilepsy in children: Case series and proposed guidelines for identification

*Jehan Suleiman, *Fabienne Brilot, †Bethan Lang, †Angela Vincent, and *Russell C. Dale

Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Epilepsia. 2013; 54(6):1036–1045

Criteria and Supportive Features to Suspect Autoimmune Epilepsy in Children with Seizures

- The following two clinical criteria are used to suspect autoimmune epilepsy associated with NSAbs and GAD antibodies (both are needed)
  1. Acute or subacute (<12 weeks) onset of symptoms.
  2. Exclusion of other causes (CNS infection, trauma, toxic, tumor, metabolic, previous CNS disease).
- The following supportive features would strengthen the suspicion of autoimmune epilepsy (patients should have at least 1 of the following):
  1. The presence of a well-defined clinical syndrome such as NMDAR or limbic encephalitis

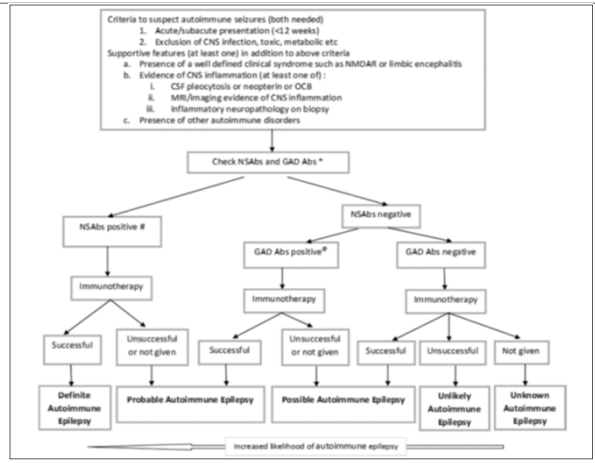
Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Epilepsia. 2013; 54(6):1036–1045

Criteria and Supportive Features to Suspect Autoimmune Epilepsy in Children with Seizures

- The following supportive features would strengthen the suspicion of autoimmune epilepsy (patients should have at least 1 of the following):
  2. CNS inflammation manifested by at least one of:
     - a. CSF pleocytosis (defined as >5 white cells/mm^3) or presence of oligoclonal bands, elevated IgG index, or elevated neopterin
     - b. MRI abnormality compatible with an inflammatory or autoimmune encephalitis including increased signal in the mesial temporal lobe
     - c. Inflammatory neuropathology on biopsy
  3. History of other antibody mediated condition (e.g., myasthenia gravis), organ specific autoimmunity or other autoimmune disorders
  4. Response to immunotherapy

Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Epilepsia. 2013; 54(6):1036–1045

Flow Chart for Approach to Children with Seizures of Suspected Autoimmune Etiology

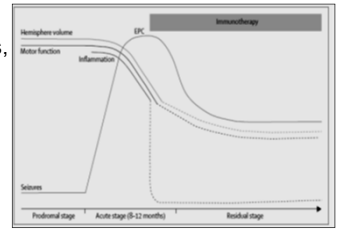


Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Epilepsia. 2013; 54(6):1036–1045

Epilepsy with CNS Inflammation & Autoimmune Encephalitis

Rasmussen's Encephalitis

- A rare progressive disease with drug resistant focal epilepsy (epilepsia partialis continua; EPC) followed by progressive hemiplegia and cognitive decline.
- 3 stages
  - Prodomal – low frequency seizures, mild hemiparesis
  - Acute – EPC & progressive hemiplegia
  - Residual – permanent deficits & continuing seizures



Cross H. Lancet Neurol 2014; 13: 195–205

Diagnostic Criteria

Part A (all three)

1 Clinical: Focal seizures (with or without EPC) and unilateral cortical deficits

2 EEG: Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset

3 MRI: Unihemispheric focal cortical atrophy and at least one of the following:

- Grey or white matter T2/FLAIR hyperintense signal
- Hyperintense signal or atrophy of the ipsilateral caudate head

Part B (two of three)

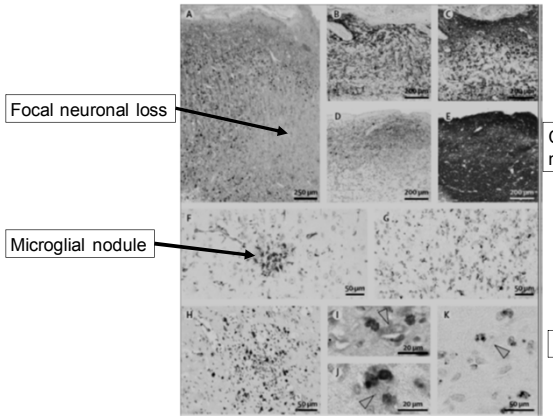
1 Clinical: Epilepsia partialis continua or progressive unilateral cortical deficits

2 MRI: Progressive unihemispheric focal cortical atrophy

3 Histopathology: T-cell-dominated encephalitis with activated microglial cells typically, but not necessarily, forming nodules and reactive astrogliosis

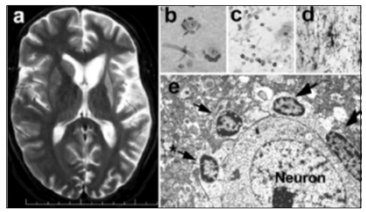
Cross H. Lancet Neurol 2014; 13: 195–205

Histopathology of Neurodegeneration and Inflammation in Rasmussen's Encephalitis



Cross H. Lancet Neurol 2014; 13: 195–205

Pathogenesis



- Unknown
- Autoantibodies- few cases
  - GluR3
  - alpha-7 nicotinic acetylcholine receptor
  - Munc-18-1, a neuronal protein essential for synaptic vesicle release
- Functionally-related genes coding interferon-γ
  - CCL5, CCL22, CCL23, CXCL9, CXCL10, and Fas ligand

Cross H. Lancet Neurol 2014; 13: 195–205
Pardo CA. Neurotherapeutics 2014; 11: 297–310

Management

- Anti-seizure medication
  - Resistant to AEDs
  - Aim: Prevent bilateral convulsive seizures
  - Botulinum toxin (facial myoclonia, painful spasms of arms)
  - VNS, TMS
- Immunotherapy (case reports or small series)
  - Pulse steroids, IVIg, plasmapheresis, tacrolimus, azathioprine
  - Pulse steroids + tacrolimus **=** IVIg **>>** Control*

    (preserved functional & structural, not seizure control)

Cross H. Lancet Neurol 2014; 13: 195–205
*Bien CG. Epilepsia 2013; 54: 543–50**

Management

- Immunotherapy (cont.)
  - Natalizumab* : block T-cells entry into CNS, stop both seizures and functional decline (single case)
- Surgery** (only mean to cure for seizures)
  - Complete disconnection of affected hemisphere (functional hemispherectomy/hemispherotomy)
  - **Timing** (protect non-affected hemisphere)
    - Short seizure duration associated with better outcome
    - Severe intractable epilepsy
    - Presence of functional decline
    - Contralateral epileptiform discharges (α poor outcome)

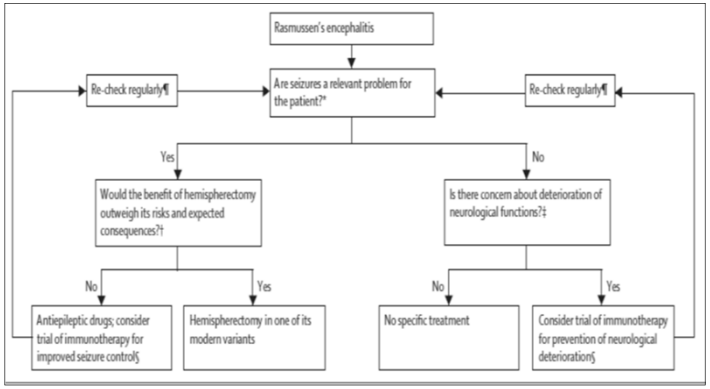
*Bittner F. Neurology 2013; 81: 395–97**
*Cross H. Lancet Neurol 2014; 13: 195–205***

Management

- Surgery; consequences
  - Hemiparesis, hemianopia
  - Language transfer (age <5-6 years)
    - Preserved receptive function
    - 2-3 words expression
    - Rare for complete aphasic
    - fMRI for presurgical decision making

Cross H. Lancet Neurol 2014; 13: 195–205

Therapeutic Management of the Patient with Rasmussen's Encephalitis



Cross H. Lancet Neurol 2014; 13: 195–205

Anti-NMDAR Encephalitis Ramathibodi Experience*

Lunliya Thampratankul, MD*
Chaiyos Khongkhatithum, MD
Metha Apiwattanakul. MD**
Anannit Visudtibhan, MD

**Oral Presentation @ The 14th AOCCNA meeting, Fukuoka Japan*

***Prasart Neurological Institute*

Anti-NMDA Receptor Encephalitis

- “Dyskinetic encephalitis lethargica”
- Firstly described in 2007 by *Josep Dalmau*
- The most common and well-known auto-antibody mediated CNS disorder
- Neuropsychiatric symptoms, behavioral changes, sleep disturbance, mutism, abnormal movements, seizures, dysautonomia and severe encephalopathy
- 4 phases: prodromal, psychotic and/or seizure, unresponsive and hyperkinetic

Demographic Data

	N	%, (range)
No. of patients	16	
Female	13	81%
Age (months)	113	(30 -181)
Duration of symptoms (days)	14	(1-180)
Missed Dx as psychiatric dis	4	25 %

Clinical Presenatation

Clinical features	N	%
Altered mental status	13	81
Abnormal movement	11	69
Insomnia	11	69
Seizure	11	69
Status epilepticus	2	13
Fever	7	44
Hallucination	7	44
Labile/depressed mood	5	31

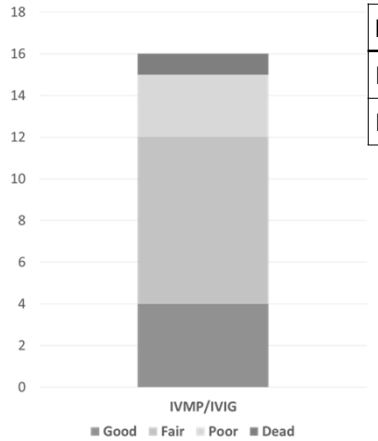
Clinical Course

Clinical features	N or median	% (range)
Neurogenic bladder	6	38
Hypertension	2	13
Hypoventilation	2	13
ICU admission	7	44
Duration of hospitalization (days)	28.5	(7-105)

Investigations

Investigations	N or median	%
CSF anti-NMDAR-Ab (+)	16	100
Serum anti-NMDAR-Ab (+)	12	75
Positive serum ANA	3	19
Ovarian teratoma	1	6
PCR for HSV 1	1	6
CSF WBC (cells/mm^3)(median, range)	9	0-195
CSF protein (mg/dL) (median, range)	28	20-62

Primary Immunotherapy Clinical Outcome



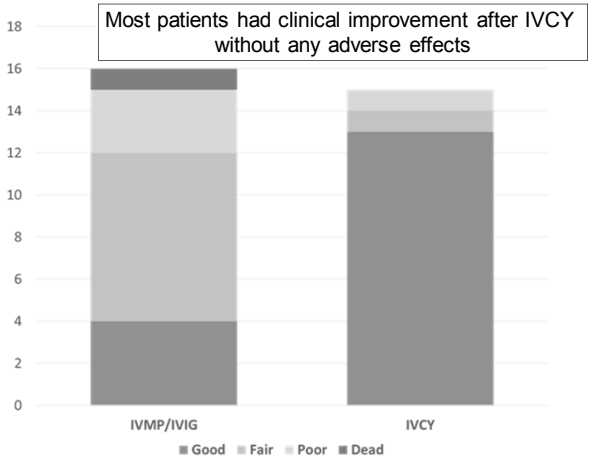
Immunotherapy	N	%
IVMP only	7	44
IVMP + IVIG	9	56

One girl with mature ovarian teratoma died from respiratory failure and severe autonomic dysfunction after tumor removal.

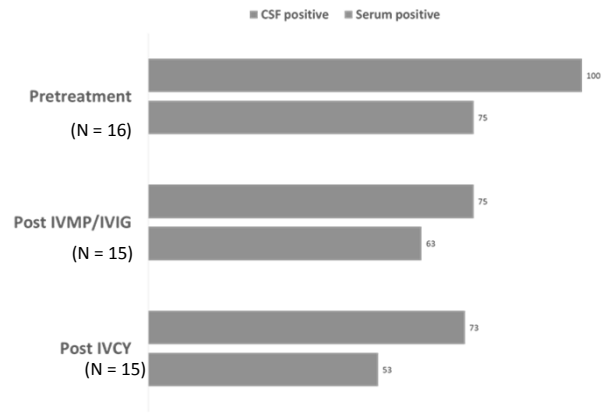
IVMP: IV methylprednisolone 30 mg/kg/day 3-5 days
IVIG: Intravenous immunoglobulin 400 mg/kg 5 days

Secondary Immunotherapy Clinical Outcome

Most patients had clinical improvement after IVCY without any adverse effects



Antibody in CSF and Serum Pre- and Post-Rx



Outcome at Final Evaluation

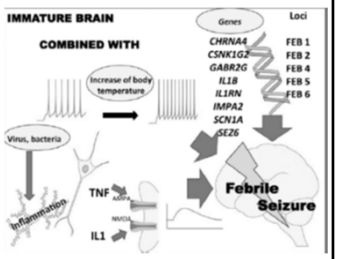
Outcome	N	%
Follow up duration (mo)	**34**	**(10-73)**
Responder	**14**	**87**
Non-responder	**1**	**6**
Relapse	**4**	**27**
Favorable outcome **mRS =0** **mRS =1** **mRS =2**	 **6** **7** **1**	 **37** **44** **6**
Mortality	**2**	**13**

Conclusion

- Treatment of anti-NMDAR encephalitis with high dose methylprednisolone and/or IVIG followed by cyclophosphamide resulted in a favorable outcome.
- Relapse mostly occur in the first 6 months after complete treatment, but could occur late up to 3 years

Acute Encephalopathy with Inflammation-Mediated Status Epilepticus

- Hemiconvulsion–hemiplegia syndrome (HHS)
- Febrile-Infection Related Epilepsy Syndrome or Fever-induced refractory epileptic encephalopathy (FIRES)
  - Previously normal school-age child
  - Severe seizures evolving into status epilepticus and are triggered by fever but without an identifiable cause



Dupuis N. CNS Neuroscience & Therapeutics. 2015; 21: 141–151

Febrile-Infection Related Epilepsy Syndrome (FIRES)

- Prevalence <1:100,000, age of onset: 2–17 (median 8) yrs, previously healthy
- Preceded by different types of febrile infections often flu-like
- Explosive onset of multifocal or generalized seizures of different types directly evolving into super-refractory status epilepticus
- EEG: global slowing or multifocal discharges with bilateral fronto-temporal predominance, or both
- CSF: normal or pleocytosis, normal protein concentration, no oligoclonal bands

Van Baalen A. Neuropediatrics. 2017 ;48(1):5-18

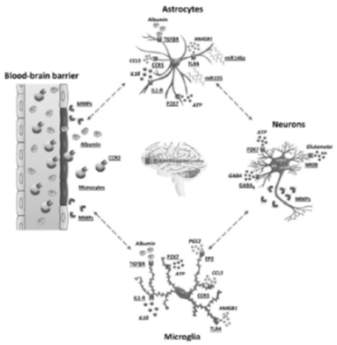
Febrile-Infection Related Epilepsy Syndrome (FIRES)

- Cranial MRI (during the acute phase):
  - None or nonextensive bitemporal or diffuse abnormalities
  - Sporadic involvement of the basal ganglia, diffuse cortical edema, and/or hydrocephalus
- Extensive etiologic investigations- NEGATIVE (rare coexisting TPO or GluR antibodies)
- Very refractory to AEDs even anesthetics
  - Ketogenic diet, high dose phenobarbital/midazolam, canabidiol
  - ??Pulse steroid, IVIg, plasma exchange, *tacrolimus, rituximab, ECT*
- Outcome:
  - Chronic epilepsy without silent period
  - Global brain atrophy after a few weeks with mild-to-severe neuropsychologic impairments

Van Baalen A. Neuropediatrics. 2017 ;48(1):5-18

Inflammation & Epilepsy

- Inflammatory molecules identified in experimental models of epilepsy and surgically resected brain tissue from treatment-resistant epilepsy
- Targeting these pathways results in anti-ictogenesis, antiepileptogenesis, and/or disease- modifying effects
- Therapeutic approaches against inflammatory mechanisms could represent new treatment in epilepsy



Thank you for Your Attention & Questions