Autoimmune & Inflammatory Epilepsies

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Disclosures

Treatments discussed in this lecture represent off-label uses.

No other conflicts of interest to disclose.

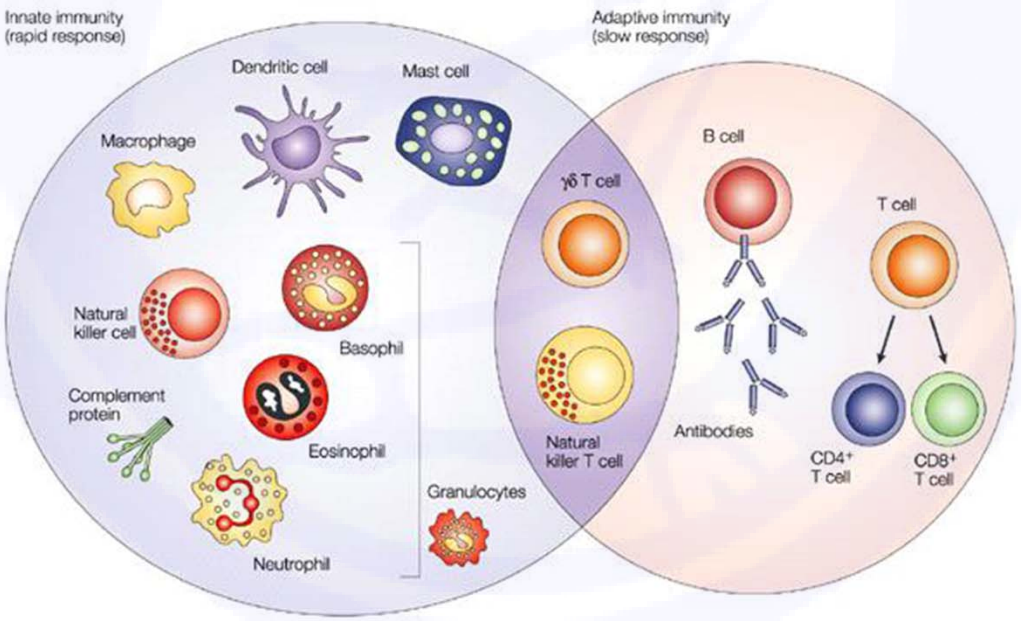
Learning Objectives

- Review the role of inflammation and autoimmunity in epilepsy
- Understand the clinical presentation, diagnostics, and treatment options in patients with Rasmussen encephalitis
- Understand the clinical presentation and potential biomarkers of febrile infection-related epilepsy syndrome (FIRES) and consider the role of novel immunotherapies targeting the innate immune system

Immunology 101

- Innate immune system
  - Acute reaction with cytokine signaling
- Adaptive immune system
  - Selective reaction to specific antigens by T and B cells

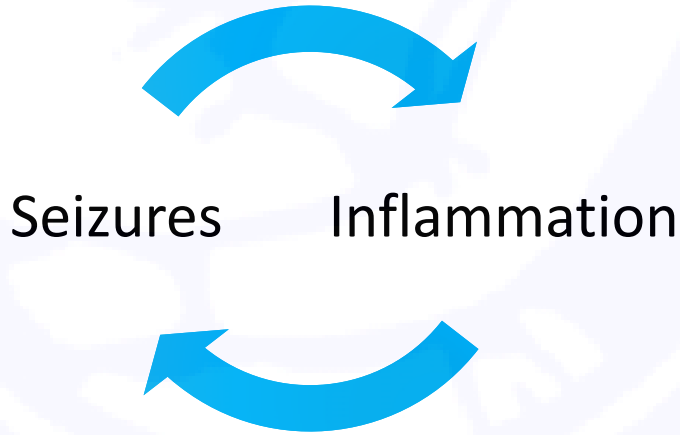
IL-1β
IL-6
TNF



Dranoff Nat Rev Cancer 2004

Inflammation in Epilepsy

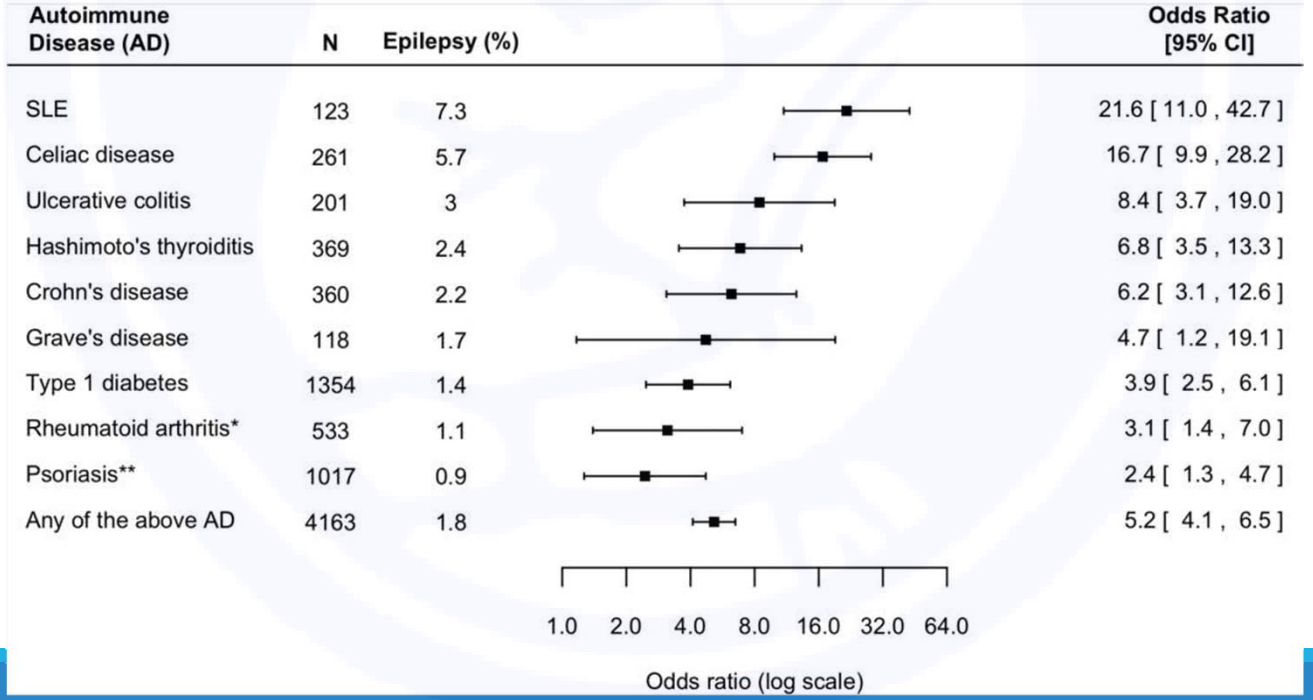
- Inflammation may be a cause or consequence of seizures
  - Autoimmune/inflammatory epilepsies
  - "Non-inflammatory" epilepsies
    - Inflammation in resected hippocampi of TLE, tubers, and FCDs



Vezzani et al Nat Rev Neurol 2011

Epilepsy & Autoimmunity

- In a large population-based study of ~2.5 million patients, there was an increased risk of epilepsy (OR 5.2, 95% CI 4.1-6.5) in children with a co-morbid autoimmune disease.
  - Specific autoimmune diseases carried a very high risk, such as SLE (OR 21.6, 95% CI 11.0-42.7)



Ong et al JAMA 2014

Rasmussen Encephalitis: Epidemiology & Etiology

- ***Clinical Symptoms***: Progressive hemiplegia, cognitive/language decline and focal epilepsy
- ***Epidemiology***: Estimated incidence of 1.7-2.4/10 million of children/adolescents
- ***Etiology***: T-cell cytotoxicity (with specificity to a yet to be defined antigen) and innate immunity (e.g. TNF and IFN-gamma) that activates microglial-induced degeneration; association with certain HLA alleles
- ***Pathology***: Cortical inflammation (microglial and lymphocytic nodules and perivascular cuffing), neuronal loss, and gliosis

Bien et al Epilepsia 2013
Varadkar et al Lancet Neurol 2015
Lamb et al Dev Med Child Neurol 2013
Dandekar et al Front in Immuno 2016

Bien Diagnostic Criteria

Part A	*Need 3/3*
1. Clinical	Focal seizures (+/- EPC) and unilateral cortical deficit(s)
2. EEG	Unihemispheric slowing +/- 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

Bien et al Brain 2005

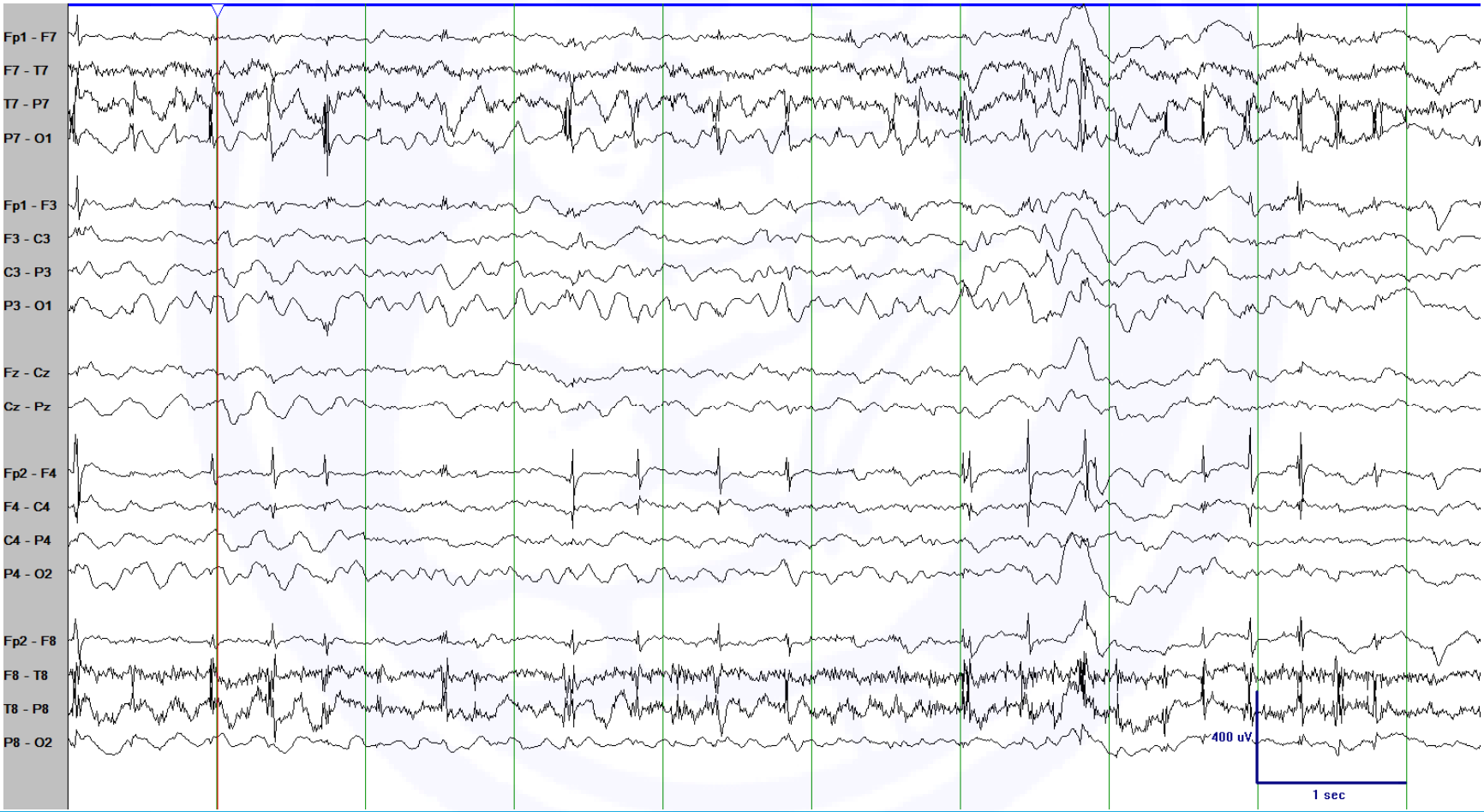
Bien Diagnostic Criteria

Part B	*Need 2/3*
1. Clinical	Epilepsia partialis continua or Progressive* unilateral cortical deficit(s)
2. MRI	Progressive* unihemispheric focal cortical atrophy
3. Histopathology	T cell dominated encephalitis with activated microglial cells (typically, but no necessarily forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages, B cells or plasma cells or viral inclusion bodies exclude the diagnosis of RE.

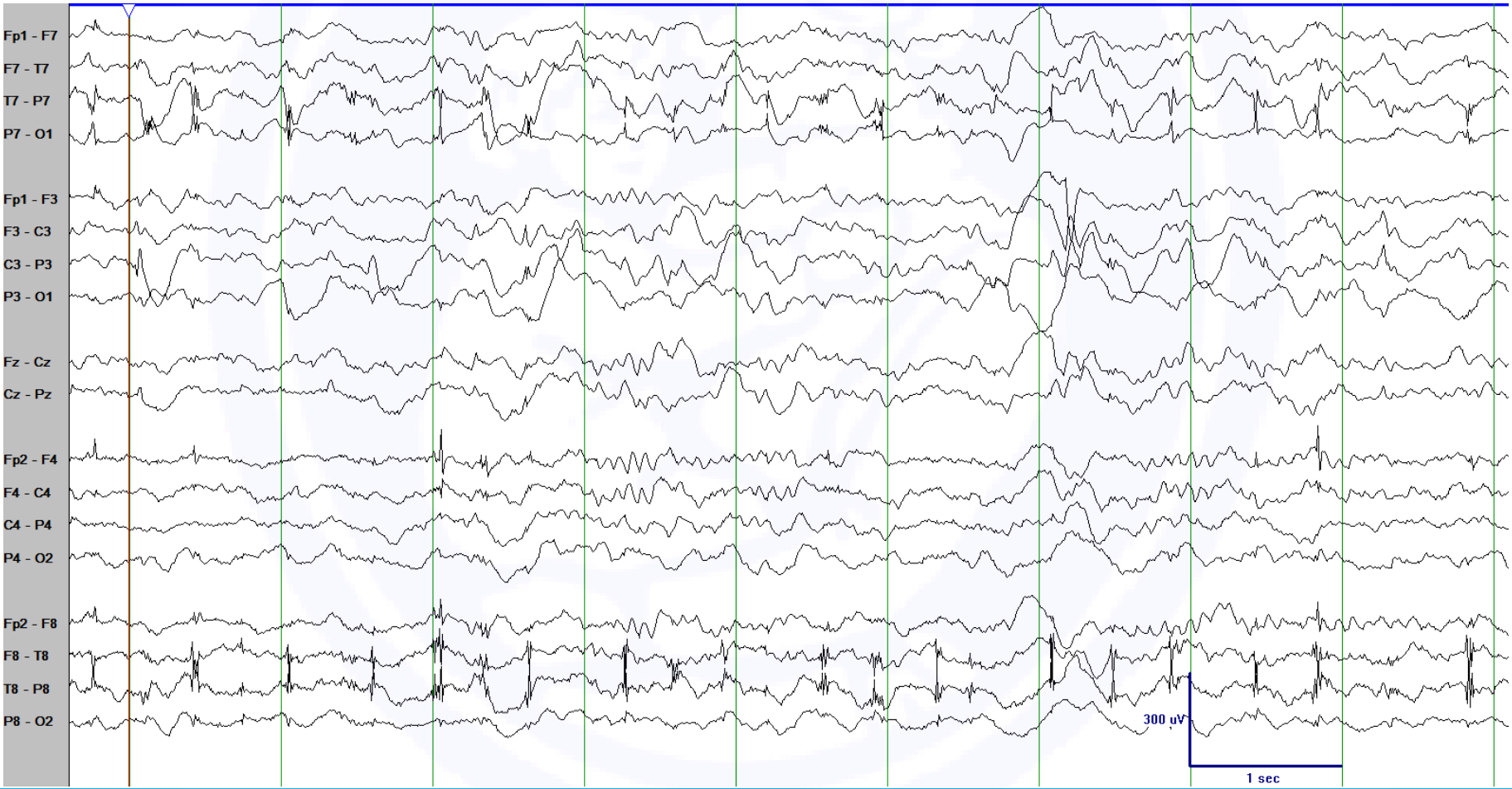
* At least 2 sequential clinical exams or MRI

Bien et al Brain 2005

Awake Sample



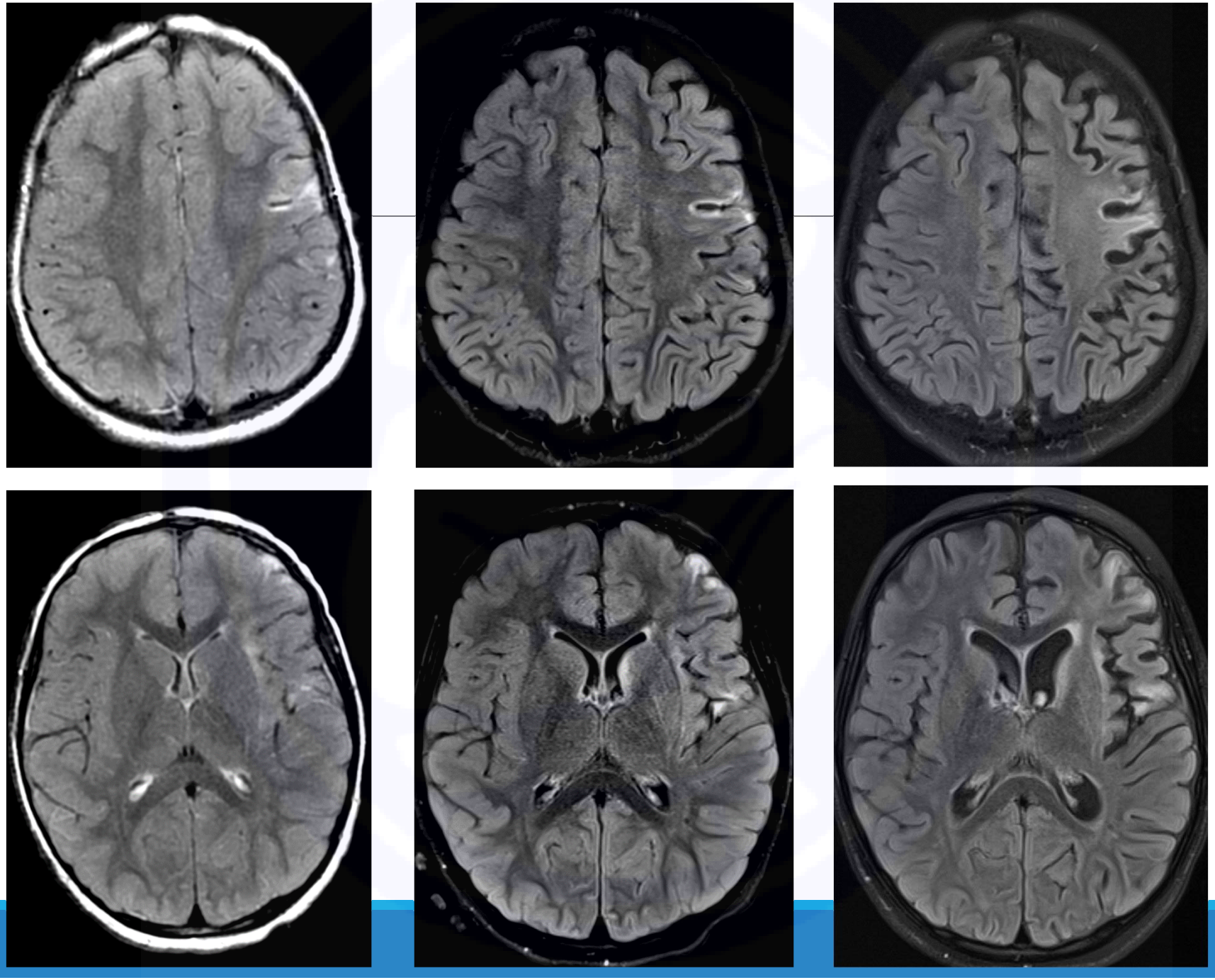
Sleep Sample



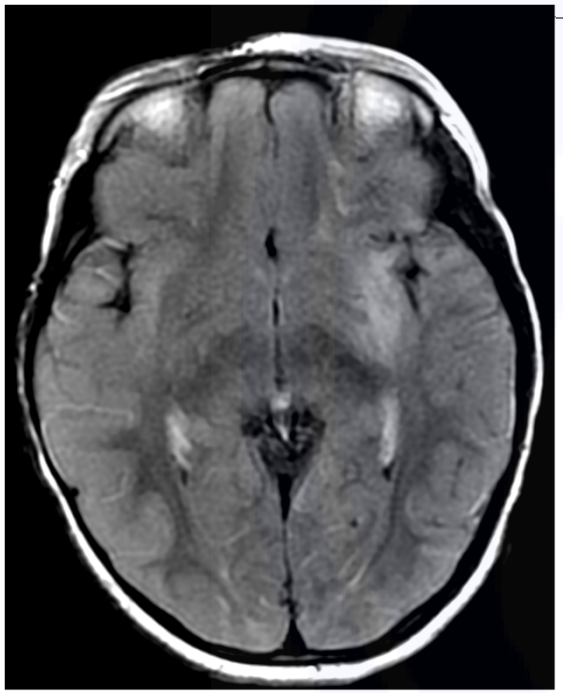
Onset

3 mo

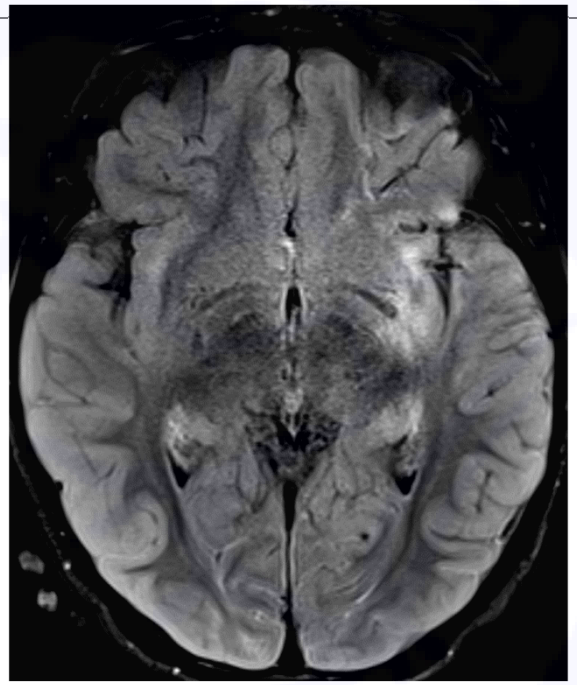
6 mo



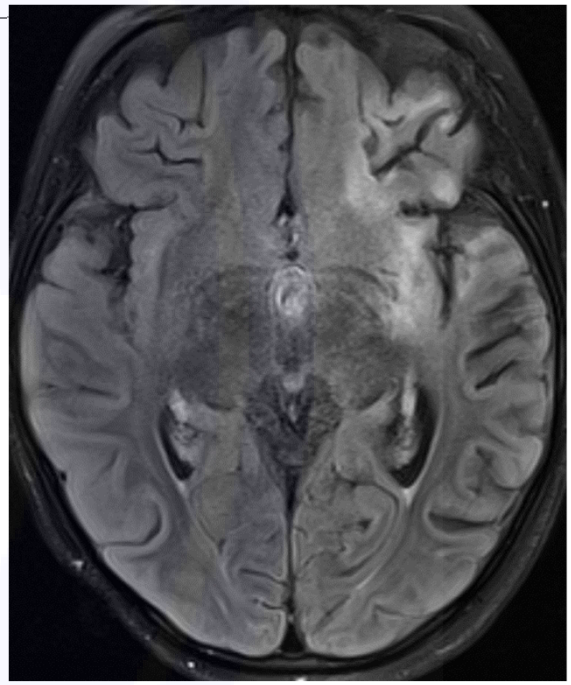
Onset



3 mo



6 mo

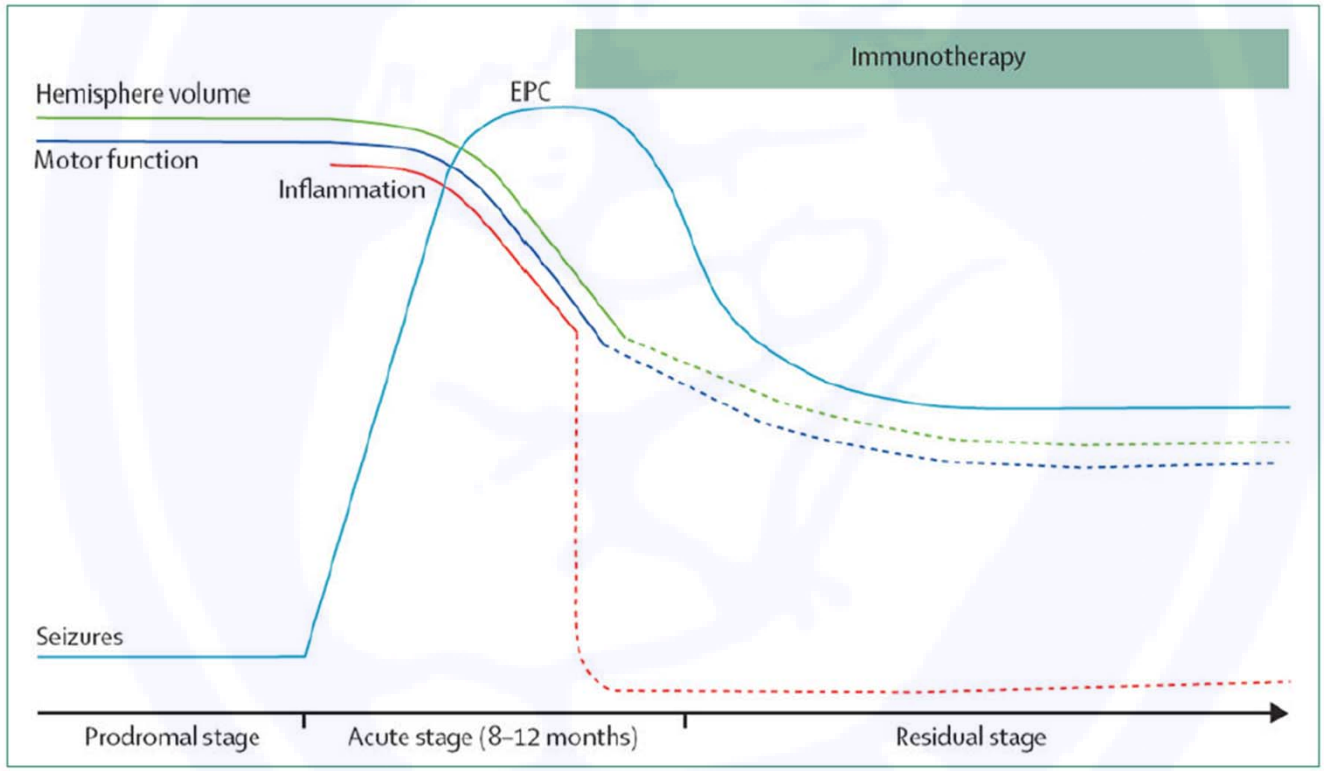


Stages of Disease

- Median age of onset = 6 years
- Stages of Disease:
  - **Prodromal** (up to years): Mild hemiparesis and infrequent focal seizures
  - **Acute**: (8-12 months): Frequent seizures (EPC in 50%, evolving focal seizure semiologies), progressive hemiplegia and cognitive/language decline
  - **Residual**: Severe, fixed deficits with ongoing seizures
- Atypical disease:
  - Late onset: adolescence or early adult (“slow burners”)
  - Delayed seizure onset (up to 2 years)
  - Very rare bilateral disease

Varadkar et al Lancet Neurol 2015

Natural History



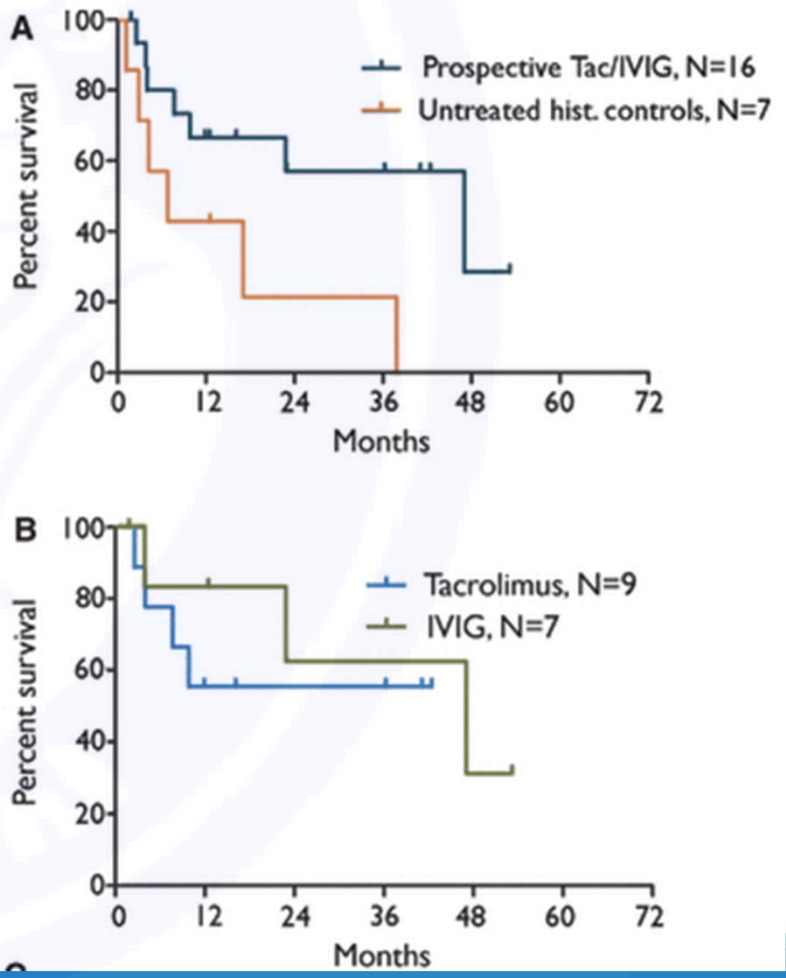
Varadkar et al Lancet Neurol 2015

Immunotherapy

- ***IVIG*** to slow cortical atrophy/motor weakness
- ***Adalimumab*** for seizure control

IVIG

- German RCT compared IVIg and tacrolimus in 16 recent-onset (<12 mo in acute phase) RE patients meeting 2/3 Part B Criteria
  - Both equally efficacious at slowing volume loss/weakness compared to historical controls
  - Tacrolimus was associated with more side effects (2 patients experienced serious AE)
- Interestingly, in patients with refractory epilepsy at immunotherapy initiation (n=9), none became treatment responsive. However, in patients without refractory epilepsy at onset (n=7), only one became treatment refractory (dropped out after IVIg x1).

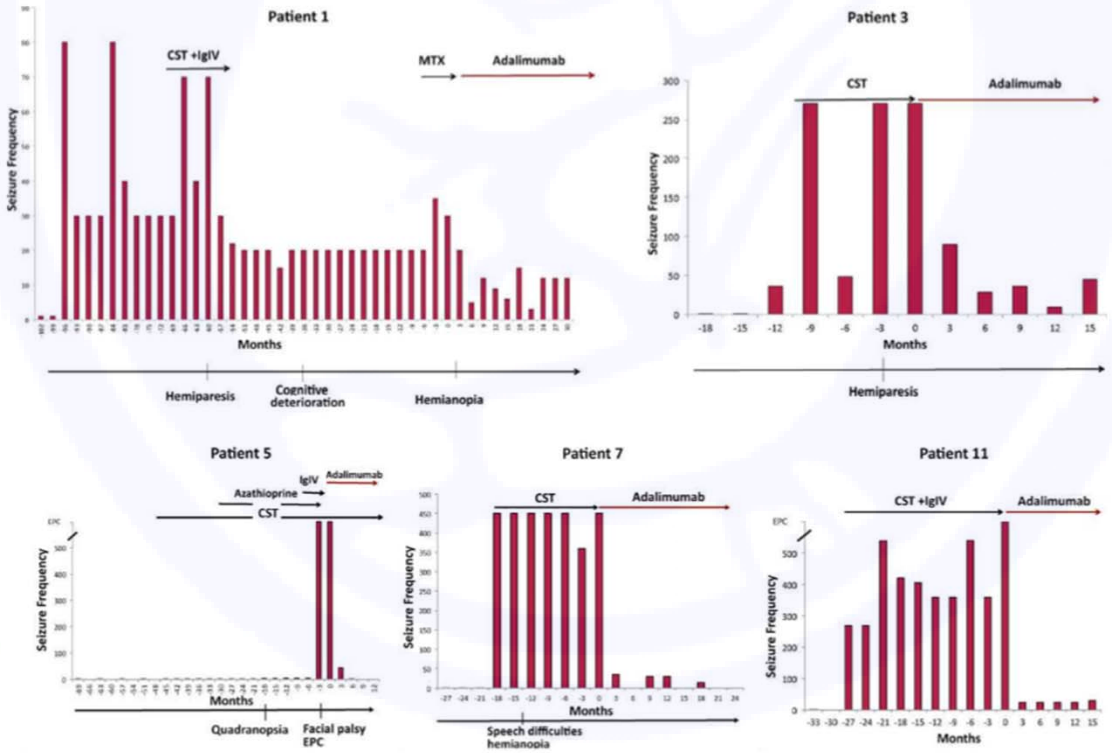


Bien et al Epilepsia 2013

Adalimumab

Open label study of adalimumab in 11 RE patients

- 5/11 patients responded (sustained decrease in seizures by ≥50% baseline)
- 3/5 responders also experienced no subsequent neurocognitive decline
- Responders were “slow burners”



Legarde et al Epilepsia 2016

Take home: RE Immunotherapy

Immunotherapy may slow the progression of MRI atrophy/weaknes but tends to have minimal effect on seizure control. Thus, patients with more preserved functioning but ongoing seizures may be harder to send for hemispherectomy – a ***Pyrrhic victory****.*

Varadkar et al Lancet Neurol 2015

Hemispherectomy

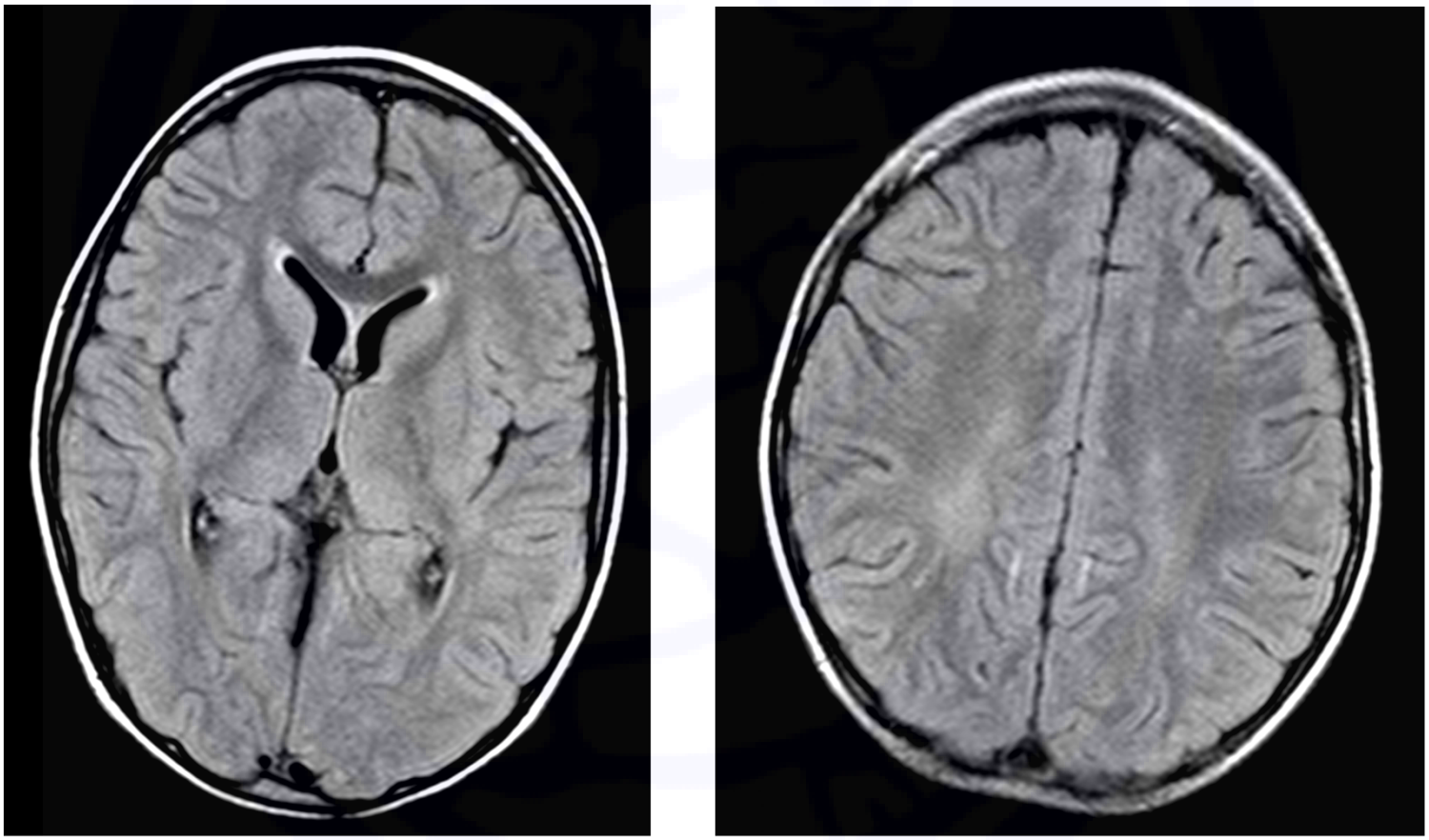
- ***Seizure freedom***: >70-80%
- ***Functional deficit***: Typically able to ambulate, homonymous hemianopia, contralateral "helper hand"
- ***Cognition and language***:
  - Pre-surgically, patients with L hemispheric RE were more affected in terms of IQ, receptive and expressive language
  - Pre-/post-surgery evaluations were similar aside from ***expressive language decline*** in patients with L and R hemispheric RE

Pulsifer et al Epilepsia 2004

Case

- 6-year-old previously healthy boy presented with headache, sore throat, and fever 1 week prior to seizure onset.
- On the day of presentation, he had 2 seizures described as full body stiffening with left gaze deviation s/p IV lorazepam and levetiracetam.
  - He was intubated at an outside hospital and admitted to the ICU.
- CSF on admission with 1 WBC, 230 RBC, protein 32, glucose 98.
- Initial MRI with non-specific scattered T2/FLAIR hyperintensities in frontal/parietal lobes.

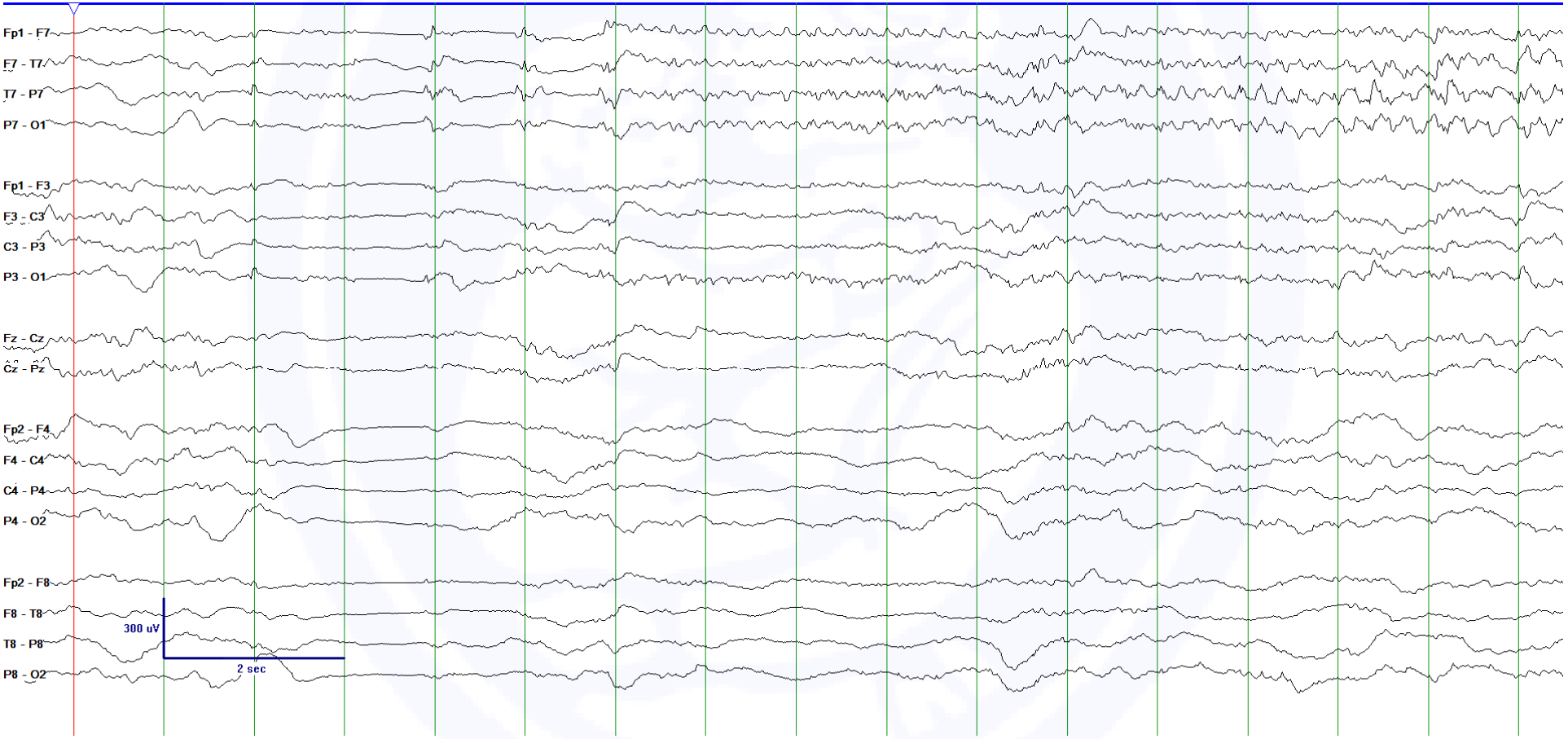
Initial MRI



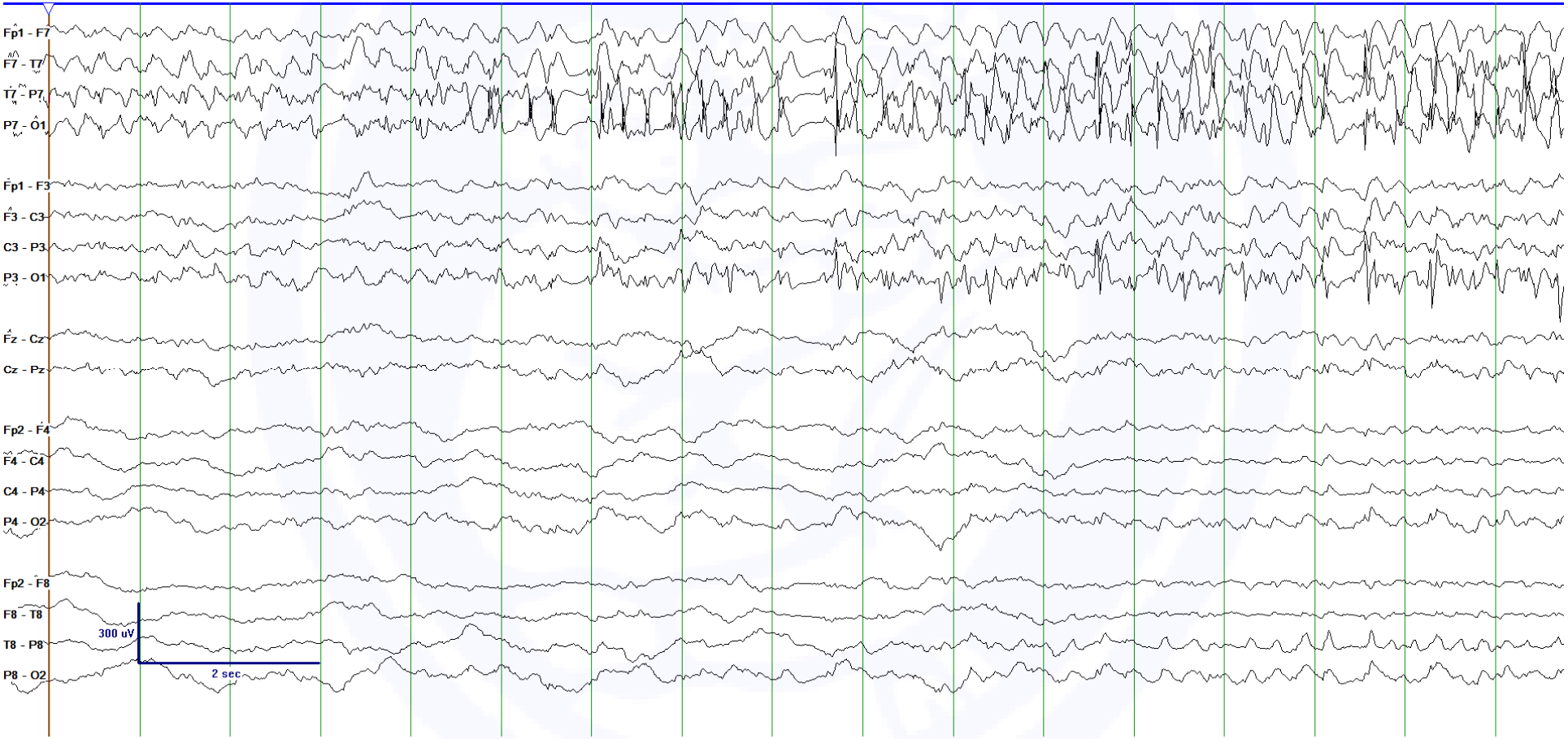
Subsequent Course

- The following day, EEG revealed electrographic seizures with left temporo-occipital and parasagittal onset, occasionally associated with right gaze deviation.
- He received IV levetiracetam, fosphenytoin, phenobarbital, and was started on a midazolam infusion for ongoing seizures.

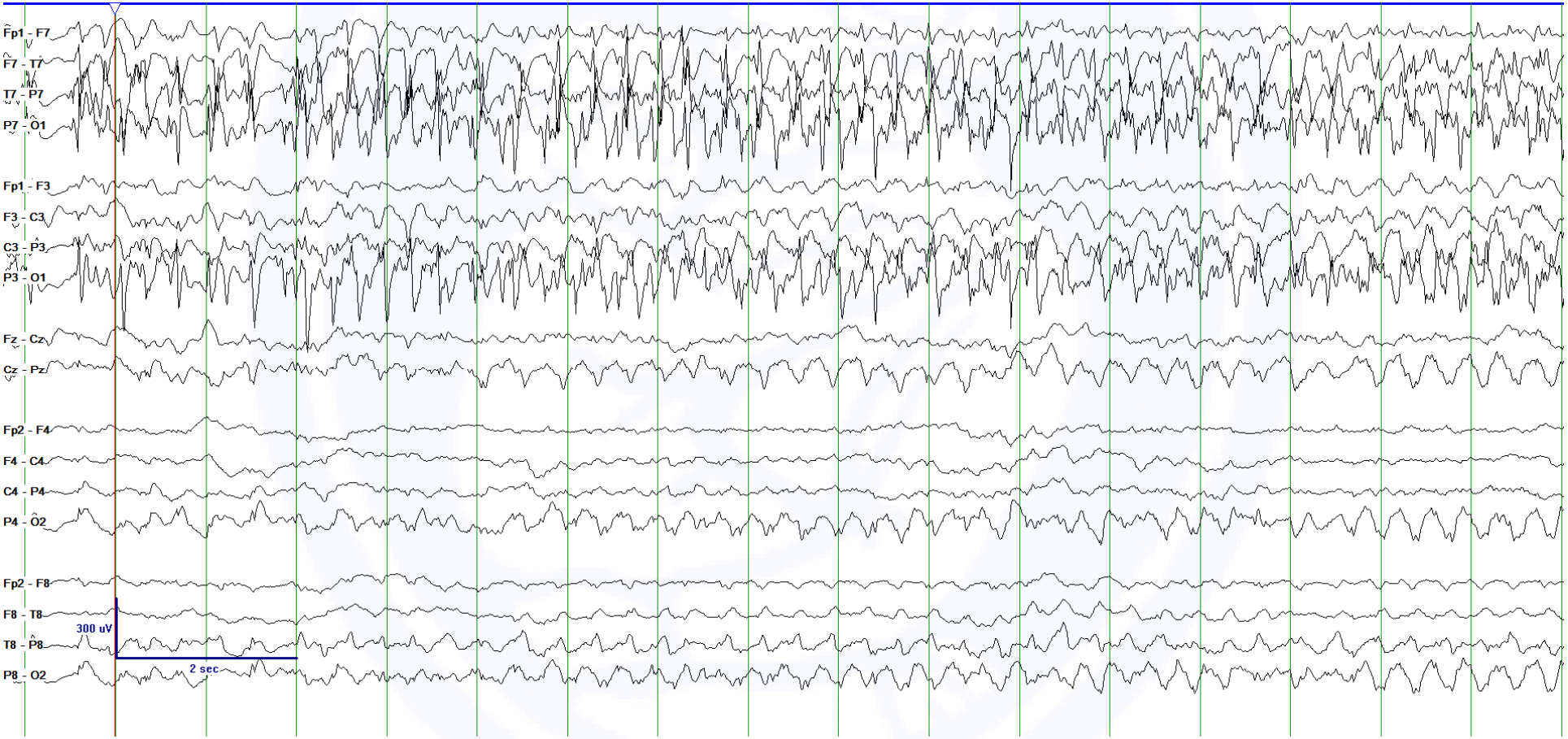
T7 electrographic seizure onset



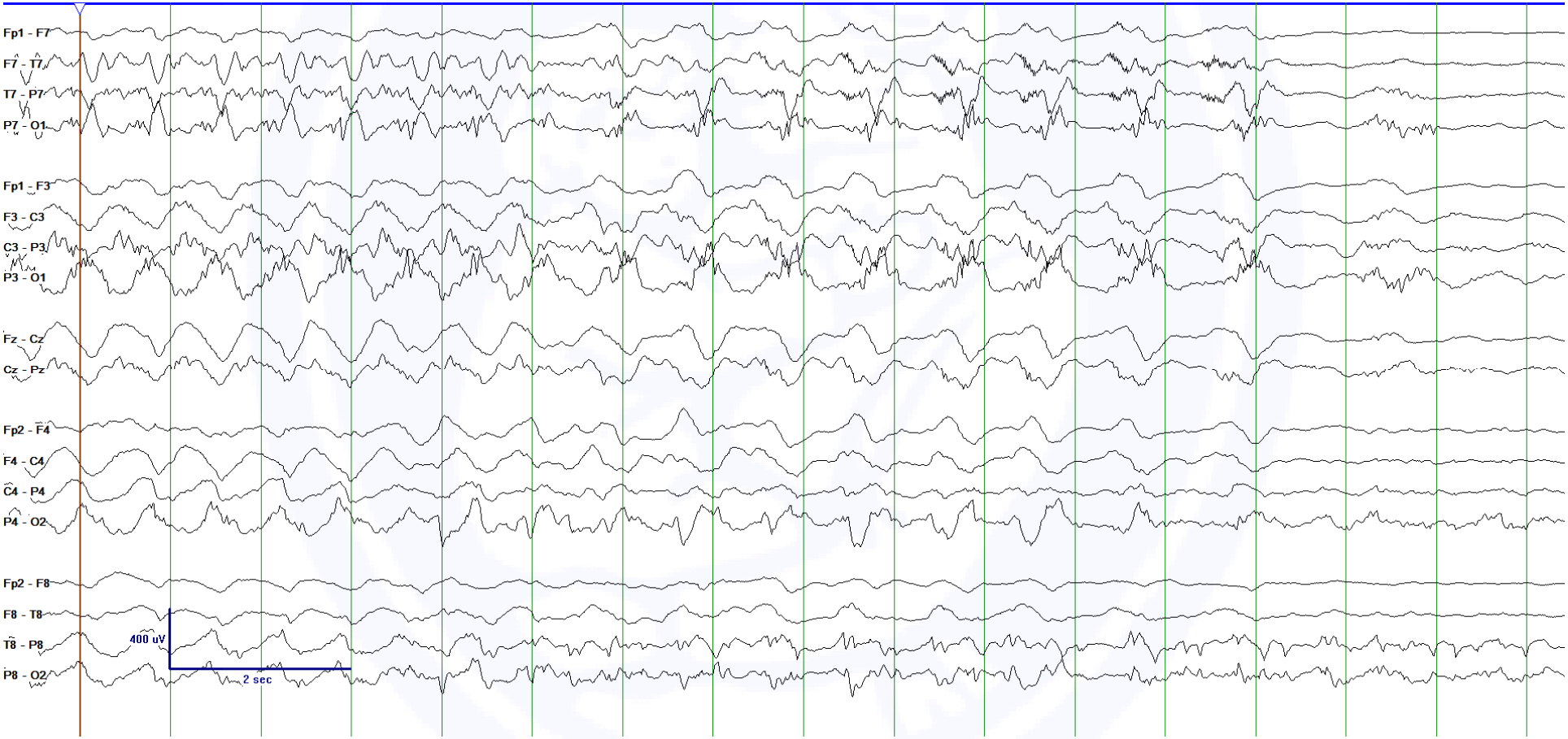
Evolution



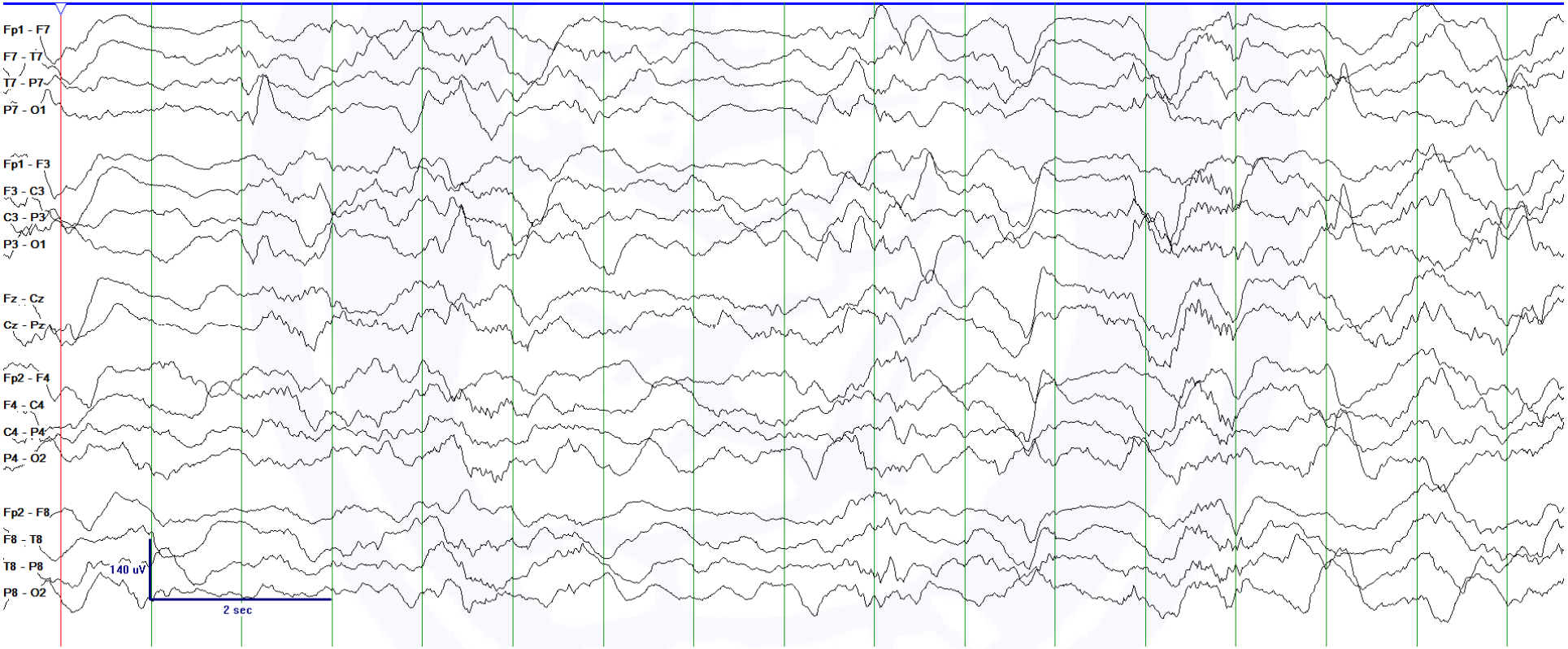
Evolution



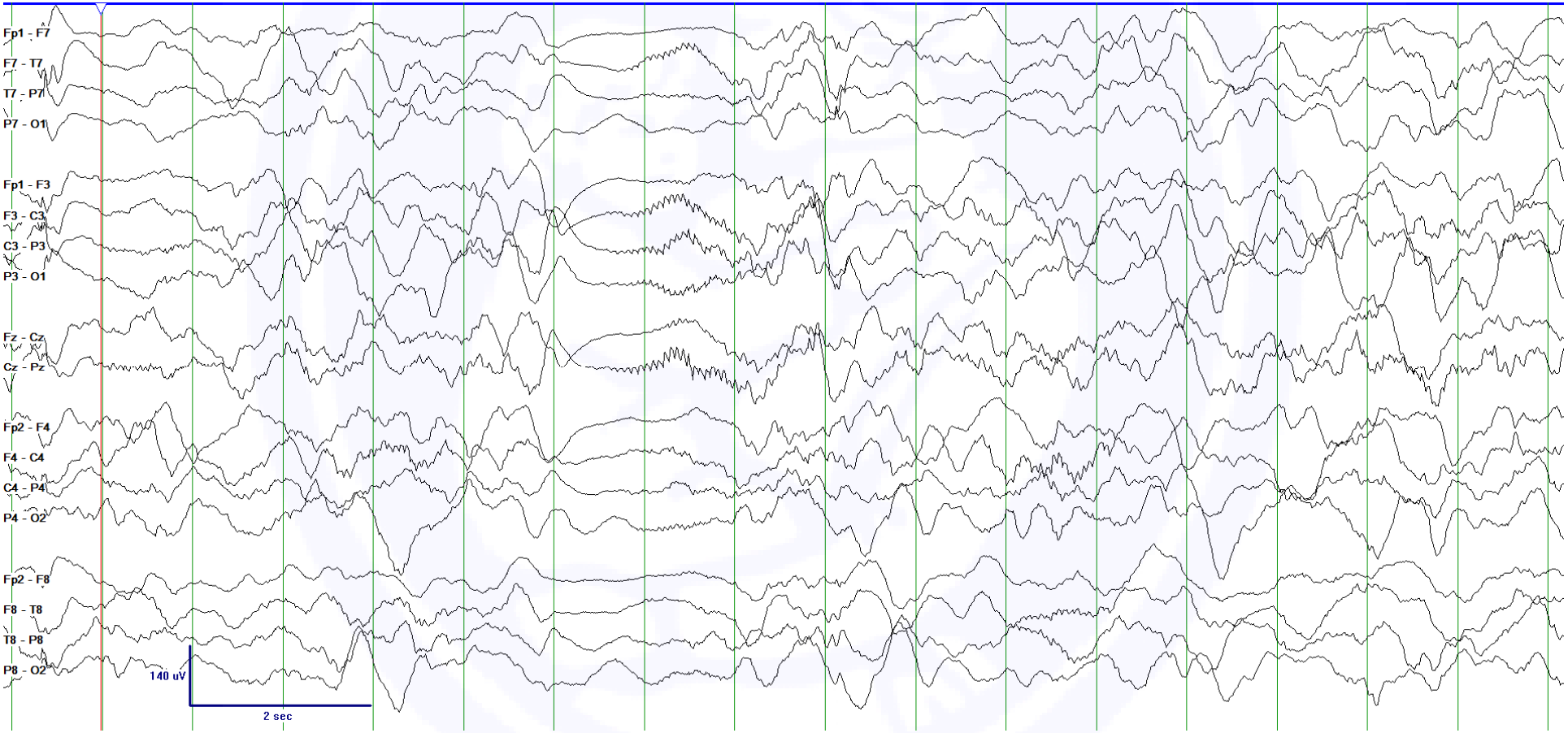
… End



Interictal EEG



Interictal EEG



Febrile infection–related epilepsy syndrome (FIRES)

Consensus Definitions:

- ***NORSE***: clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause.
- ***FIRES***: subcategory of NORSE, applicable for all ages, that requires a prior febrile infection starting between 2 weeks and 24 hours prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus.

Hirsch et al Epilepsia 2018

Clinical Presentation

- ***Patient***: Previously neurologically healthy with peak age of onset in school-aged children (median 8 years)
- ***Preceding History***: Preceding febrile illness, most often URI, often with a brief afebrile period
- ***Monosymptomatic course***: Seizures progressing to refractory SE not responsive to typical AEDs or first-line immunotherapy

Van Baalen et al Epilepsia 2017
Kramer et al Epilepsia 2011
Farias-Moeller et al Epilepsia 2017

Diagnostics

- ***EEG***: Multifocal, with epileptic foci being frontotemporal in the majority
  - Seizures were initially brief and infrequent, with a gradual evolution to SE over days.
  - Beta-delta complexes resembling extreme delta brush
  - Seizures had a characteristic electrographic pattern: beginning with prolonged focal fast activity, followed by the gradual appearance of well-formed rhythmic spike or spike-and-wave.

Van Baalen et al Epilepsia 2017
Kramer et al Epilepsia 2011
Farias-Moeller et al Epilepsia 2017

EEG: Extreme Delta Brush

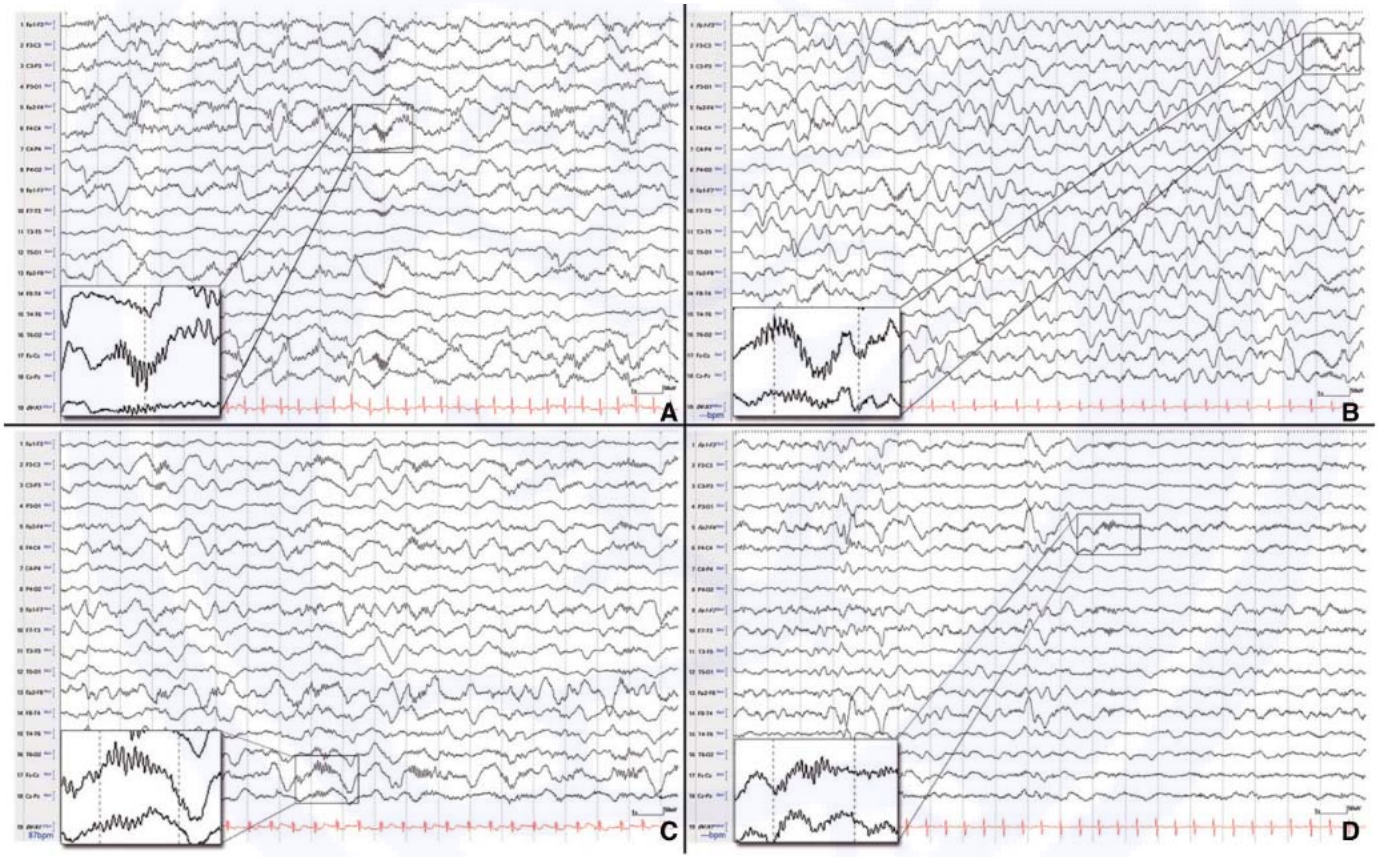


Figure 1.
Extreme delta brush on a bipolar montage demonstrated in four patients. (**A**) Patient 4, (**B**) patient 3, (**C**) patient 6, and (**D**) patient 2.
Epilepsia © ILAE

Farias-Moeller et al Epilepsia 2017

EEG: Focal fast activity

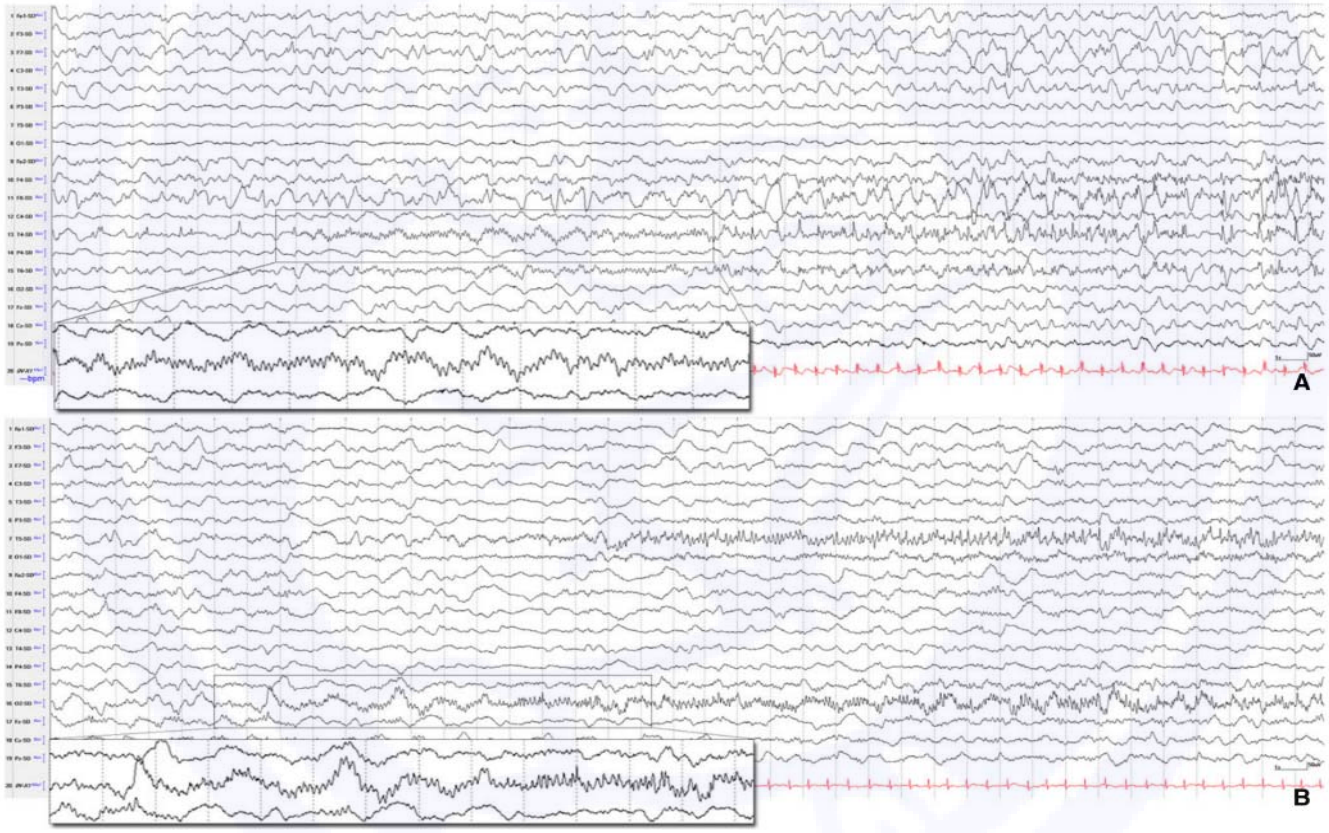


Figure 2.
Typical seizure pattern with focal fast activity preceding spikes or spike/wave complexes on a referential montage. (**A**) Patient 3 and (**B**) patient 6.
Epilepsia © ILAE

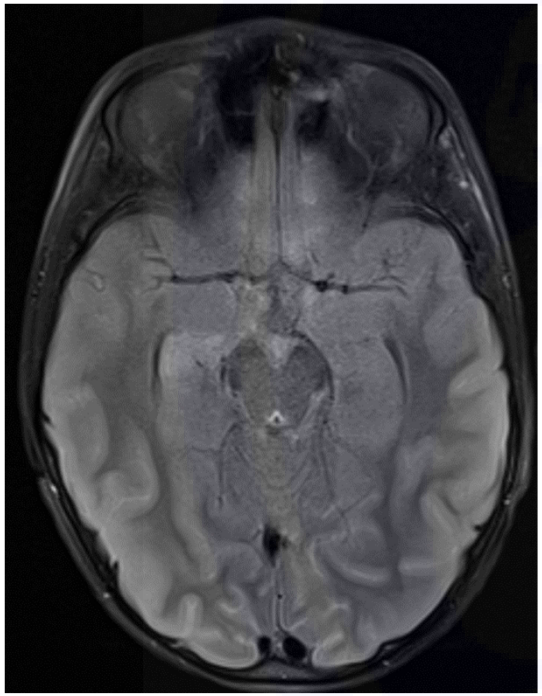
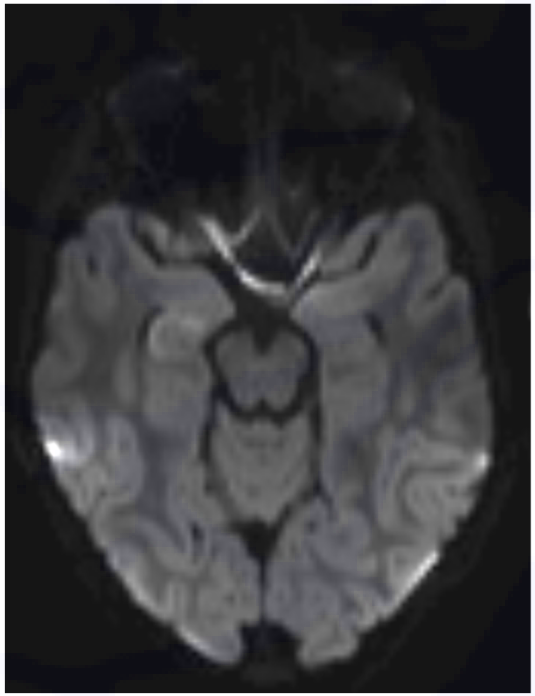
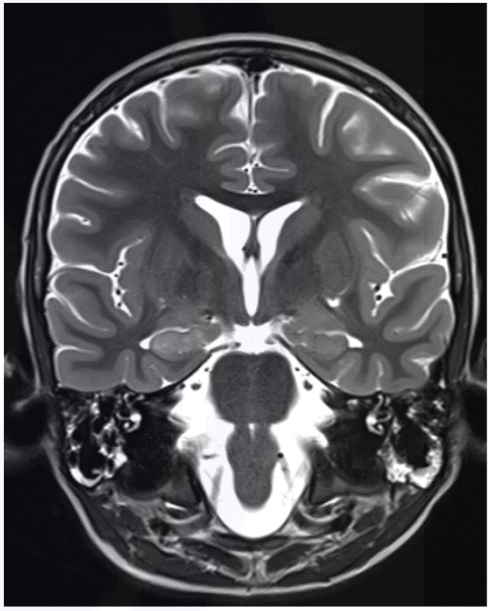
Farias-Moeller et al Epilepsia 2017

Diagnostics

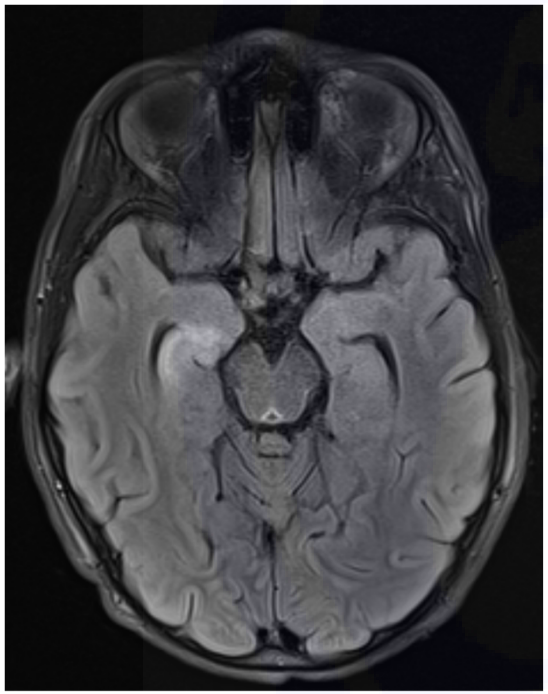
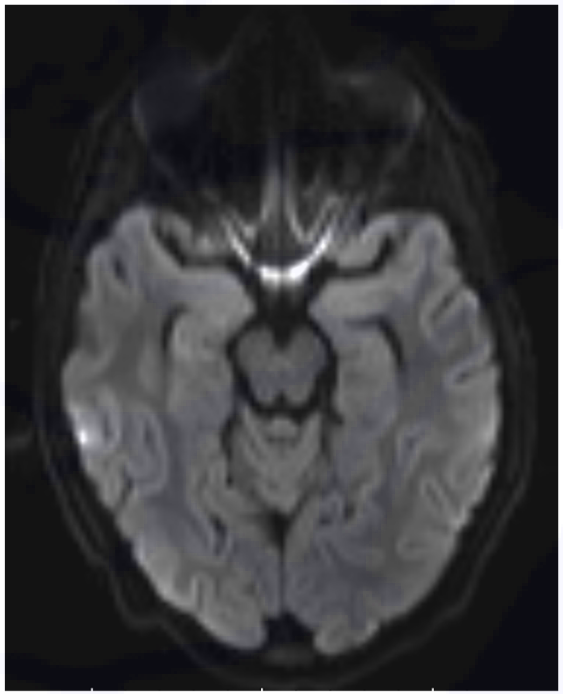
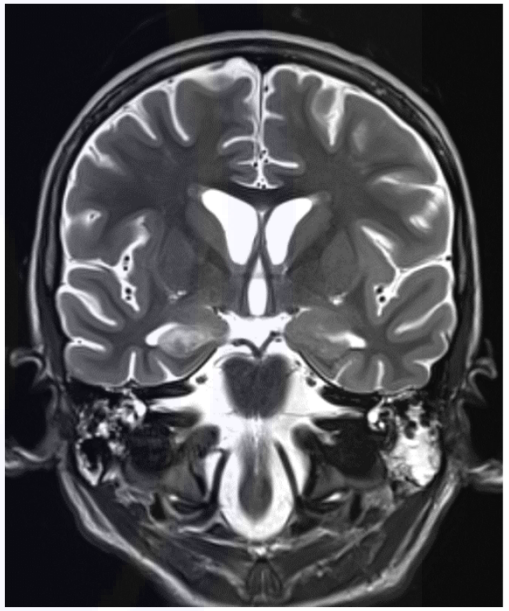
- ***CSF***: Slight pleocytosis (<10 WBC) in majority with +OCB in ~33%
- ***Initial MRI***: Normal in majority +/- hippocampal or insular hyperintensity or rarely leptomeningeal enhancement
- ***Repeat MRI***: Normal or generalized atrophy +/- hippocampal hyperintensity

Van Baalen et al Epilepsia 2017
Kramer et al Epilepsia 2011
Farias-Moeller et al Epilepsia 2017

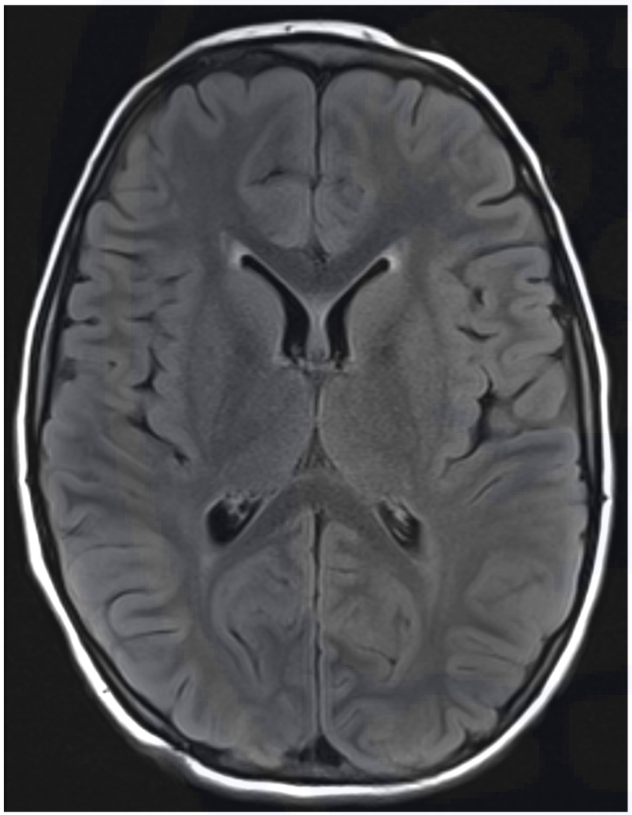
Case: HD 7 MRI

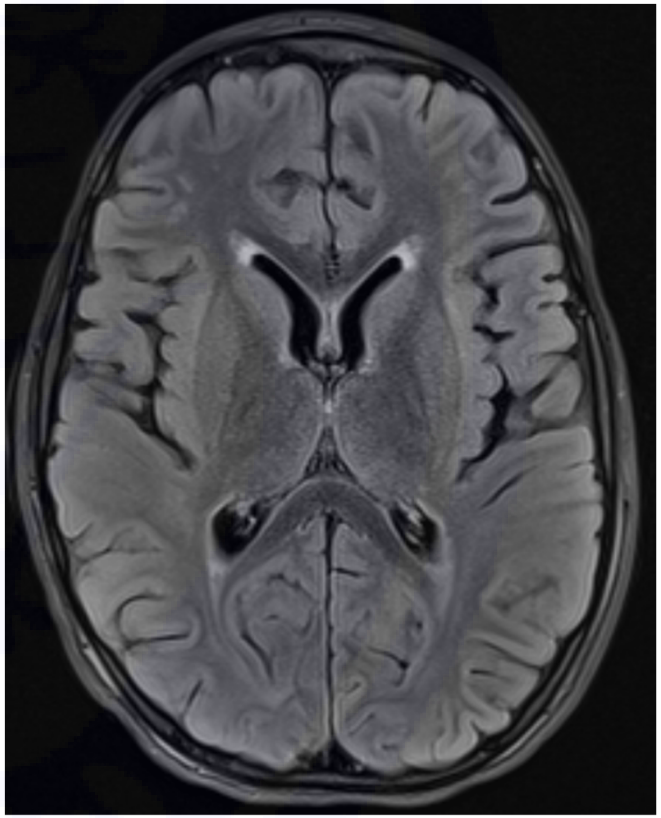
Case: HD 16 MRI

Case: Progressive Cortical Atrophy



HD 2



HD 16

Differential Diagnosis

Infectious Encephalitis

- MRI and CSF profile can help differentiate

Autoimmune Encephalitis

- Typically polysymptomatic with seizures that respond to first-line immunotherapy

CNS Small Vessel Vasculitis

- Typically with parenchymal enhancing lesions

Genetic/Metabolic

Van Baalen et al Epilepsia 2017

Acute Treatment

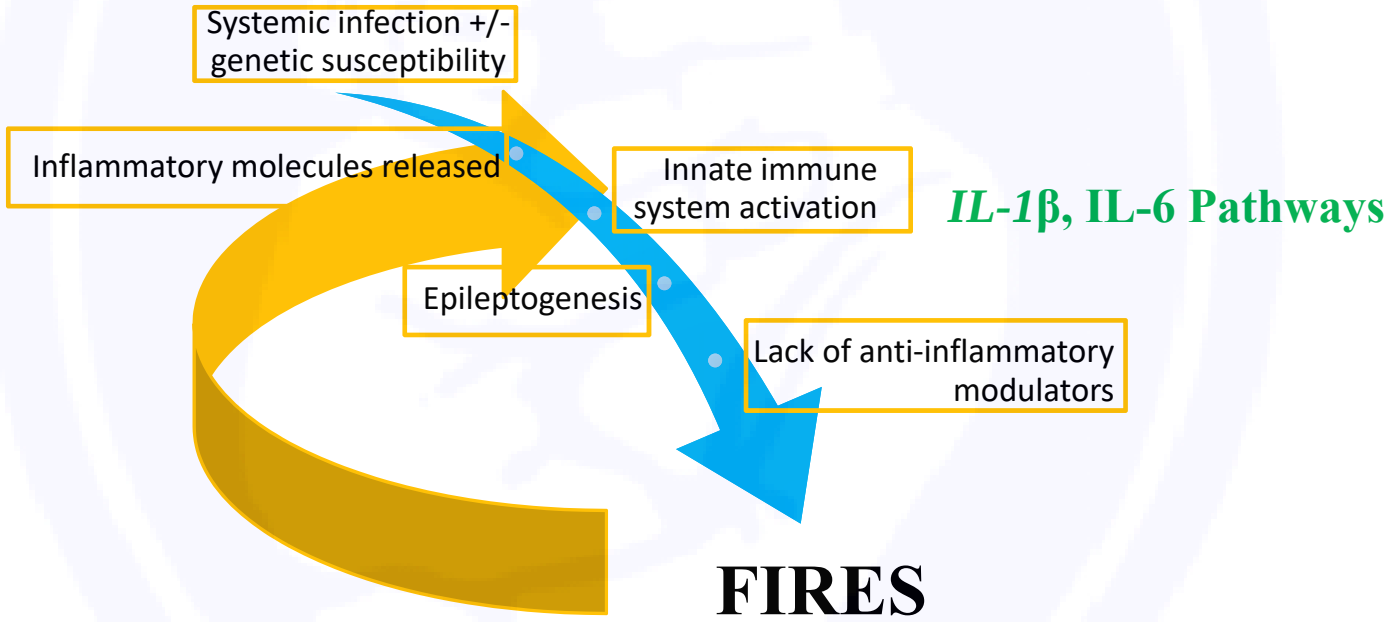
- Traditional AEDs
- Burst-suppression coma
- Immunotherapy
- Ketogenic Diet

Immunotherapy

		Cryptogenic FIRES (N = 225)		Cryptogenic NORSE (N = 101)	
Therapies	**Suggested dosage**	**Number of treatments**	**Positive effects (some cases only transient) (%)**	**Number of treatments**	**Positive effects (some cases only transient) (%)**
Steroids	IV methyldprednisolone 1000 mg per day for 3-5 d (adults) IV methyldprednisolone 10 to 30 mg/kg (up to 1000 mg) per day for 3-5 d (children) Sometimes followed by oral prednisone 1 mg/kg per day	63	11 (17)	40	15 (38)
Intravenous immunoglobulins	1.2 to 2 g/kg over 3-5 d	94	5 (5)	17	5 (30)
Ketogenic diet	N/A	35	19 (54)	12	8 (67)
Plasmapheresis	3 to 5 exchanges, one every other day	18	2 (11)	15	6 (40)
Hypothermia	N/A	5	3 (60)	4	2 (40)
Rituximab	N/A	3	1 (33)	0	NA
Azathioprine	N/A	1	0 (0)	0	NA
Tacrolimus	N/A	1	0 (0)	0	NA
Cyclophosphamide	N/A	1	0 (0)	0	NA

Gaspard et al Epilepsia 2018

Pathophysiology



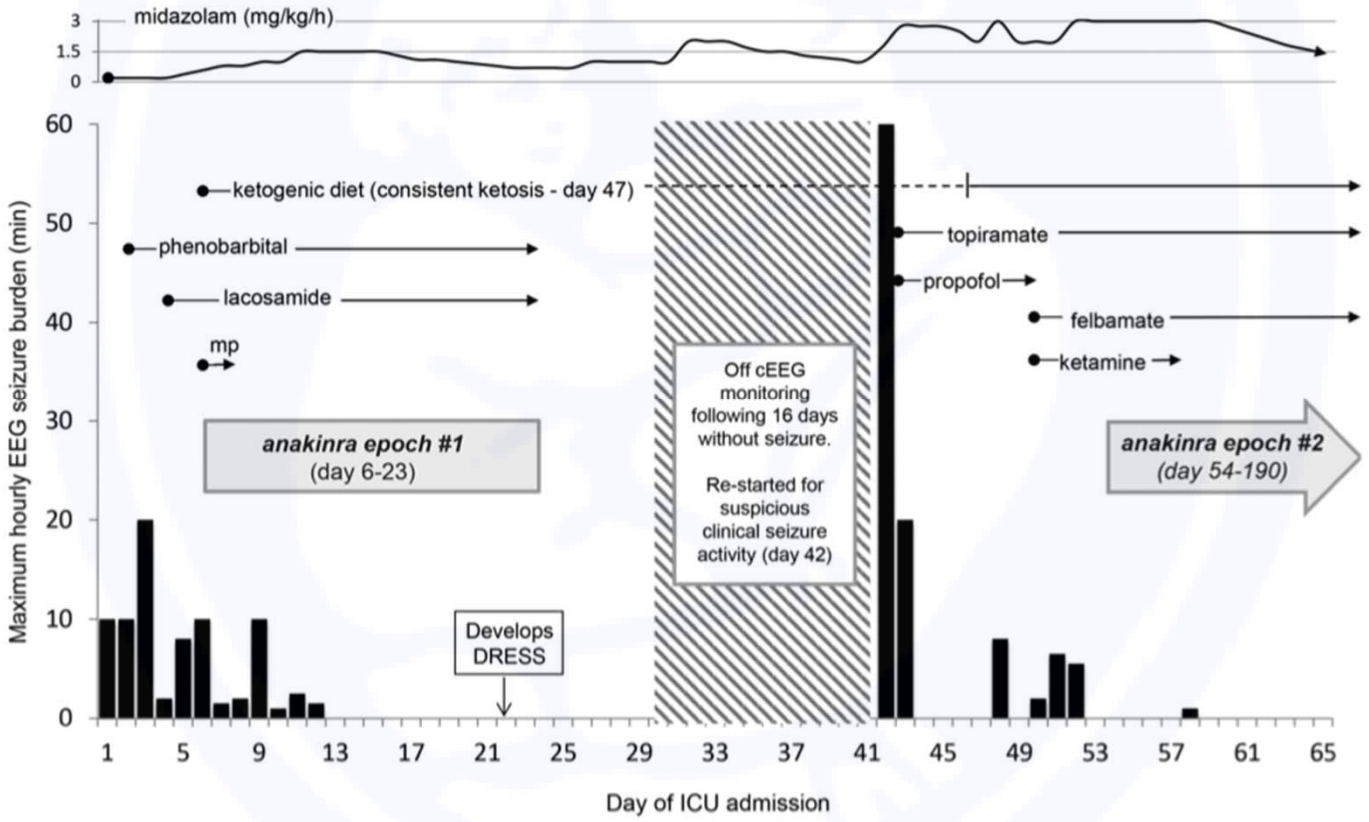
Van Baalen et al Epilepsia 2017

IL-1β & Anakinra

- IL-1β and endogenous IL-1RA are elevated in FIRES patients compared to controls
- However, one patient was found to have decreased functioning of endogenous IL-1RA
- The increased IL-1 activity was partially suppressed by addition of exogenous IL-1RA

Clarkson et al Ann Neurol 2019

Anakinra Case Report



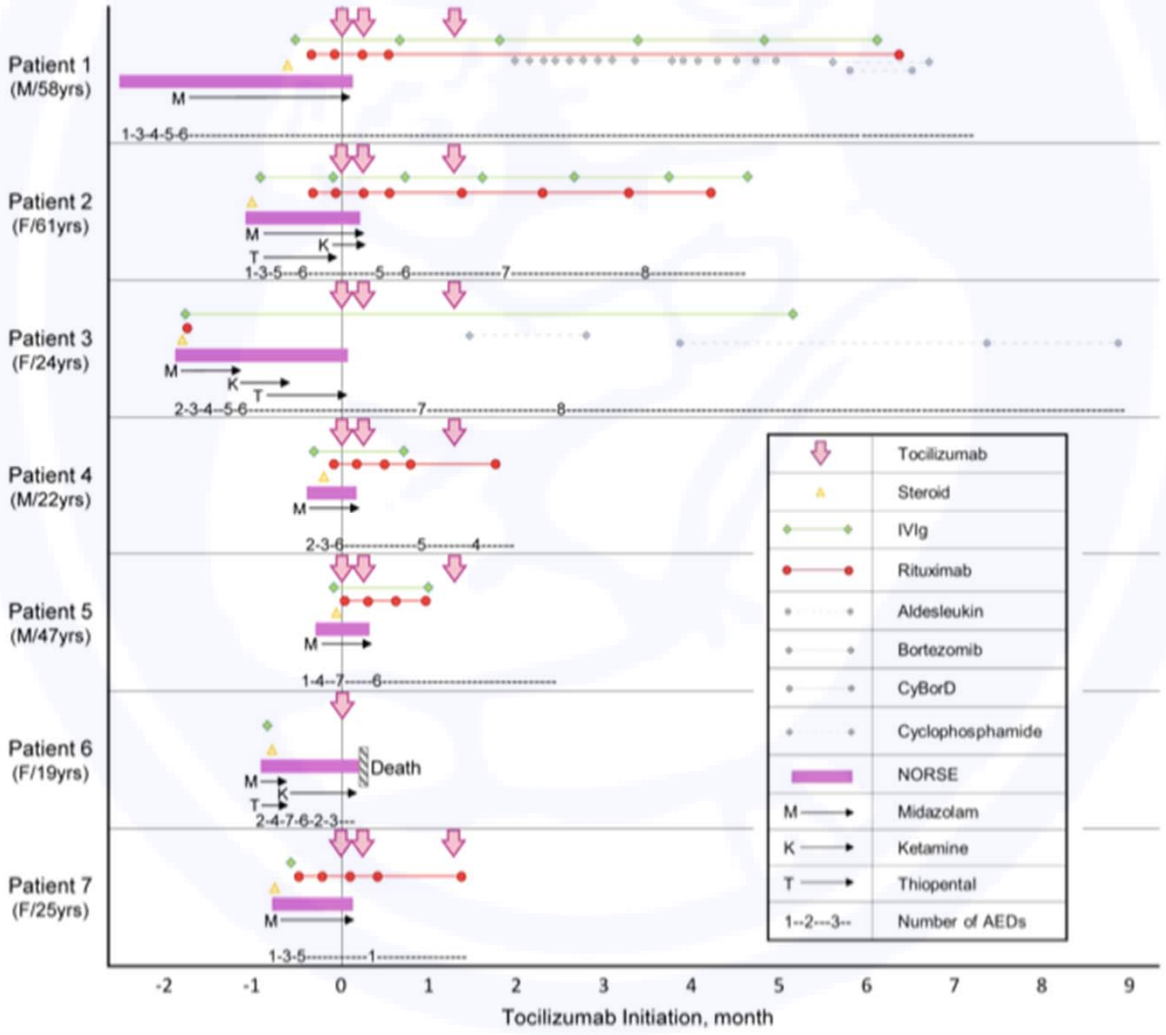
Kenney-Jeung et al Ann Neurol 2016

Anakinra Case Series

- ***Patient population***:
  - 25 children with FIRES who received anakinra in 6 countries
  - Anakinra was started at a median of 20 days after the onset of seizures
- ***Adverse events***:
  - Anakinra was not associated with a significant increase in infections, and anakinra was discontinued in only one child due to infection
  - Other adverse effects included DRESS (n=3), that did not require withdrawal of anakinra, and cytopenias (n=2)
- ***Outcomes***:
  - **Later anakinra** correlated with **increased ICU and hospital LOS** [r=0.50 (p=0.01) and r=0.48 (p=0.03)]

Muscal et al CARRA Abstract 2019

IL-6 & Tocilizumab



Jun et al Ann Neurol 2018

Acute Treatment

- Traditional AEDs
- Burst-suppression coma
- Immunotherapy
- Ketogenic Diet

IL-1β & Ketosis

- β-hydroxybutyrate (BHB) decreases IL-1β production in human monocytes.
- BHB/ketogenic diet decreases IL-1β secretion in mouse models of NLRP3-mediated diseases.

Youm et al Nat Med 2014

Ketogenic Diet

- 9 patients were followed over a period of 12 years in 5 centers:
  - Seizures stopped in 7 patients, within 2–4 days (mean 2 days) following the onset of ketonuria and 4–6 days (mean 4.8 days) following the onset of the diet.
  - KD failed to control seizures in 2 patients, one on steroid therapy did not reach ketonuria and another without clear reason
  - Diet was continued for 6 months – 2 years (mean 1 year) with ~1-2 seizures/week v
- In one case, KD was abruptly stopped 3 days after SE cessation felt to be secondary to KD. Upon stopping KD, SE recurred within a few hours and the patient died 10 days later.

Nabbout et al Epilepsia 2010

Case: Lab Evaluation

- **CSF Studies**:

Hospital Day	WBC (cell/mm^3)	RBC (cell/mm^3)	Protein (mg/dL)	Glucose (mg/dL)
1	1	230	32	98
2	**15** (75% L)	924	**121**	91
17	**7** (88% L)	16		

  - Autoimmune encephalitis panel negative, OCB negative, **neopterin** elevated at 91

- **Serum Studies**:
  - AE panel with low-titer GAD positivity (0.09 nmol/L) after IVIg
  - Pancytopenia from onset, normal ferritin

- **Infectious Studies**:
  - NP **RSV** PCR +, serum **Mycoplasma** IgG/M + (CSF PCR and Ab -)
  - CSF metagenomic next generation sequencing negative

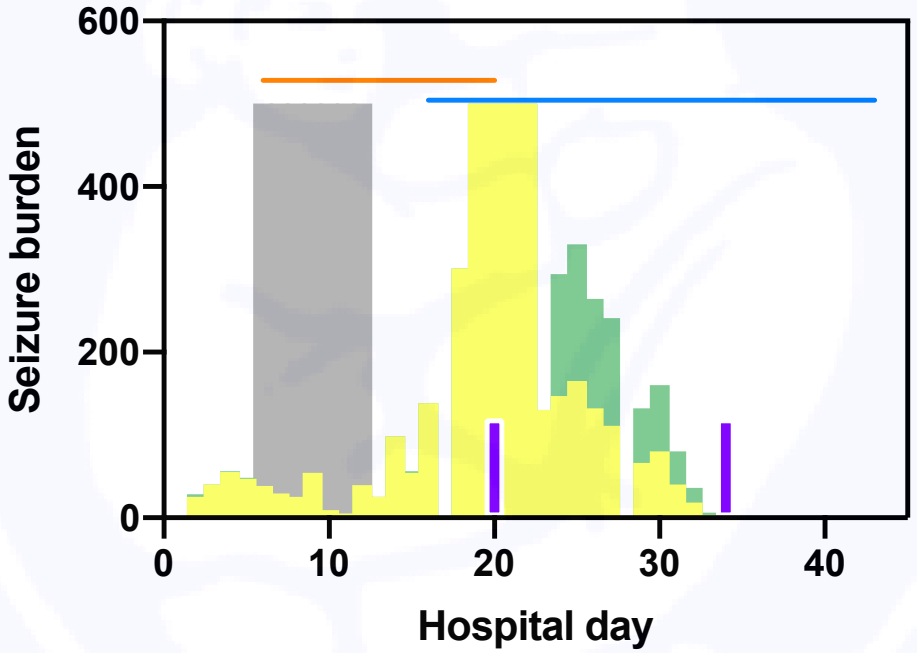
- **Whole Exome Sequencing**:
  - Hemizygous for VUS in TFE3

Case: Cytokine Analysis

Cytokine	CSF (pg/mL)	Reference Range (pg/mL)	Serum (pg/mL)	Reference Range (pg/mL)
IL-1 beta	<5	≤5		
IL-2	**2**	≤1	<5	≤12
IL-4	**10**	≤7	<5	≤5
IL-5	1	≤2	<5	≤5
IL-6	**84**	≤25	<5	≤5
IL-8	**605**	≤205	<5	≤5
IL-10	**3**	≤2	<5	≤18
IFN-gamma	1	≤4	<5	≤5
TNF-alpha	1	≤4	<5	≤22

Case: Seizure Trends

- Seizures/day
- Seizure minutes/day
- Burst suppression



- Anakinra
- Beta-hydroxybutyric acid (>1.5 mmol/L)
- Tocilizumab

Chronic Treatment

Effective in several cases
Ketogenic diet (possibly, monotherapy sufficient)
Cannabidiol (titrated to 25 mg/kg/d)[81]
Phenobarbital
Clobazam (also an option during the acute phase)[137]
Partially effective
Valproate
Phenytoin
Lamotrigine (especially indicated, if improvement of behavior is necessary)
Sulthiame
Levetiracetam
Topiramate

Van Baalen et al Epilepsia 2017

Prognosis

In a cohort of 77 patients:

- 11.7% mortality
- 93% with refractory epilepsy

- Cognitive levels at follow-up were as follows:
  - 23 (34%) normal (with out without ADHD or LD) or borderline
  - 26 (38%) mild/moderate ID
  - 19 (28%) severe ID/vegetative

- Worse cognitive outcomes were associated with:
  - Younger age of onset
  - Longer burst-suppression

Kramer et al Epilepsia 2011

Case: Follow-up

- Rare seizures on 5 ASMs except when ill or with medication weans
- Ambulating independently with some imbalance, ongoing PT/OT
- IQ subsets for processing speed, performance and verbal IQ are 60, 86 and 81, respectively.
- Speaking in full sentences, attending kindergarten with IEP
- New onset behavioral dysregulation post-diagnosis

Summary

- Seizures may be a cause or consequence of inflammation, and patients with co-morbid autoimmune disease are at increased risk of epilepsy.
- ***RE***: Current immunotherapy may be helpful in "slow burners," but its benefit is otherwise limited and caution should be used given the "Pyrrhic victory" (slowed cortical atrophy/weakness with ongoing seizures such that hemispherectomy decision becomes even more challenging)
- ***FIRES***: Immunotherapy targeting the innate immune system is promising, but controlled studies are needed

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