Approach To Autoimmune Encephalitis

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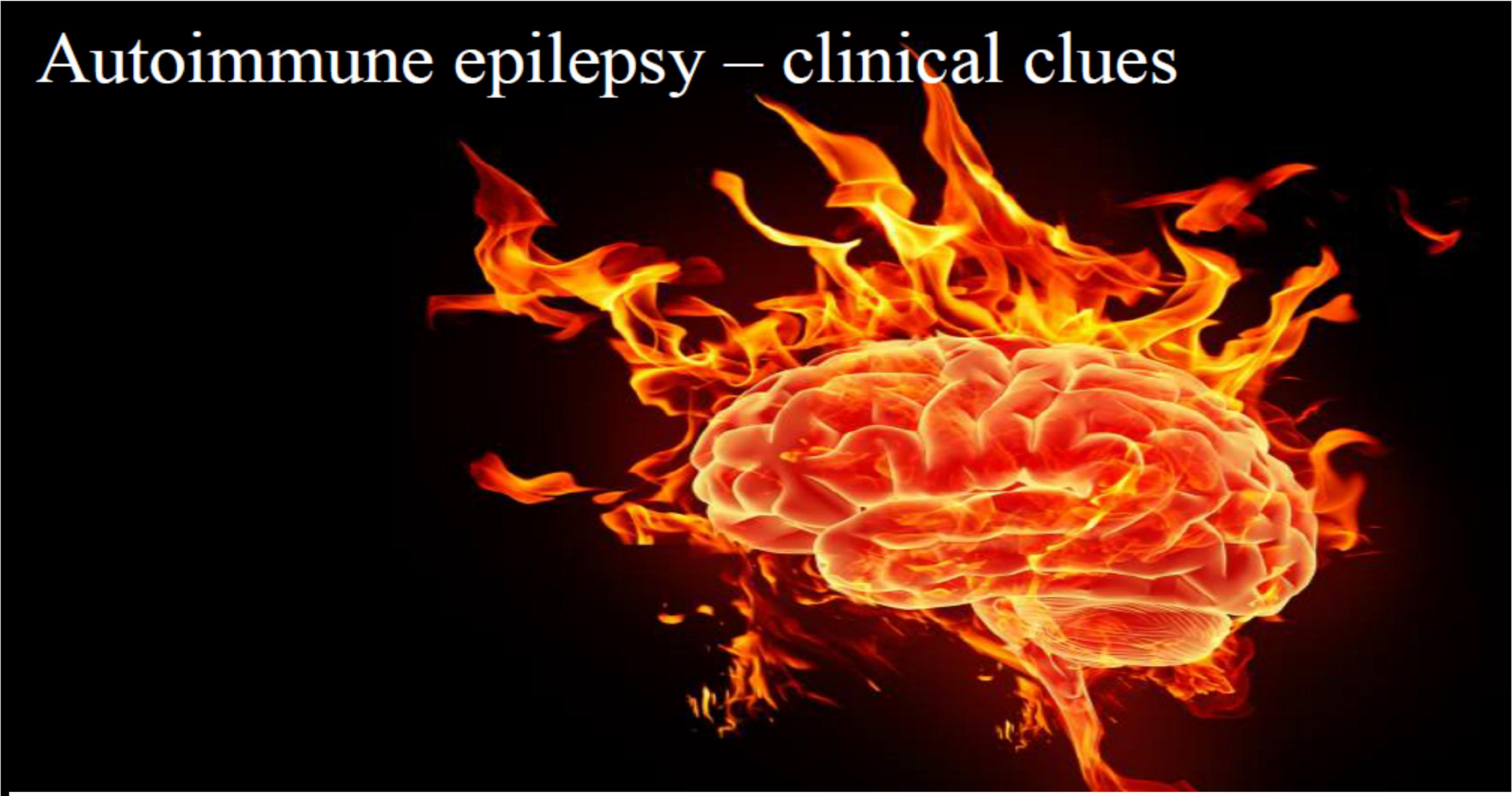
1400

Autoimmune epilepsy – clinical clues

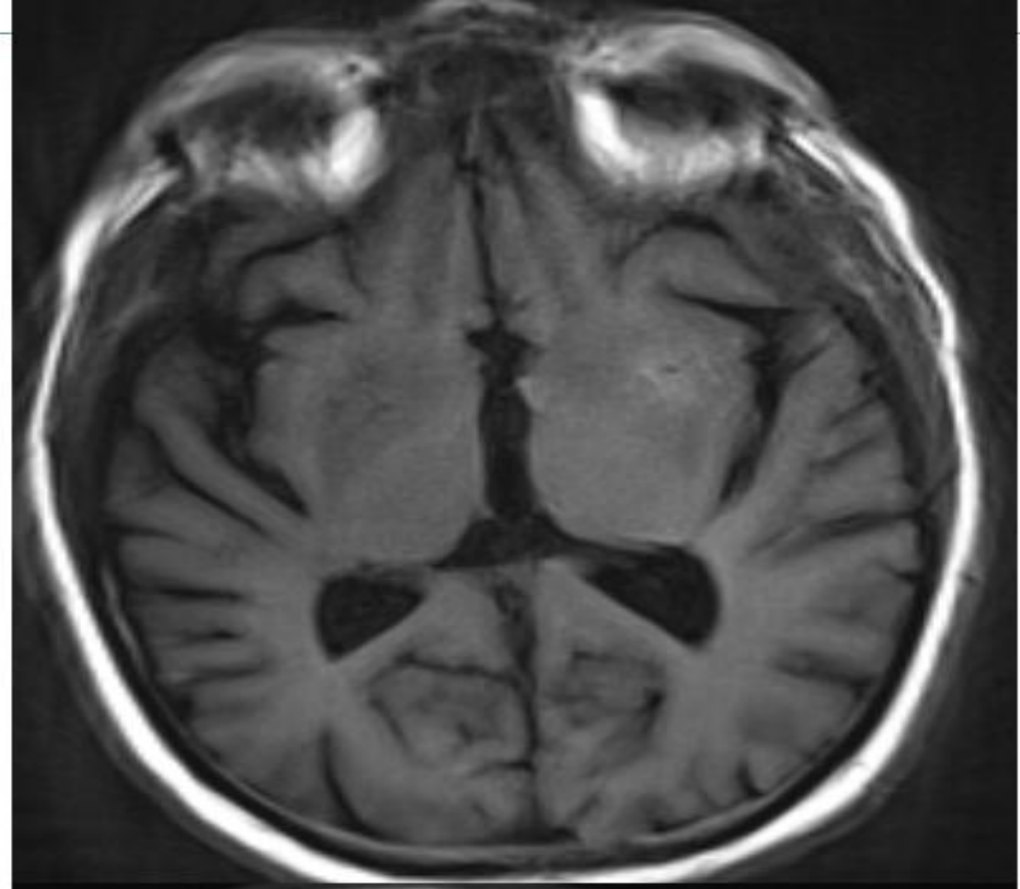


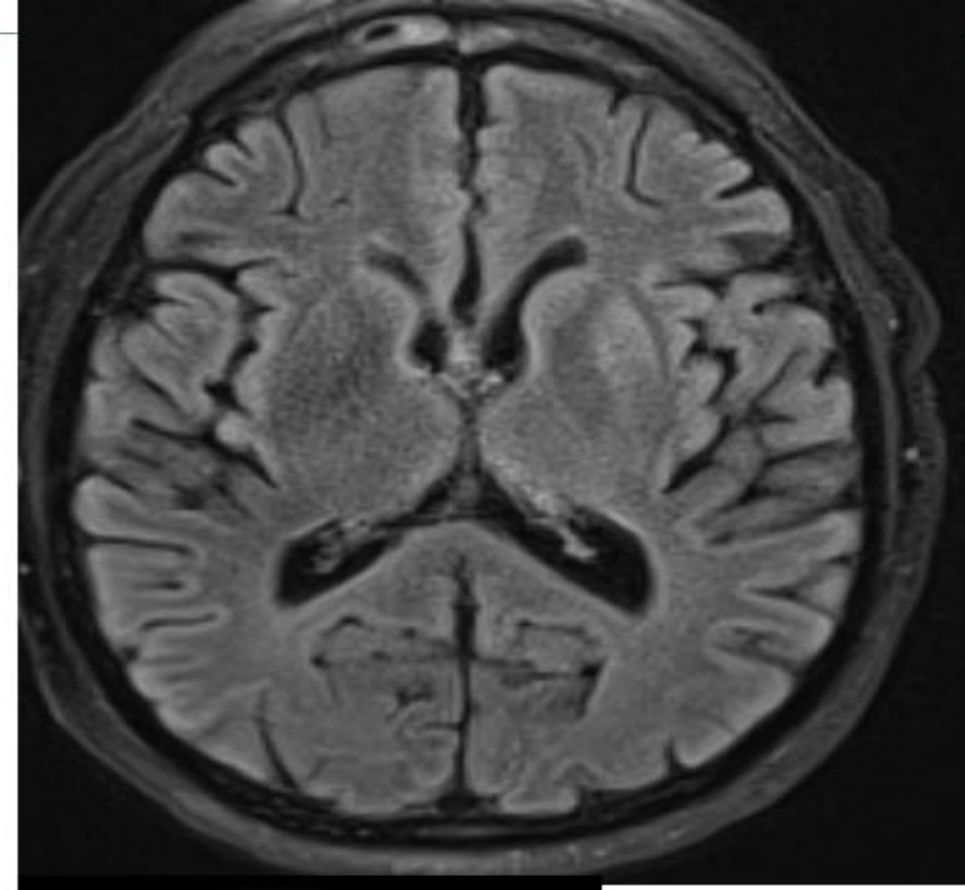
Case History

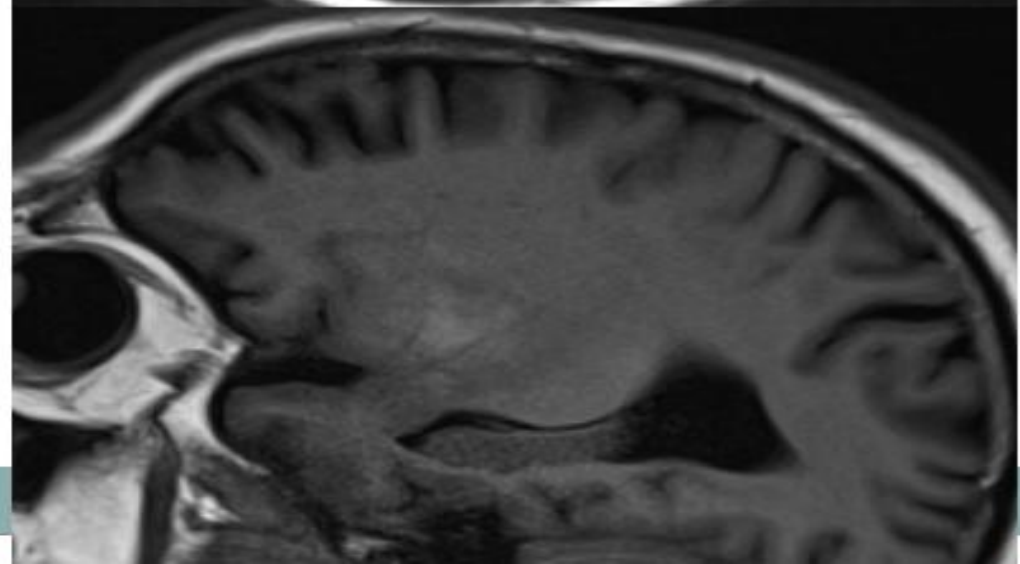
- 74 yr old man
- Spells
  - Brief 2-10 seconds
  - Right face, arm twitch (leg sometimes involved)
  - Crying
  - Up to 10/hr
  - Awareness preserved during episodes
  - Not sad when crying

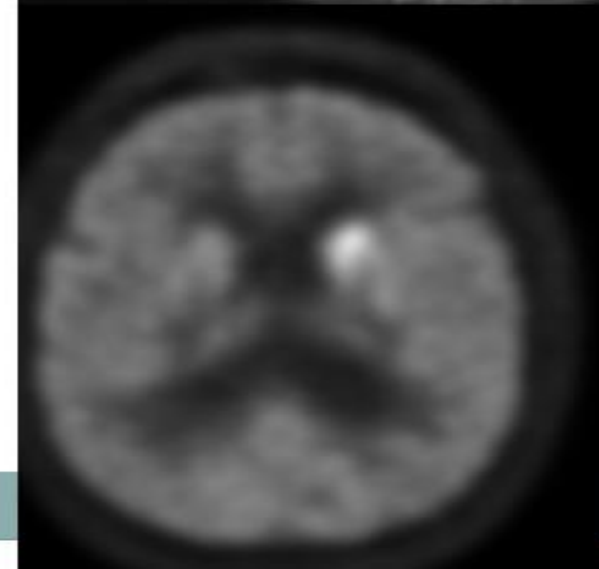
Case History and Exam

- Psych meds – no response
- Rx: phenytoin, phenobarbital, lacosamide topiramate but episodes continued
- PM Hx: Nil
- FHx: diabetes (mother)
- Exam:
  - MOCA 25/30 – delayed memory 2/5
  - myoclonic like movements (R arm)









Investigations

- Na 123
- ANA +
- Anti TPO 110
- EEG: central spikes; 2 episodes captured with no EEG correlate
- CSF: WBC 2/µL, Protein 67 mg/dL, OCB neg
- Neuronal specific enolase 24

What is the diagnosis ?

1. Hashimoto encephalitis (Anti TPO 110)
2. Psychogenic
3. Lupus cerebritis (ANA +)
4. Autoimmune encephalitis
5. Hyponatrmia induced chorea (Na 123)

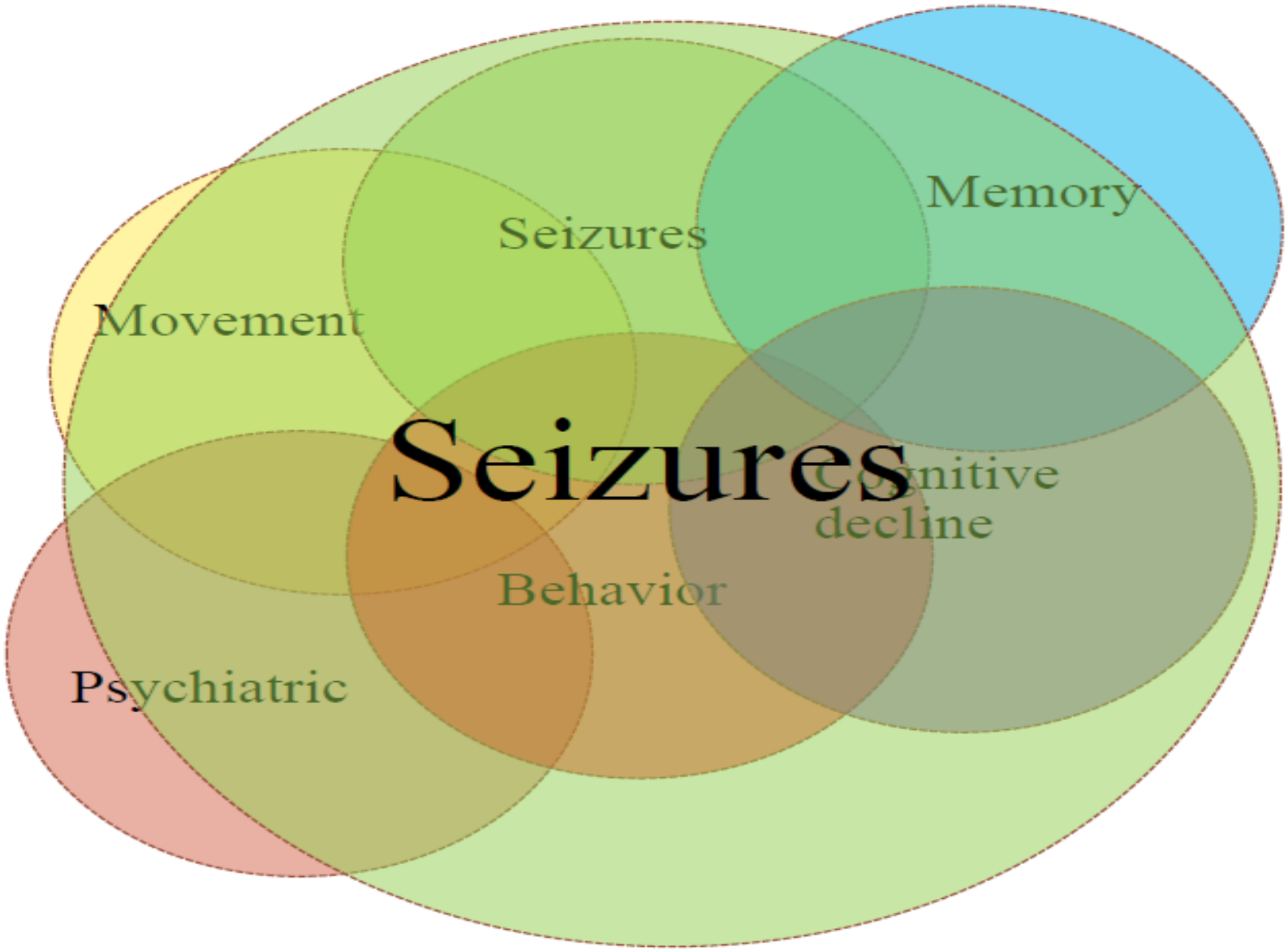
Diagnosis

- Autoimmune encephalitis/epilepsy LGI1
- Facio-Brachial Dystonic Seizures (FBDS)
- Dacrystic Seisures

Autoimmune Epilepsy

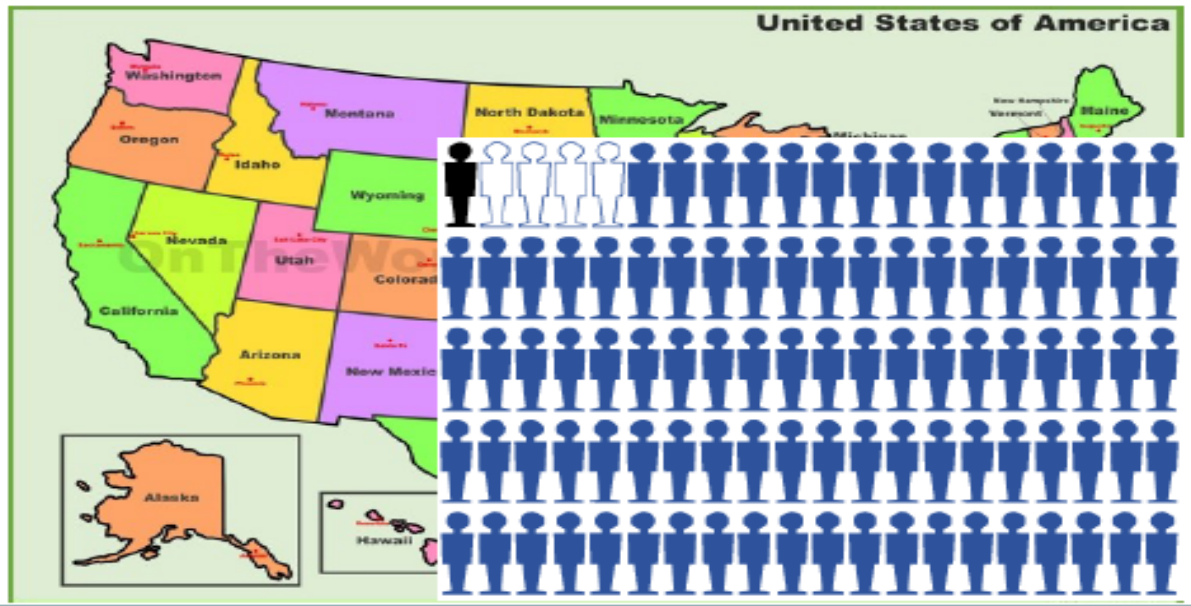
- Isolated Epilepsy
- Presenting symptom of Autoimmune encephalitis
- A part of autoimmune encephalitis syndrome

Autoimmune encephalitis



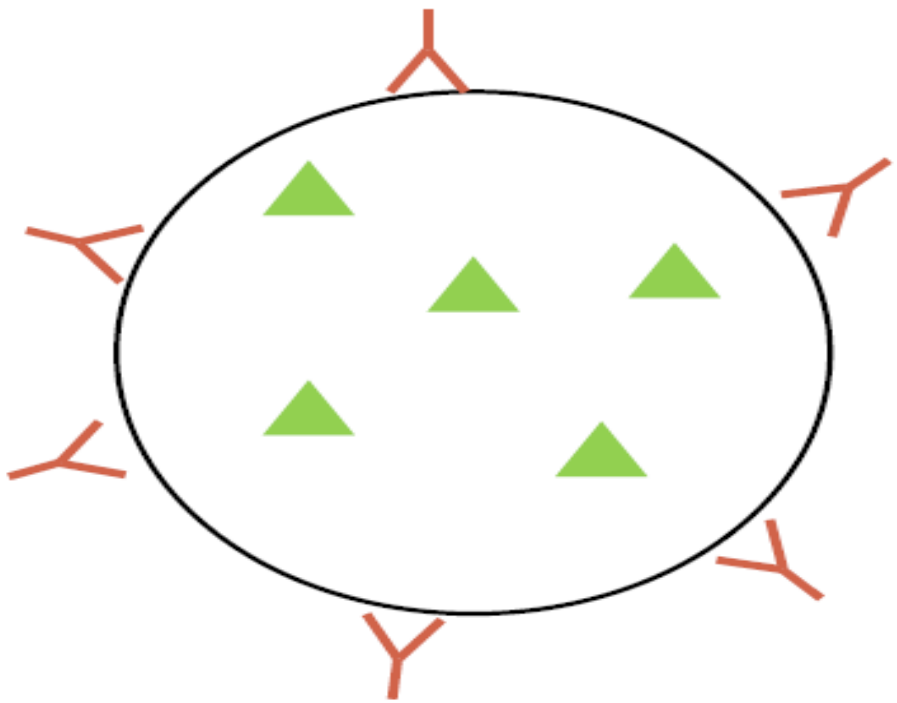
Numbers

- At least as common as infectious
- 1/100,000 a year (probably more)
- At least **3270** cases in the US

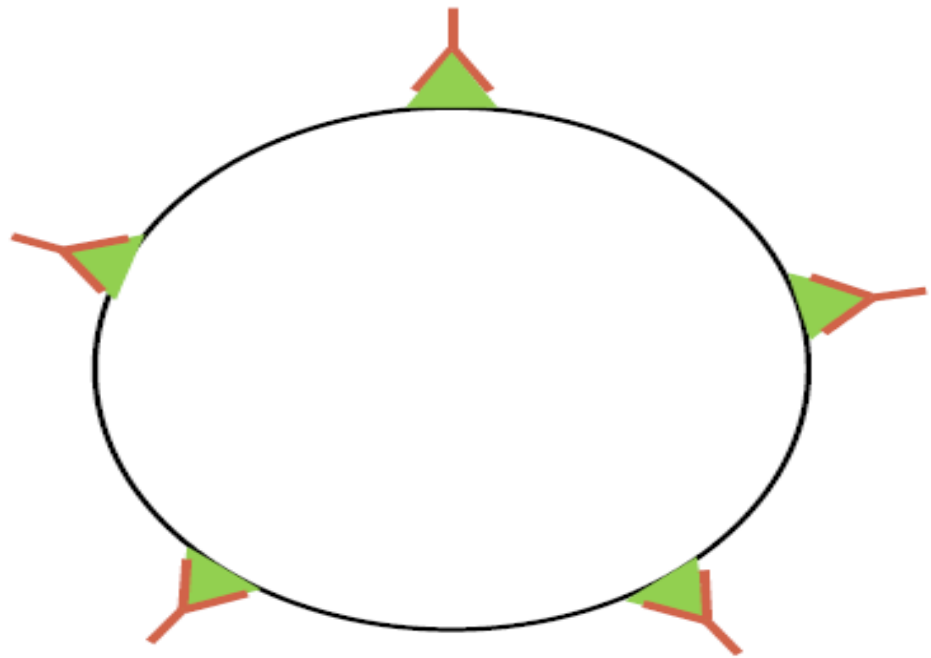


Categories

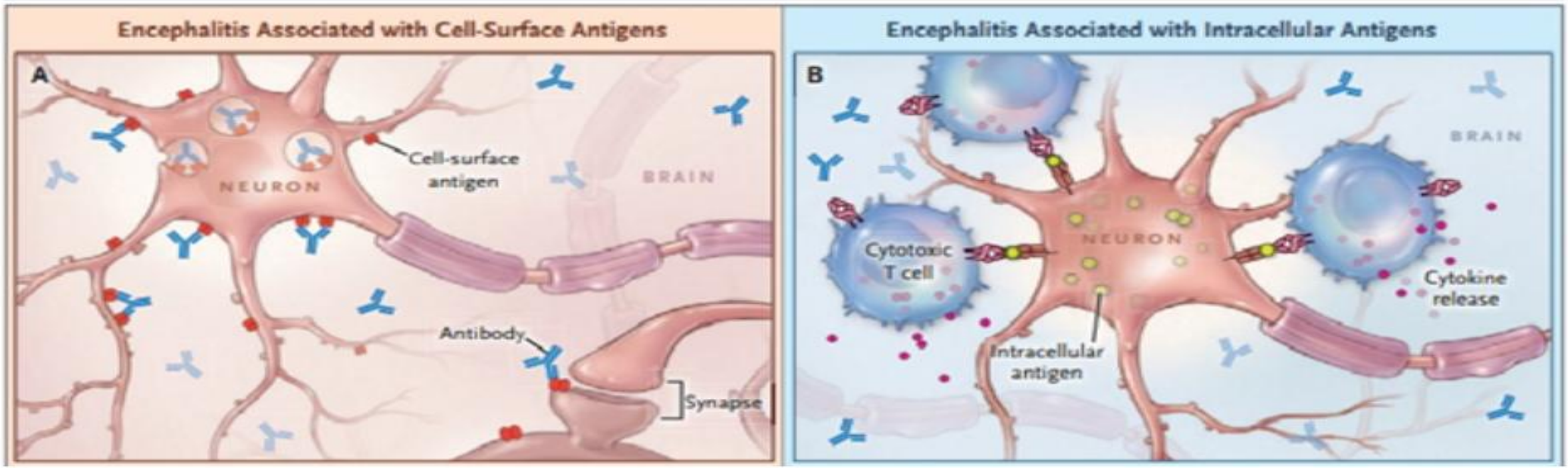
Intracellular antigens
ANNA-1/Anti Hu
Non paraneoplastic
Anti GAD



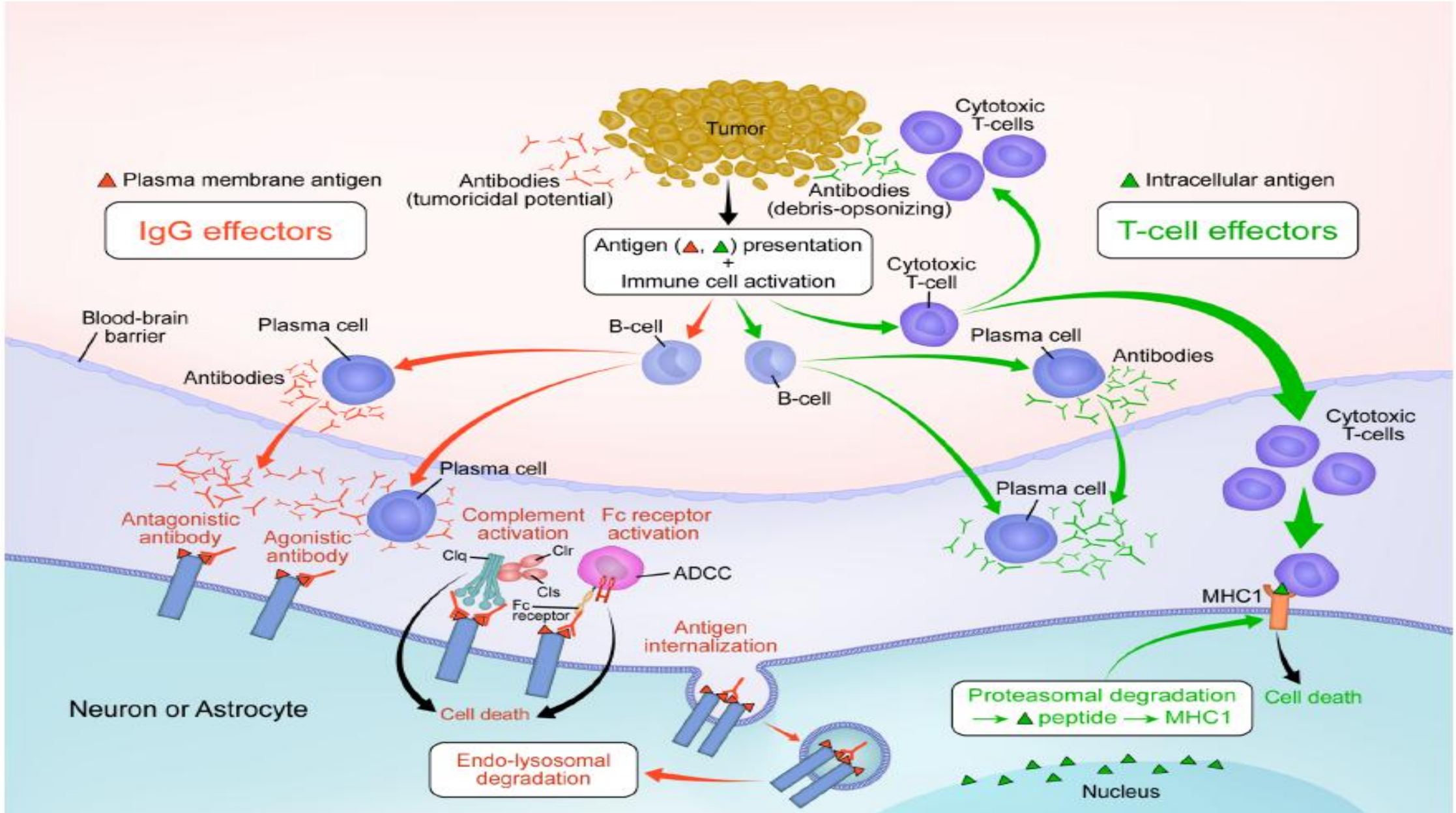
Extracellular antigens
GABA-B / AMPA
Non paraneoplastic
LGI1



Intra Vs extra cellular

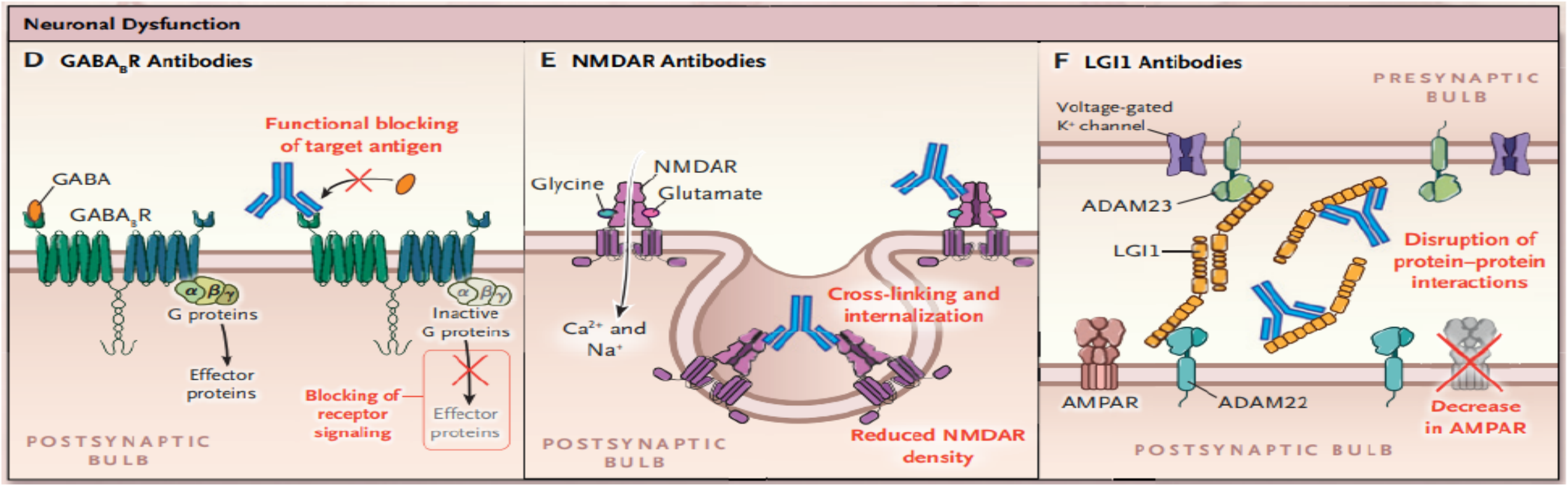


Dalmau , NEJM 2018



McKeon & Pittock, Acta Neuropath 2011

Antibody mechanism of action



Dalmau , NEJM 2018

Cell surface antibodies

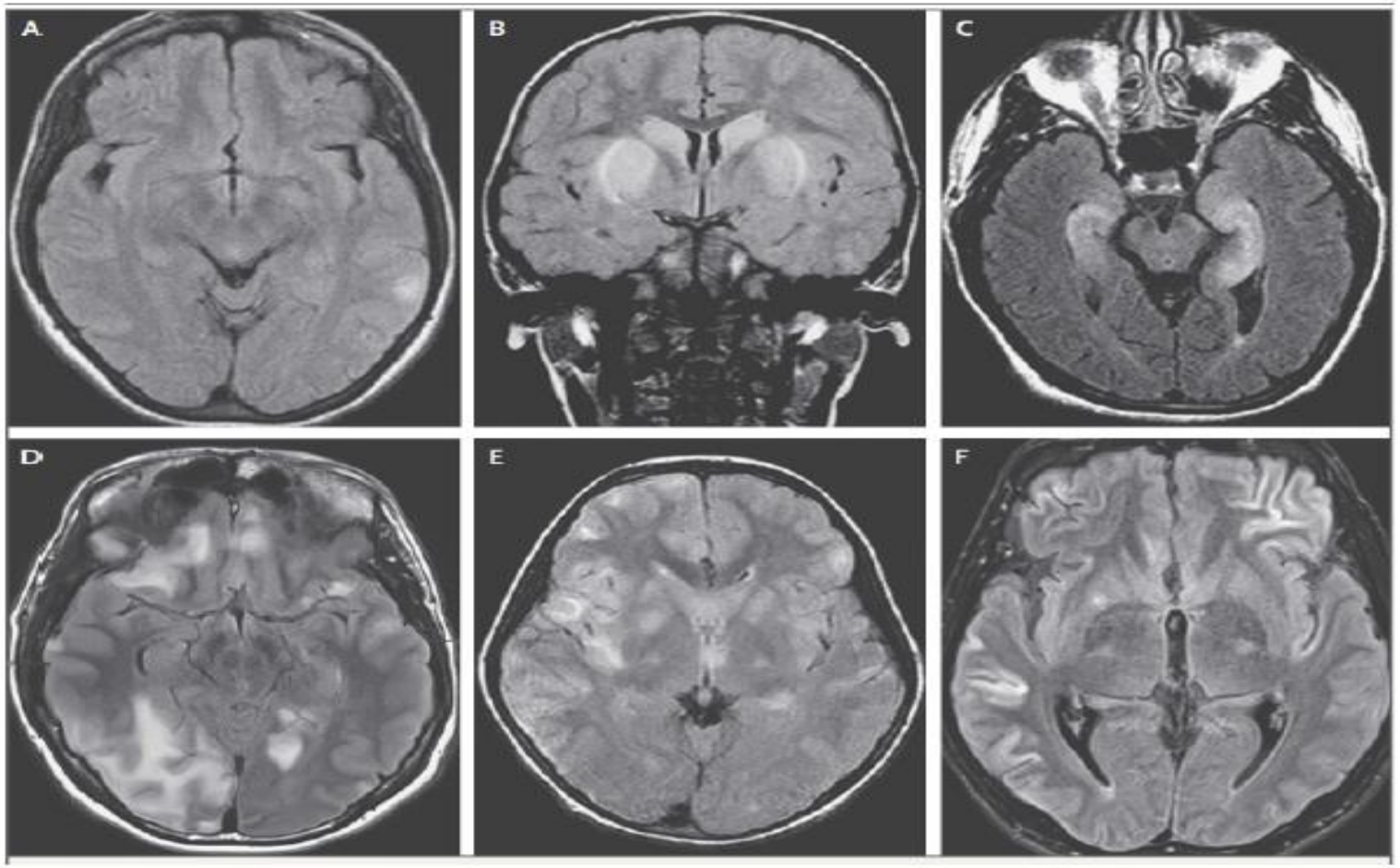
Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

Imaging

DR2

NMDA



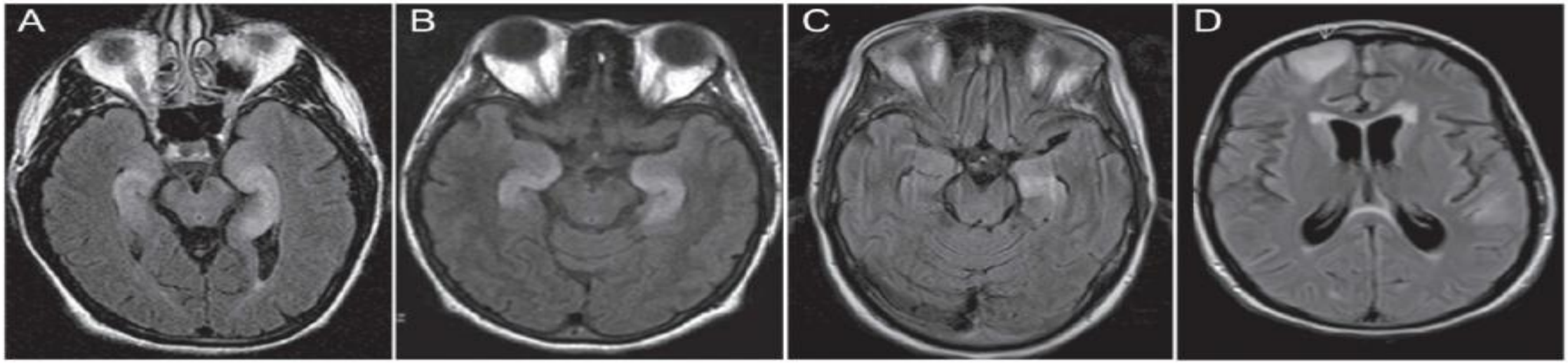
Limbic

GABA-A

AMPA

MOG

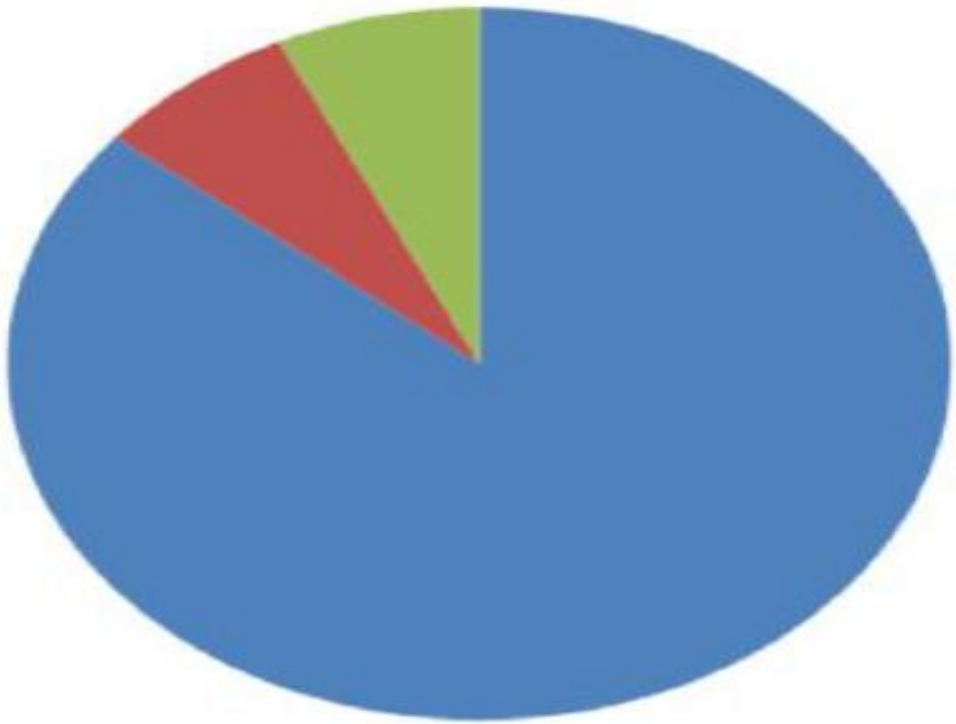
LGI1 AMPA GABA-B MgluR5



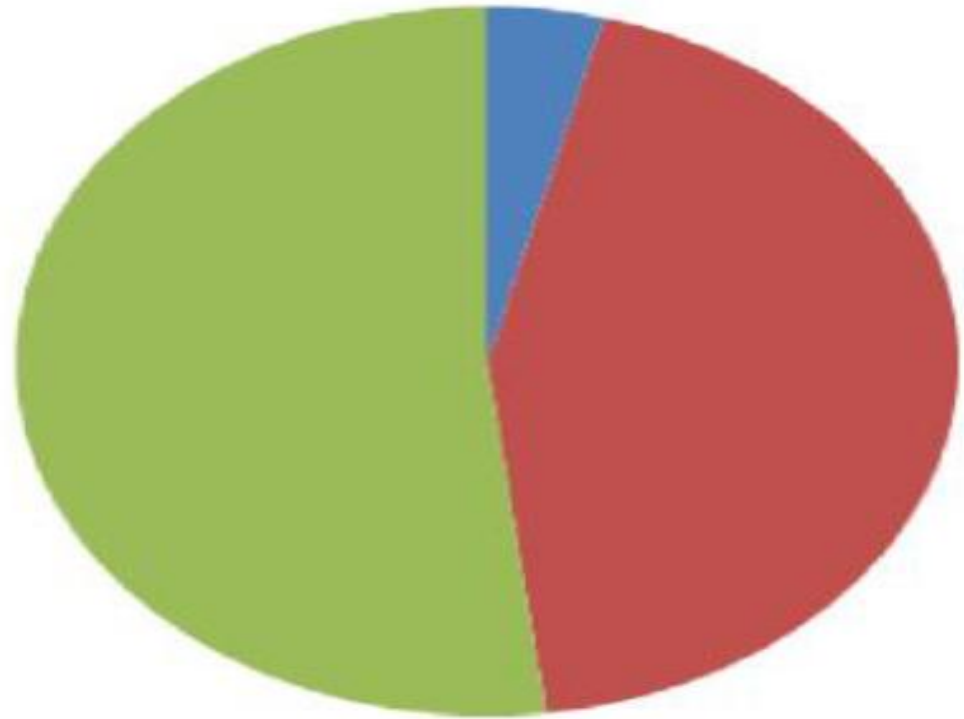
Panels A–C, from Lancaster and colleagues,
panel D from Petit-Pedrol and colleagues

FBDSz Respond Better to Immunotherapy than Anti-epileptic Treatment

Response to AEDs



Response to Immunotherapies



<20%

20 - 50%

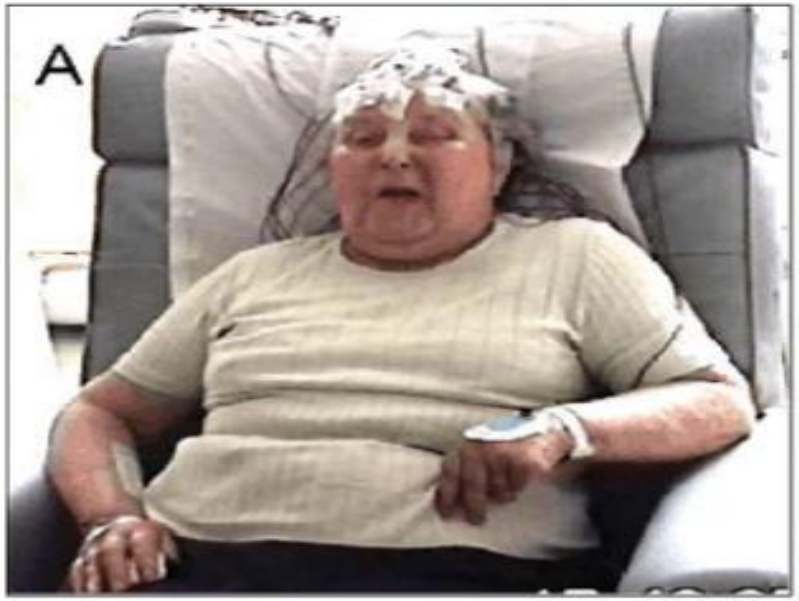
Antibody	Seizure clinical presentation	Seizures	Age	Isolated seizures	Clinical accompaniment	EEG findings
NMDA	Most commonly generalised tonic–clonic seizures followed by focal seizures	70%	21	?	Behavior cognitive movement psychiatric	epileptic 25% EEG "extreme delta brushes"
LGI1	FBDS 35% CPS 50% Simple partial 40% PDS 15% piloerection 6%	80%	65	10-20% - especially FBDS at early stage	Limbic encephalitis hyponatremia	14% positive initial EEG 50% epileptic at some point temporal activity

Antibody	Seizure clinical presentation	Seizures	Age	Isolated seizures	Clinical accompaniment	EEG findings
CASPR2	CPS 37% Secondary genegal 9% no isloated simple partial	50%	66	?	Cognitive decline Psychiatric hyperexcytability	45% epileptic
GABA-B	CPS and secondary generalization. 20% Status epilepticus	90%	62	5%	Limbic encephalitis Cognitive decline	40% epileptic
GAD 65	90% CPS some with secondary generalization 10% simple partial	10-20%	27	30% (out of seizures)	SPS Ataxia cognitive decline encephalitis	Temporal origin 75%, 48% uni and 52% bilateral.

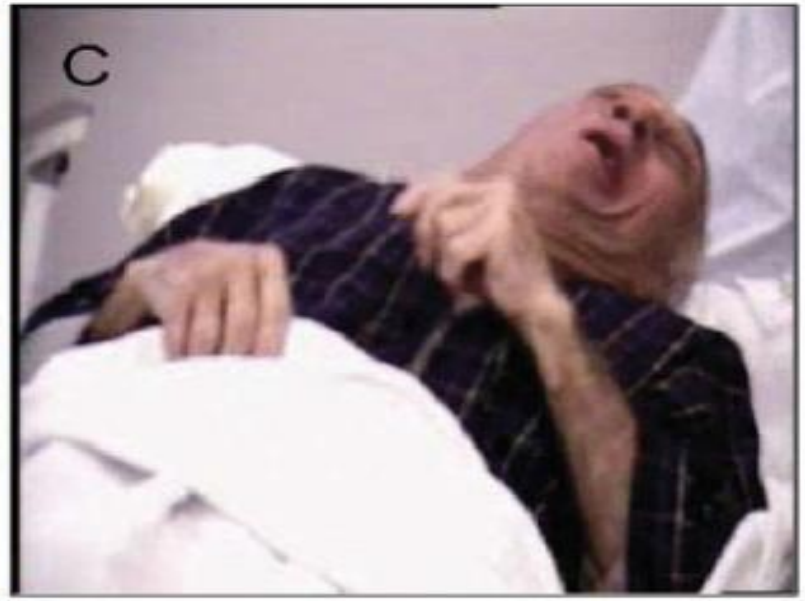
Faciobrachial Dystonic Seizures

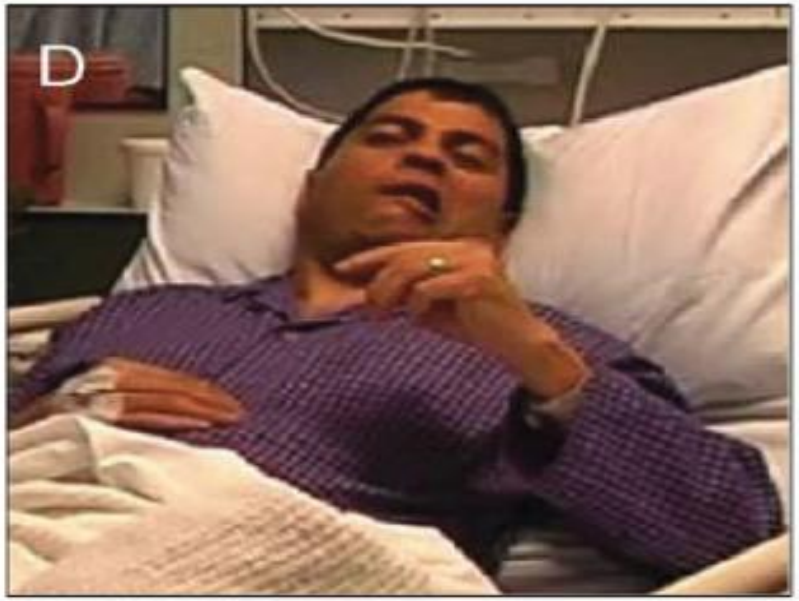
- Dystonic posturing in hand often with ipsilateral facial grimace
- Lasts seconds
- Multiple times per hour
- May be initial manifestation
- Usually not evident on scalp EEG
- LGI1 subtype of VGKC autoantibodies
  - LGI1 knockout mice develop dystonia
  - LGI1 mutations cause AD partial epilepsy with auditory features

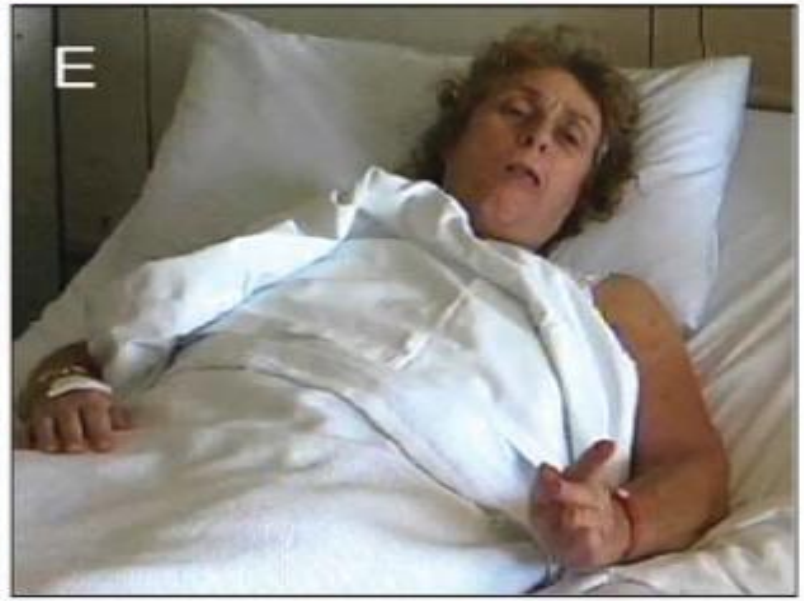
Irani et al. Ann Neurol 2011
Irani et al. Brain 2012
Kalachikov et al. Nature Genetics 2002

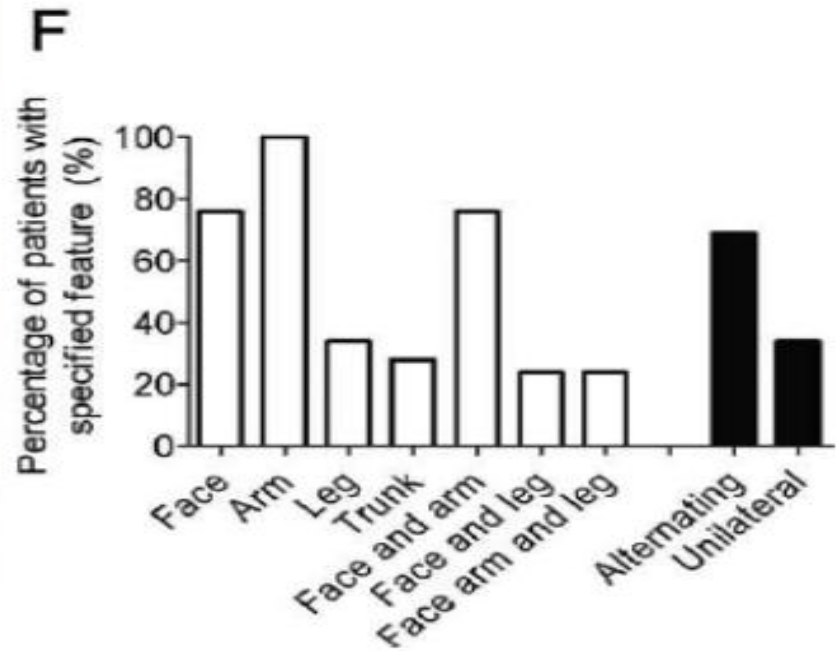

A


B


C


D


E


F
Percentage of patients with specified feature (%)
100
80
60
40
20
0
Face
Arm
Leg
Trunk
Face and arm
Face and leg
Face arm and leg
Alternating
Unilateral

Isolated autoimmune epilepsy

- Common seronegative
- CSF findings – diverse – protein, OCB
- Very resistant to AED
- Diverse MRI findings
  - Normal
  - Post seizure
  - Temporal lobe
- Seizure type

Clues to Autoimmune epilepsy

- Age of onset
- Temporal origin
- Multiple times per day
- Very resistant to AED
- Accompanying symptoms
- MRI findings – positive or negative
- CSF – WBC, protein, OCB
- Specific – FBDS, PDS, piloerection, Anxiety, Delta brush

Take home message

- Autoimmune epilepsy is real - Level of suspicion
- Seronegative cases
- CSF findings are variable
- MRI – variable
- Repeat testing – MRI, EEG
- AED resistant

EEG Features of Autoimmune Epilepsy

- About 80% Autoimmune epilepsy (AE) patients showed abnormal EEG. A normal EEG does not rule out the possibility of AE
- EEG findings of AE
  - Poorly sustained posterior dominant rhythm (PDR)
  - Generalized or focal slow activity (could be rhythmic)
  - Interictal epileptic discharges (unilateral, bilateral, multifocal, or periodic)
  - EEG seizures
  - Different EEG onset patterns were related to different seizure types
- EEG features of AE could change along with disease progression

Britton JW. Handbk of Clin Neurol, Vol. 133 (3rd ser) Autoimmune Neurology, S.J. Pittock , A. Vincent, Eds, 2016
Limotai C, et al. Epilepsy Behav. 2018; 84:29-36.

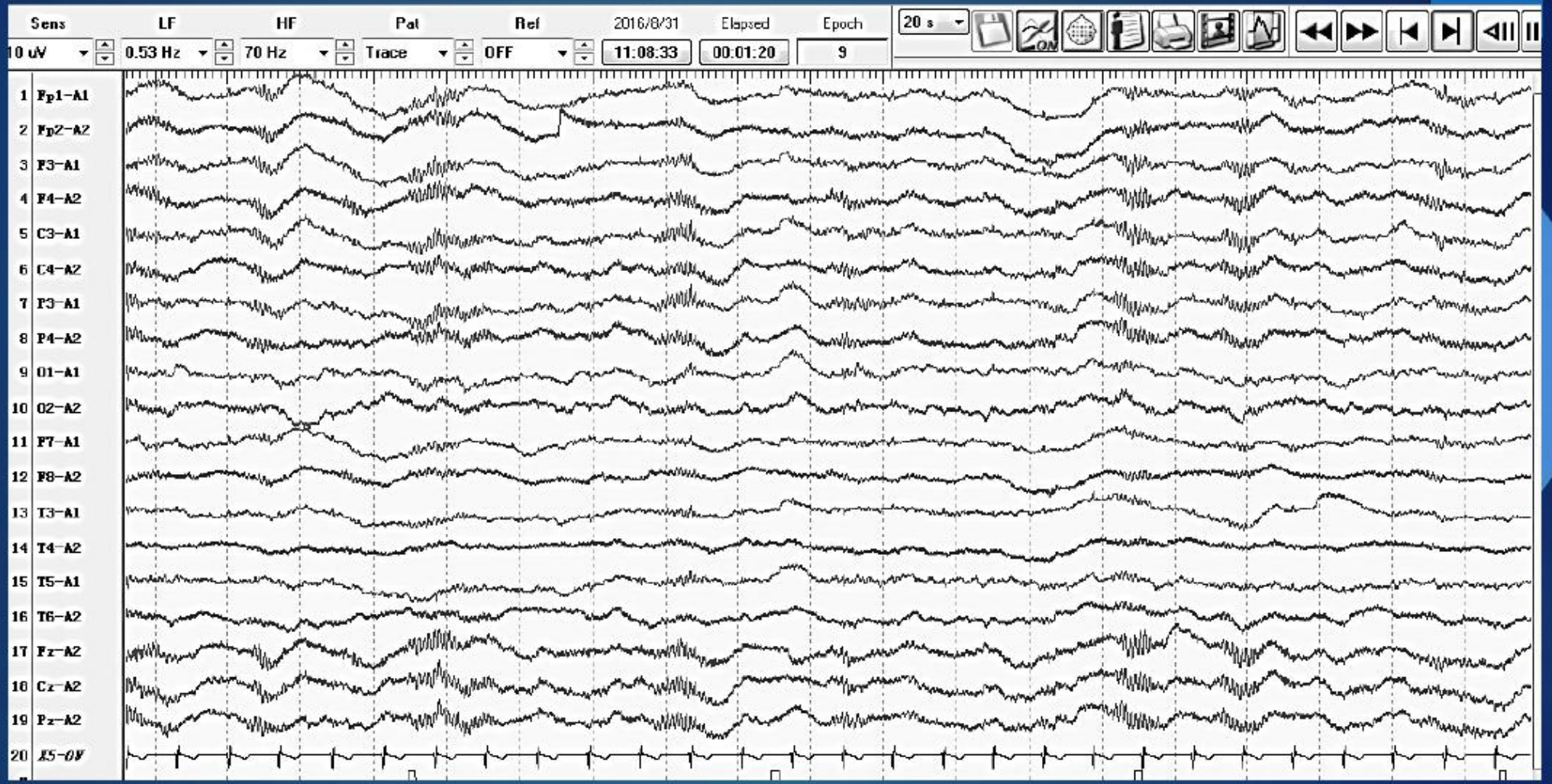
EEG features of NMDAR

- Most commonly seen in children and adolescent，especially in NICU
- EEG manifestations may vary. A study included 23 NMDA-R antibody positive cases, who accepted EEG monitoring in hospital and the EEG showed
  - Generalized rhythmic delta activity（47.8%）
  - Severe diffuse slowing（39%）
  - Focal slowing（34%）
  - Extreme delta brush（EDB）（30%）：EDB is a unique EEG pattern for anti-NMDA receptor encephalitis, which can be observed in severe patients. The presence of EDB is associated with a more prolonged illness

Sarah E. Schmitt. Neurology, 2012,79:1094-1100

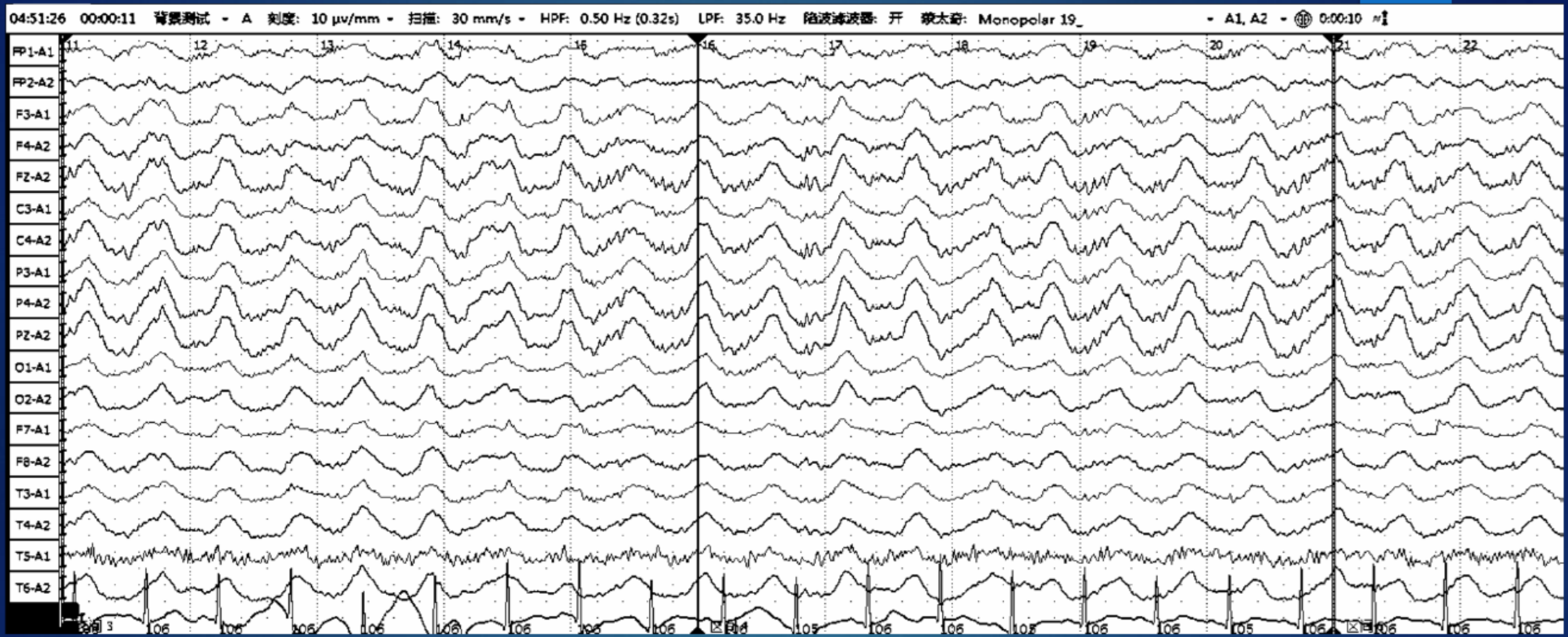
Extreme Delta brush

Diffuse rhythmic δ activities superimposed intermittent bursts of fast activities

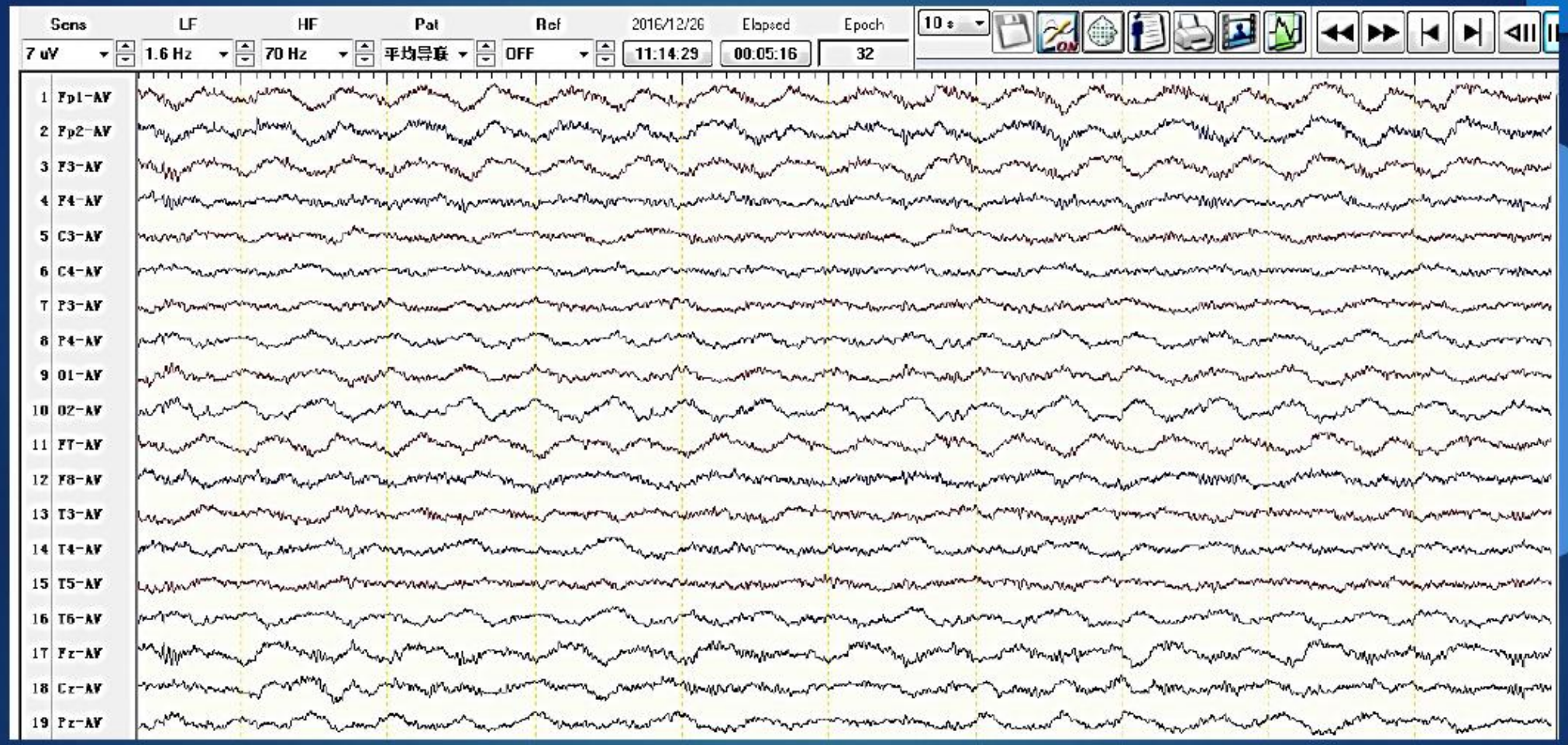


Male, 21y, epileptic seizure and psychiatric symptoms lasting for 2 weeks. Stupor and hypoxemia 1 week after hospital admission. The EEG showed above was recorded about 40 days after onset.

Generalized delta activity



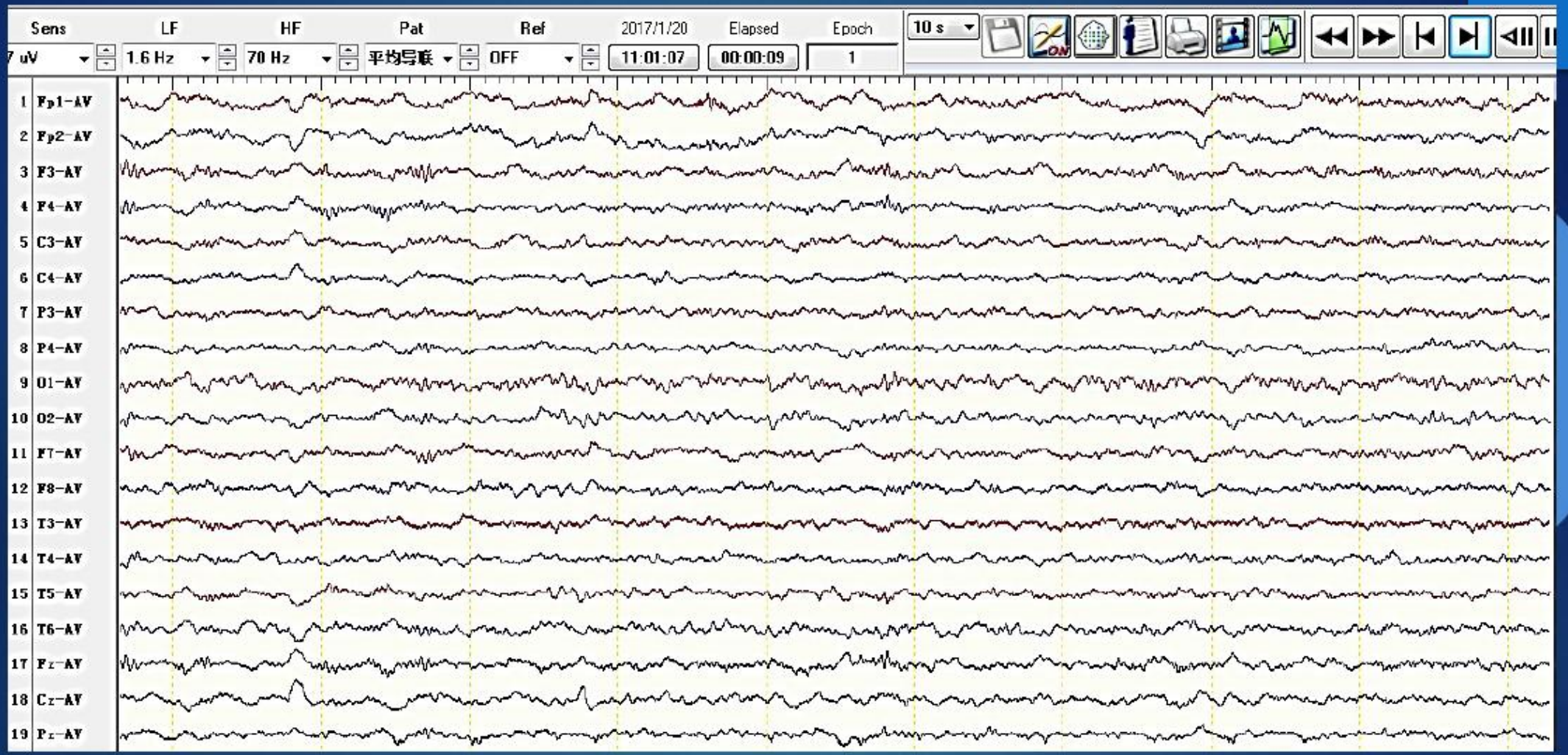
Bilateral rhythmic delta activity



Female, 31y, epileptic seizure and psychiatric symptoms

The EEGshowed above was recorded about 35 days after onset

Same patient

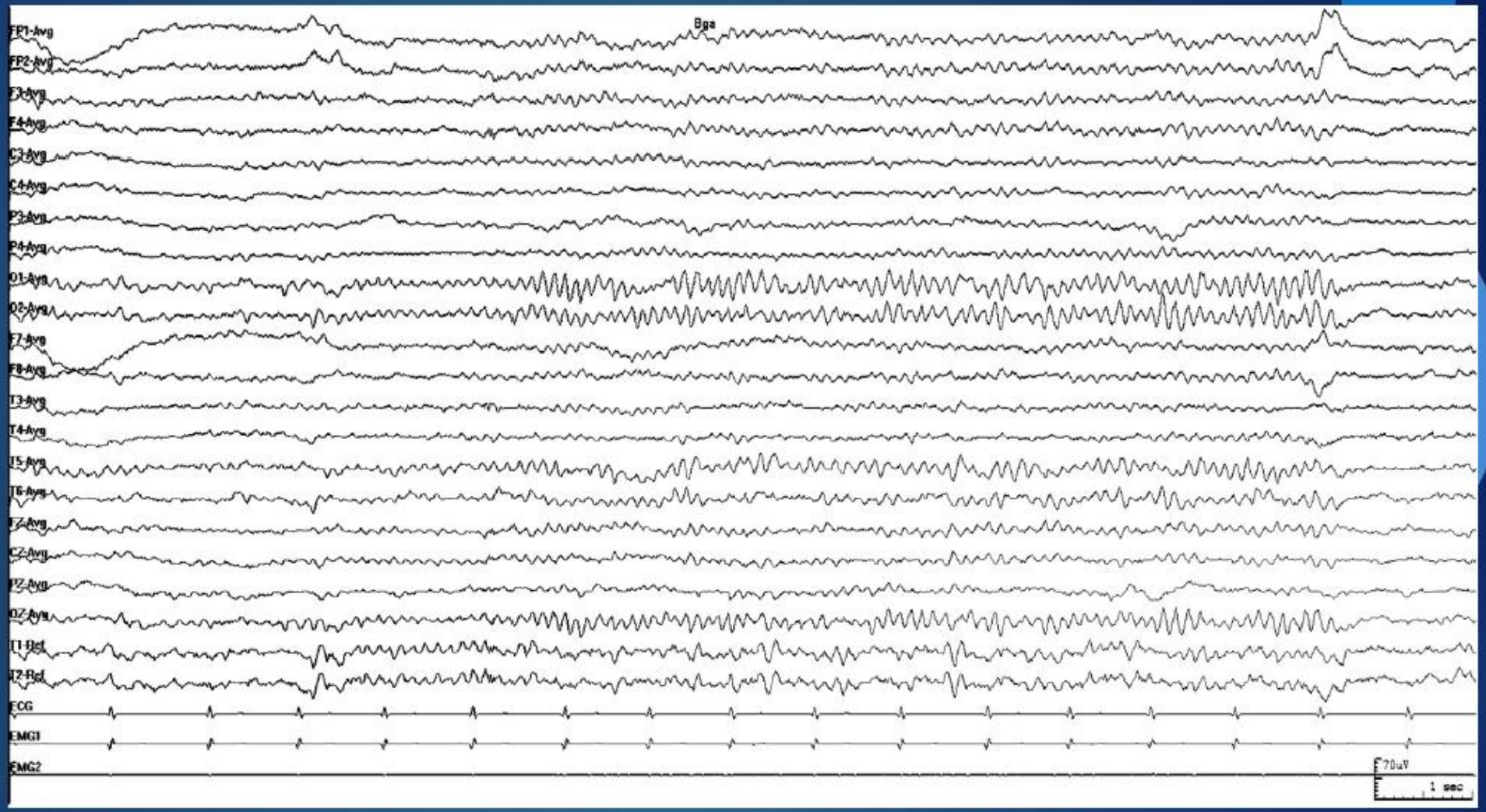


NMDA receptor (NMDAR) antibodies was positive (1:320).

EEGof 60 days after onset showed obvious improvement after IVIG and methylprednisolone pulse therapy was administrated

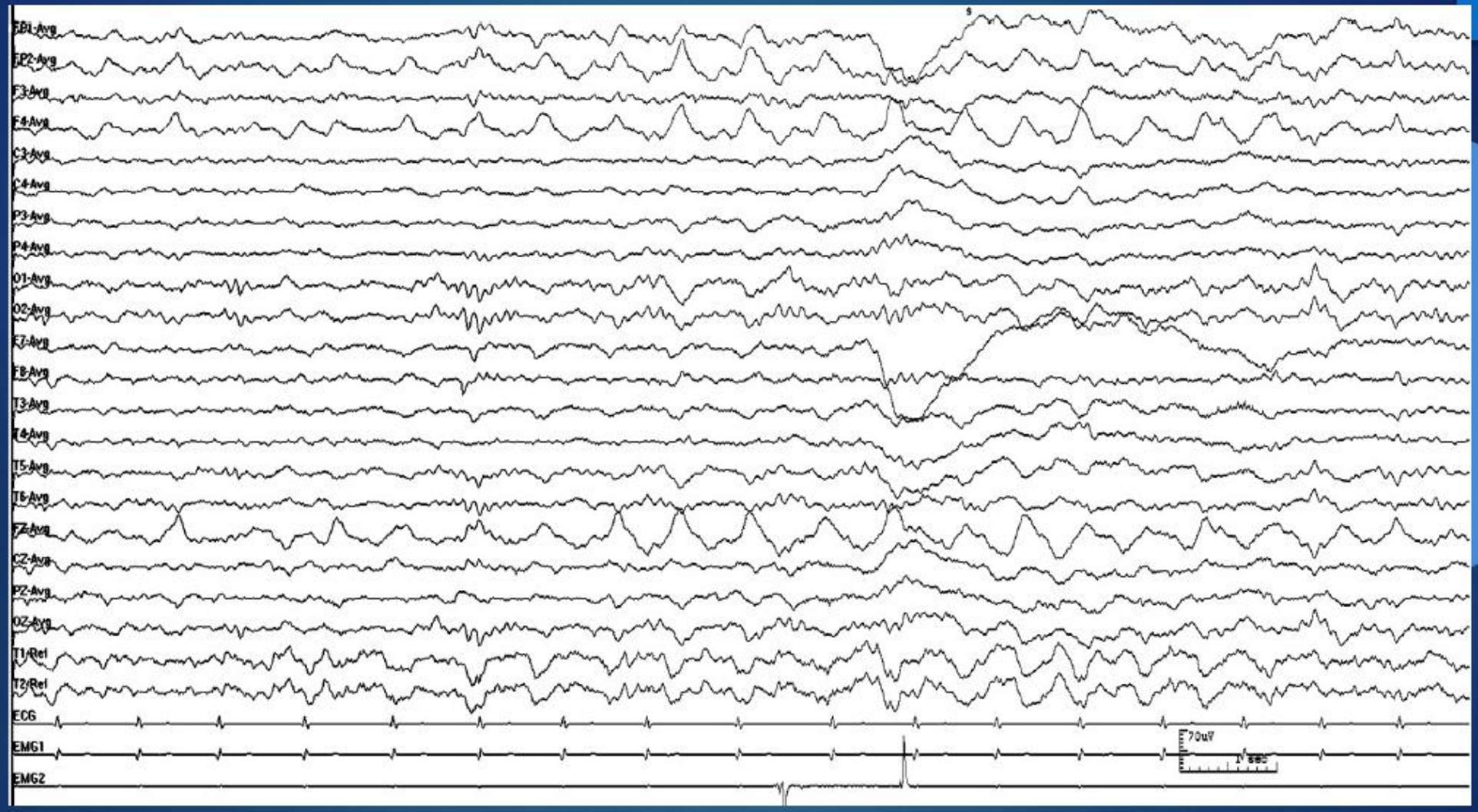
EEG—10 days after initial seizure（2018.5.3）

Normal background

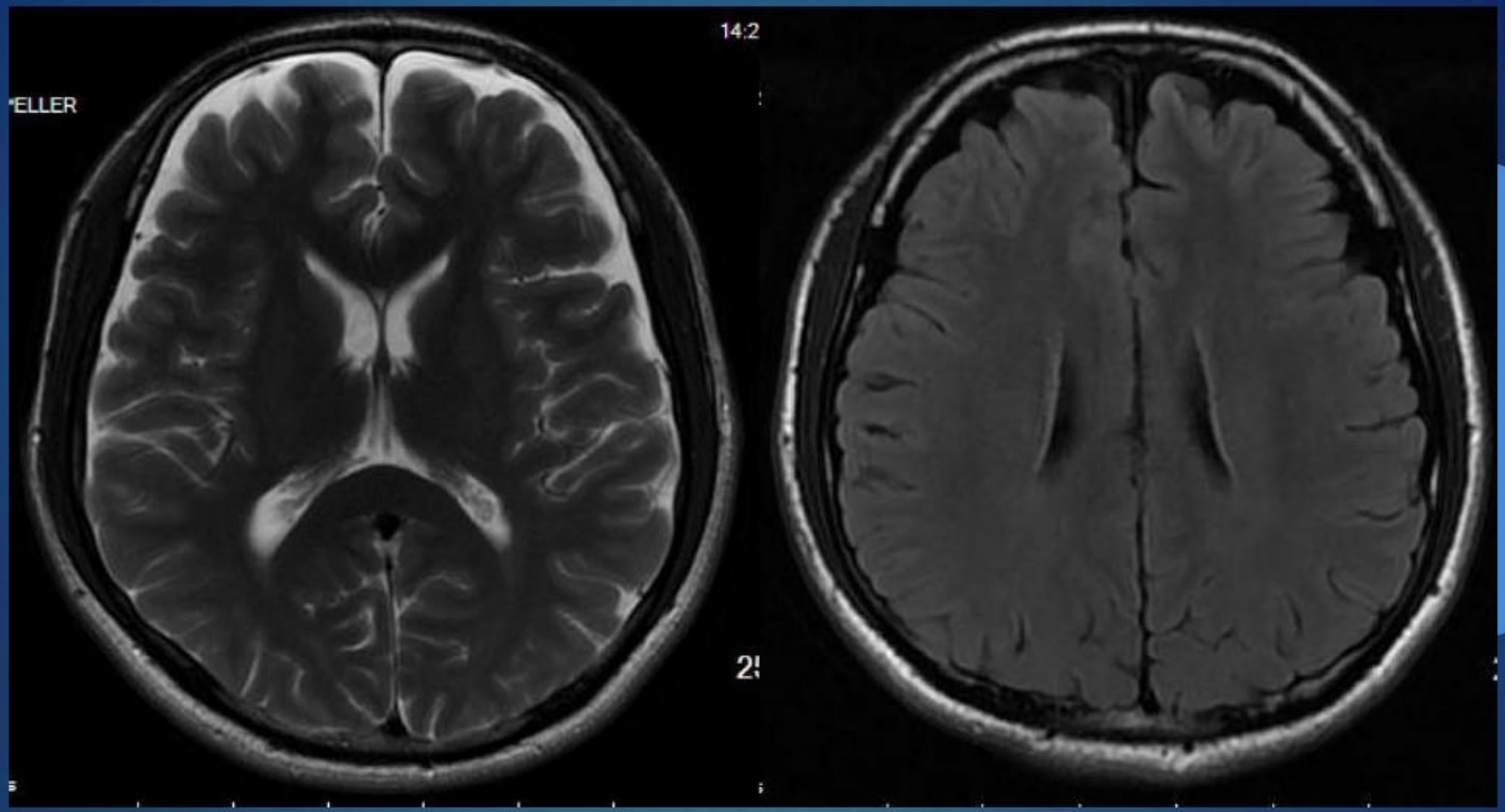


Male, 18y, 2 seizures within 1day in the beginning, no psychiatric symptoms or cognitive decline (MoCA: 30). EEG above was recorded 10 days after onset

EEG—10 days after initial seizure（2018.5.3）



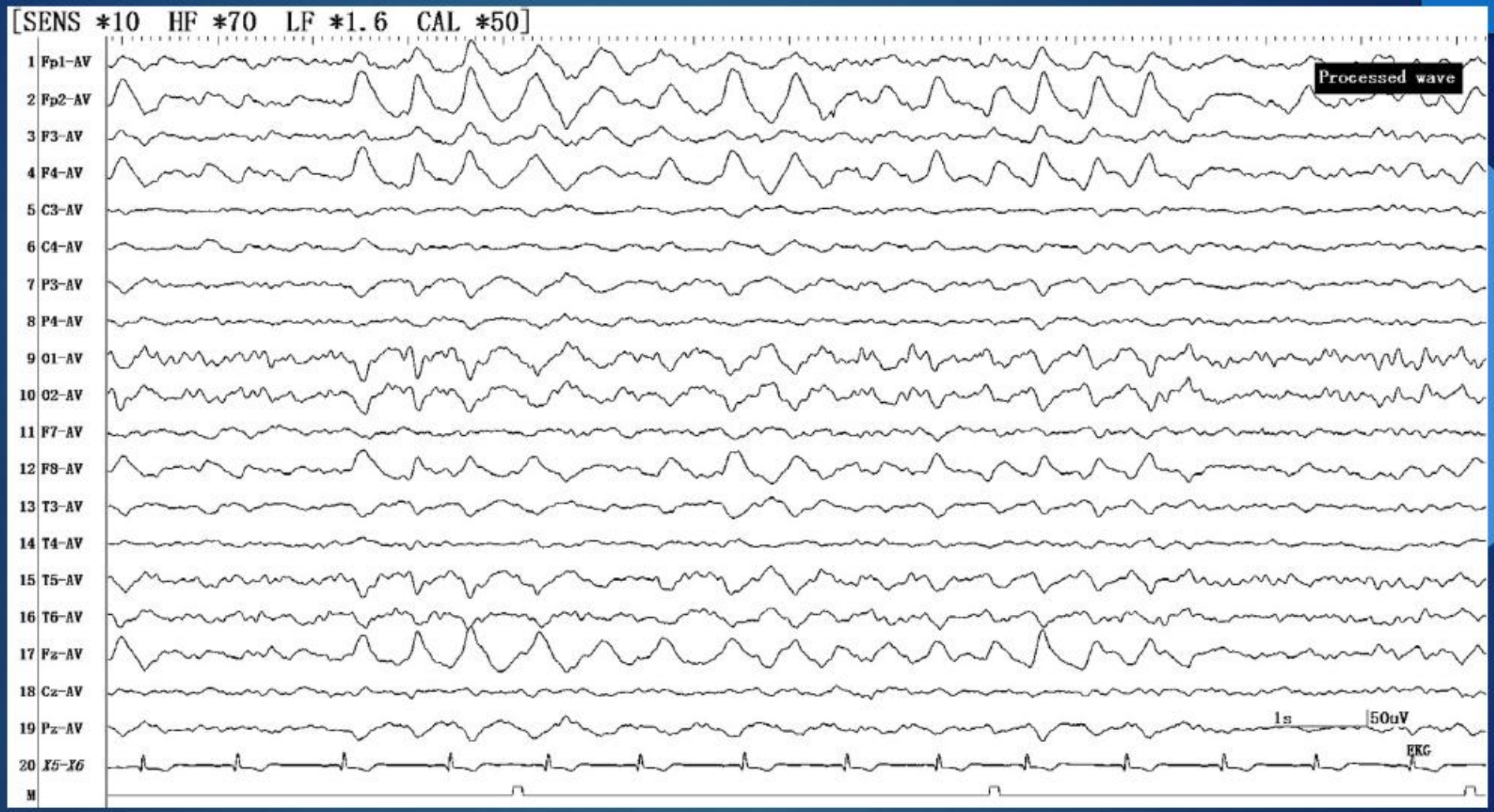
Rhythmic Delta activity in right frontal region



MRI : Normal

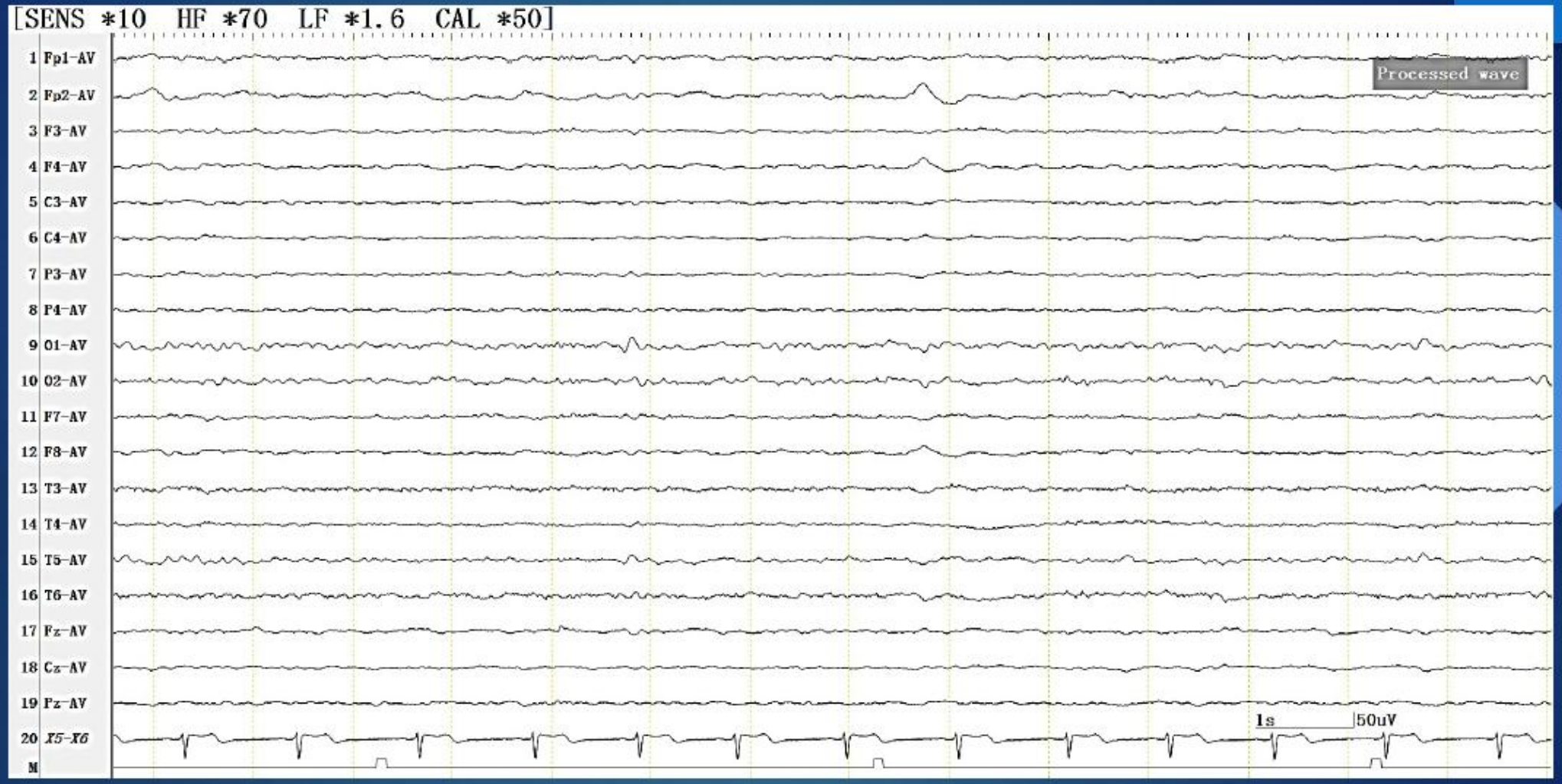
Immunology test : NMDAR antibodies in blood and CSF(1:320)

EEG—22 days after initial seizure（2018.5.15）



Immunotherapy was administrated from this day：Methylprednisolone 1g +IVIG

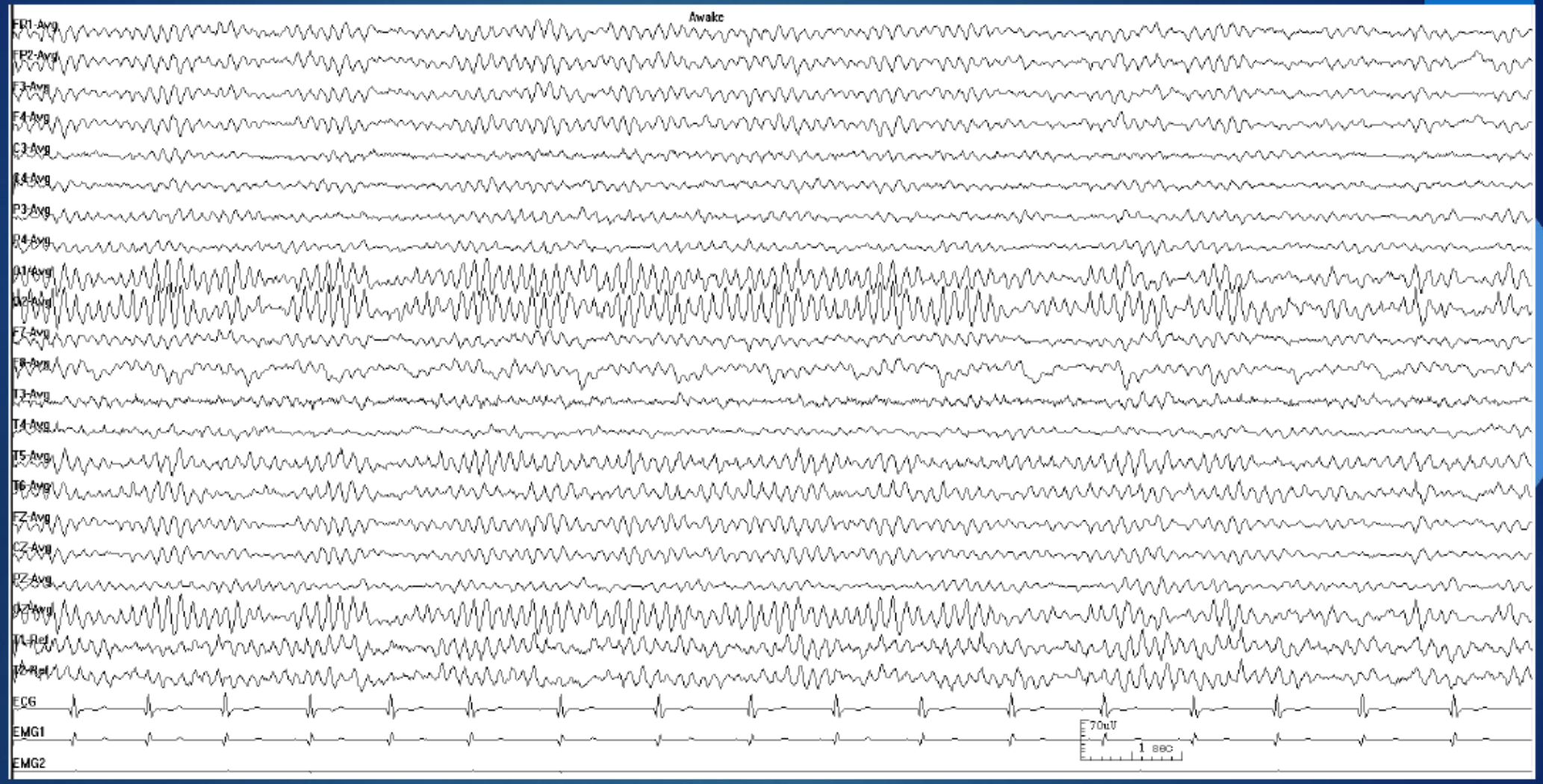
EEG—30 days after initial seizure (2018.5.23)



EEG showed obvious improvement after 8 days treatment

Only occasional sharp wave can be observed in right frontal regions

EEG—3 month after initial seizure (2018.8.9)



Immunotherapy and AEDs have been stopped. EEG was normal.

EEG features of NMDAR

- Ictal EEG patterns：depending on seizure types
  - GTCS
  - Focal seizures
  - Status epilepticus：Convulsive status epilepticus and Nonconvulsive status epilepticus（NCSE）

Dalmau J, et al. Lancet Neurol. 2008;7:1091-1098.

EEGfeatures of LGI1

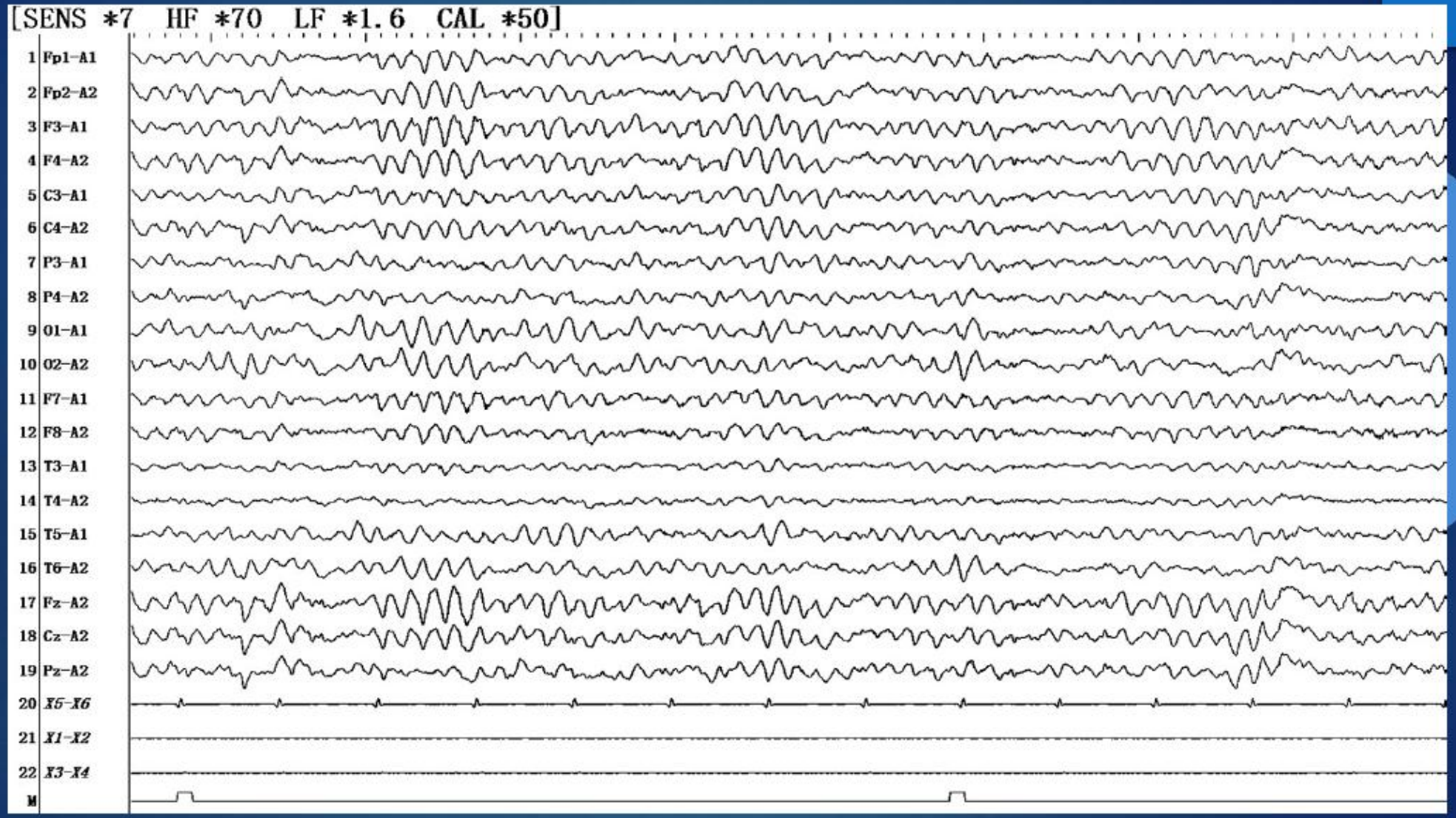
- LGI1 anti-body is most commonly seen in adult epilepsy with autoimmune etiology, especially in focal epilepsy onset in middle age
- Interictal EEG
  - Diffuse slowing
  - Focal slowing
  - Epileptiform discharges (most commonly seen in temporal lobe region, could also be been in peri-sylvian region or multifocal)
  - Periodic discharges
  - normal

EEGfeatures of LGI1

- **Ictal EEGfeatures： depend on different seizure types**
  - **Faciobrachial dystonic seizures(FBDS) is the most characteristic seizure，seen in about 25% patients：only FBDS， periodic FBDS，FBDS plus, etc.**
  - **Focal seizures：**
    - **Mainly manifested as temporal lobe seizures, but extratemporal seizures and multifocal seizures can also be seen.**
    - **Autonomic seizure (unilateral piloerection or palpitations）**
    - **A brief ascending or descending "wave" passing through their body**
  - **sGTCS：occurred mainly during sleep**
  - **LGI1-antibodies associated focal seizures are very frequent brief events (lasting for a few seconds occuring multiple times per day), which can be accompanied with brief amnesia**

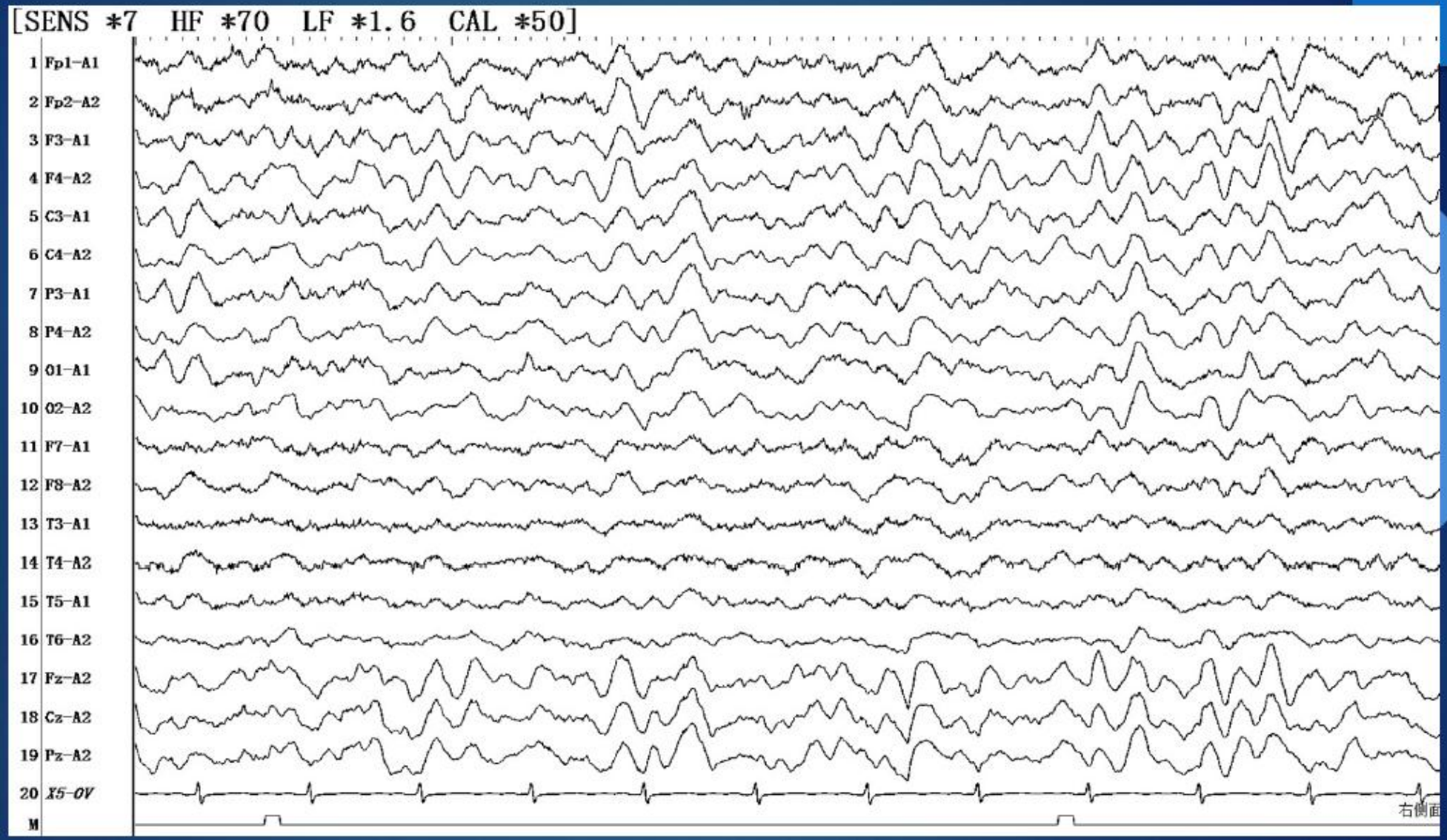
Quek, Britton, Pittock et al. Arch Neurol 2012; 69: 582-93
Lv and Shao et al. Ann Clin Transl Neurol. 2018; 5:208-15
Aurangzeb et al. Seizure 2017;50:14-7

Female, 77y, LGI1(+). FBDS (Left side) and mild memory decline



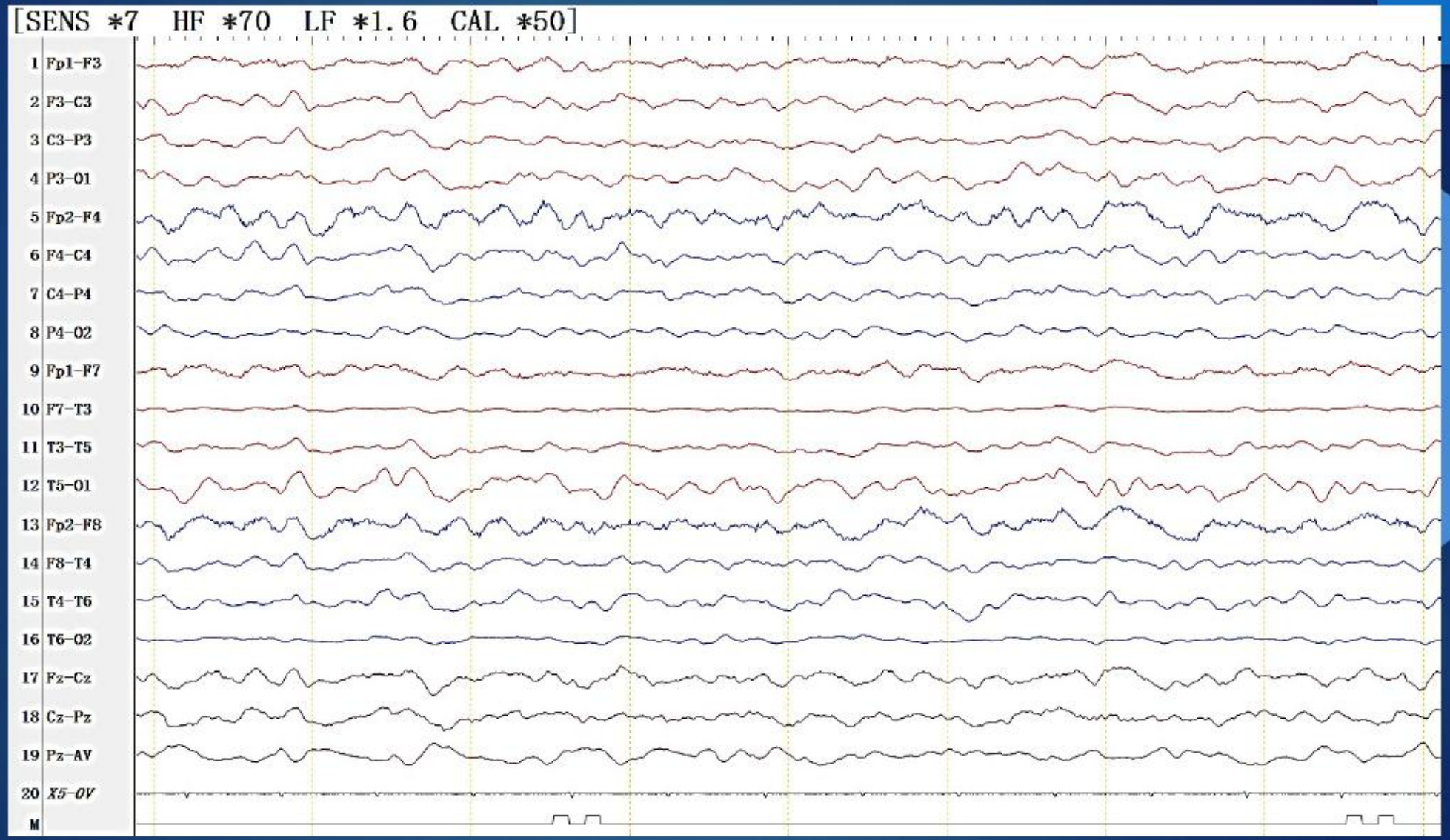
Intermittent theta slow wave

Same patient , one month later, FBDS(Right side)



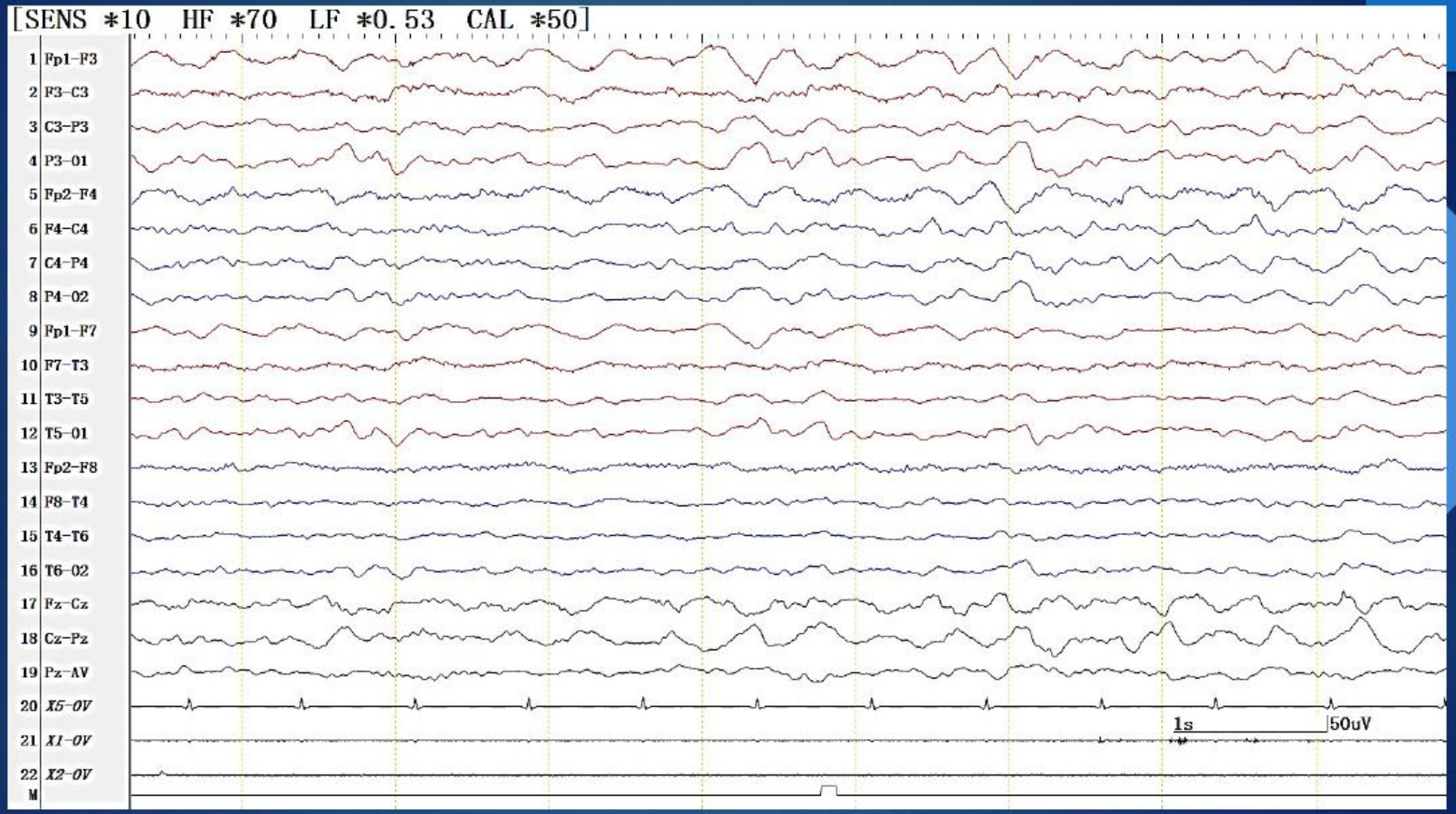
Intermittent delta slow wave

Same patient , one month later, FBDS(Right side)



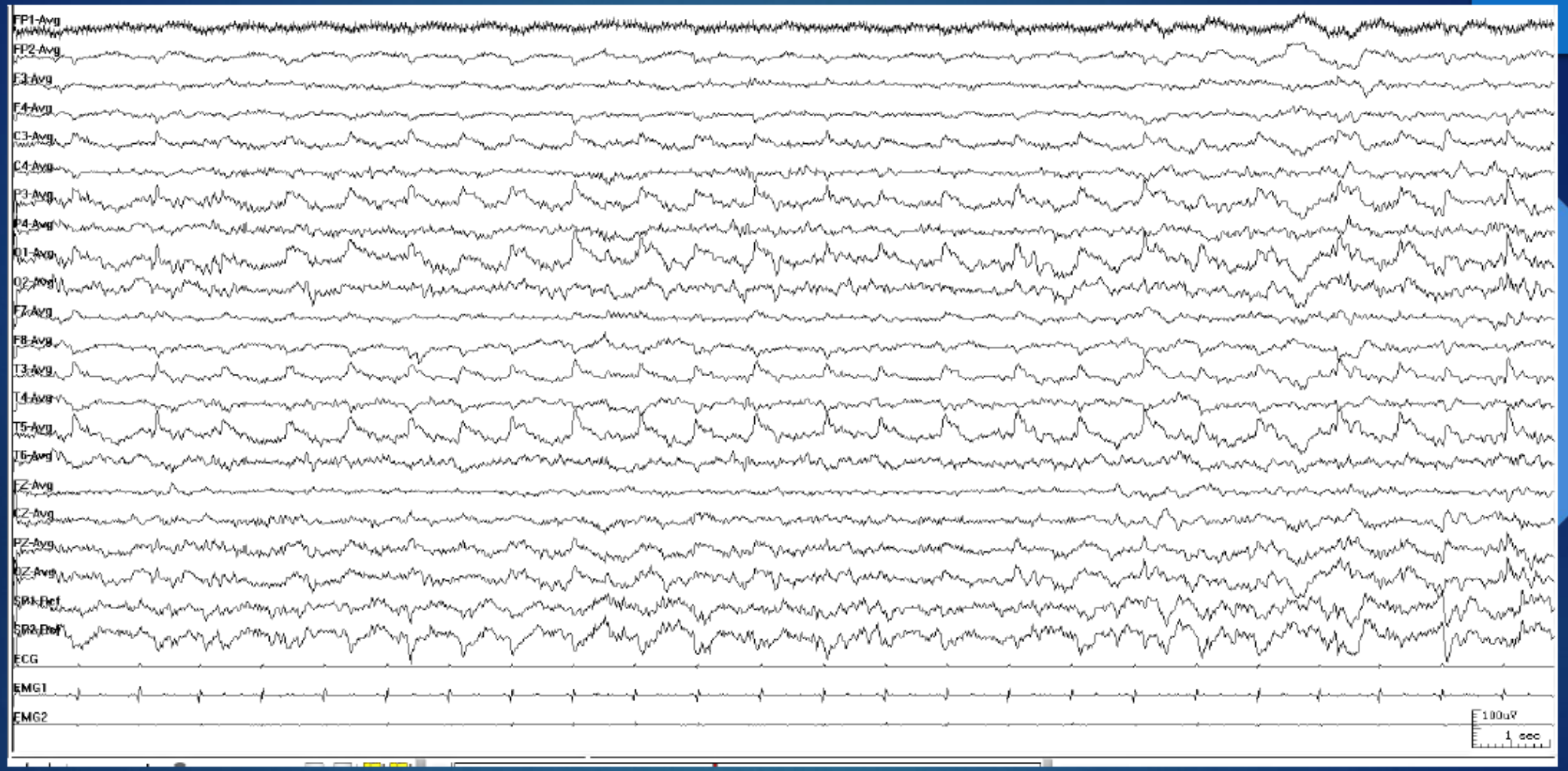
Continuous delta slow wave

Male , 59y , LGI1 (+) , GTCS、 CPS (daily), memory decline and hyponatremia



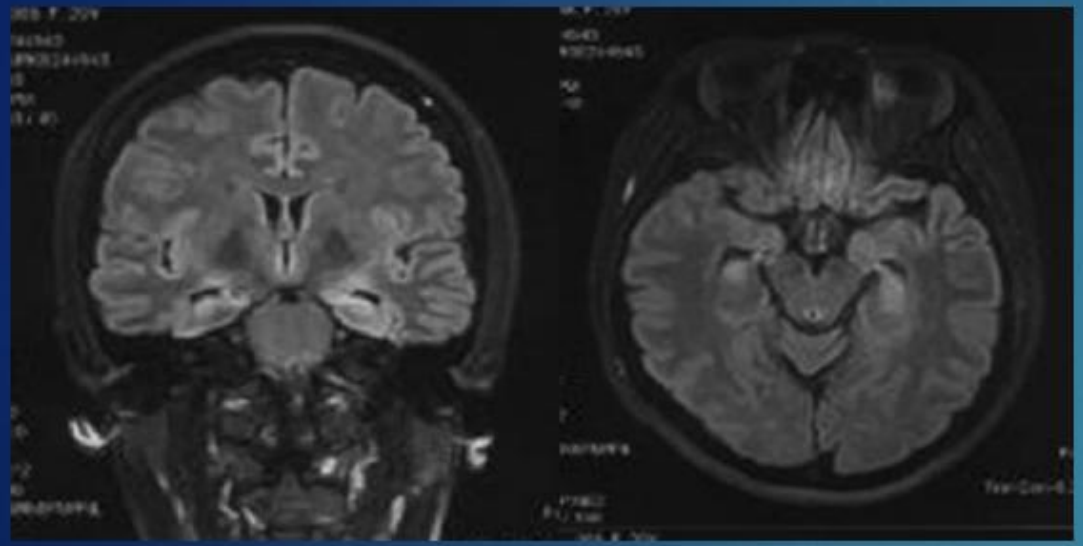
Diffuse slowing

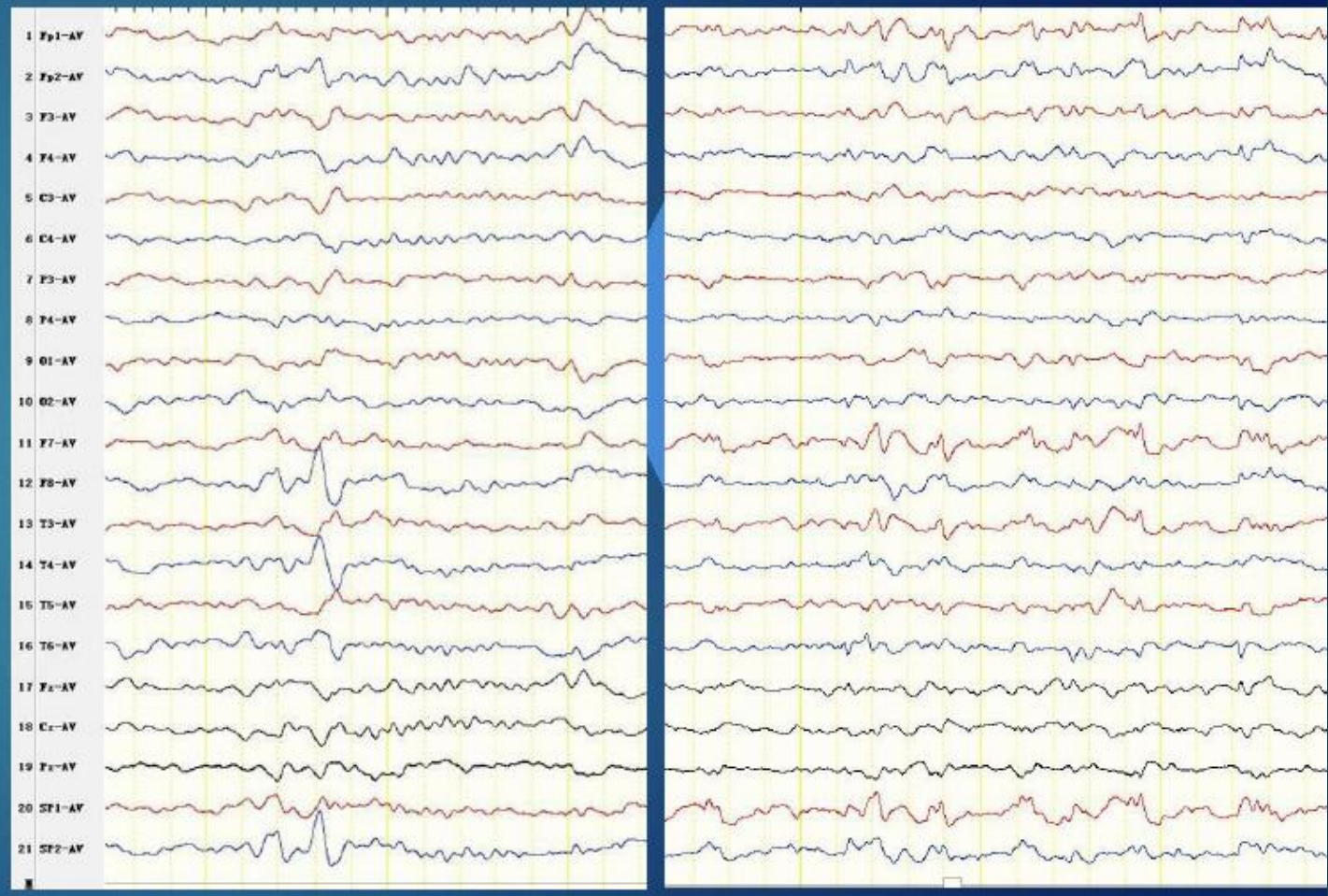
Female, 65y, 2 GTCS during sleep within 2 months, mild memory decline



Periodic discharges

GAD-65





- Female，29 y，medical history（-）
- Semiology: left limbs numbness, sometimes stepping，lasting for about 1 minute，1-2/day
- Stiff-person syndrome（EMG confirmed）
- Blood and CSF GAD-65 positive（high titer)

EEG seizures

- EEG seizures was not uncommon in autoimmune epilepsy. Routine EEG can be normal and long-term EEG monitoring is better able to capture abnormal EEG activity
  - NMDA：60.8%（14/23）with EEG seizures
  - LGI1: 18%（7/38）with EEG seizures（our unpublished data）
  - GABA-B: 28.5%(2/7) with EEG seizures（ our unpublished data ）

Sarah E. Schmitt. Neurology, 2012,79:1094-1100

Summary

- Extreme delta brush (EDB) is a unique EEG pattern for anti-NMDAR antibody encephalitis, which can be observed in about 30% patients. The presence of EDB is associated with a more severe and prolonged illness.
- Generalized Delta, diffuse delta and focal delta activity can be observed in AE , especially in patients without corresponding neuroimage abnormalities (neuroimaging and EEG mismatch). When other differential diagnosis were excluded and AE diagnosis was considered, patients should undergo immunological testing as soon as possible

Summary

- Except that FBDS is the characteristic seizure of LGI1, temporal lobe seizure and peri-sylvian seizure are also common in AE. Compared with other etiologies, AE related seizures are extremely frequent (daily) and brief (lasting for a few seconds)
- EEG seizures are common in AE, especially in patients with NMDA, LGI1 and GABA-B antibodies. When EEG showed frequent EEG seizures with temporal and peri-sylvian distributions, AE should be considered

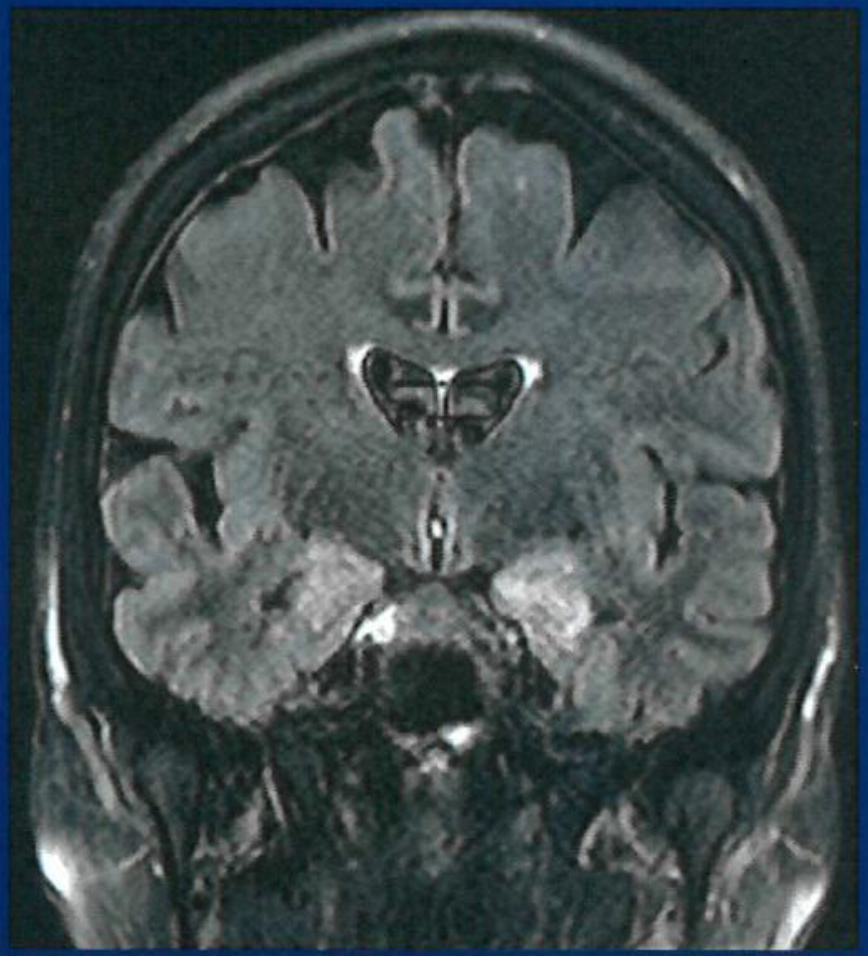
Lisa Gillinder, et al.Epileptic Disord 2017; 19 (4):439-49

Schmitt SE,et al. Neurology. 2012;79:1094-1100.

Questions

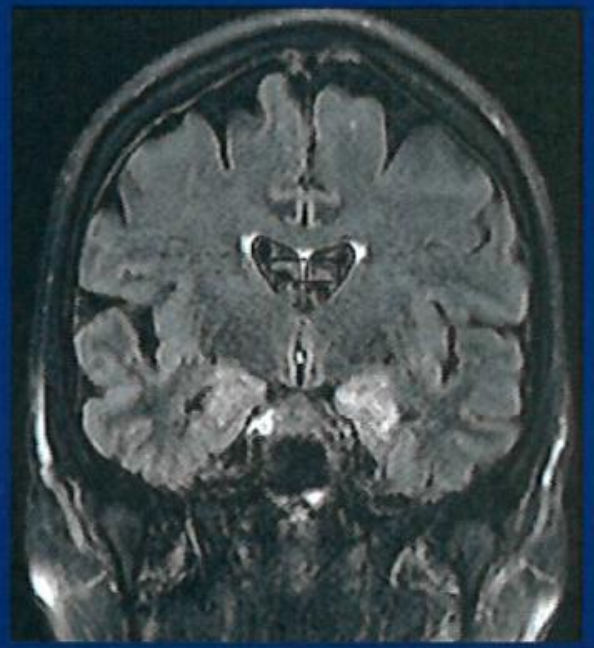
- Which interictal EEG pattern is unique for autoimmune encephalitis or epilepsies ?
  - Extreme delta brush (EDB)
- Which interictal characteristic EEG findings should be aware of the epilepsies with autoimmune etiology ?
  - Generalized Delta, diffuse delta and focal delta activity , especially in patients without corresponding neuroimage changes
- Which seizure semiology and ictal EEG pattern should be aware of the epilepsies with autoimmune etiology ?
  - FBDS
  - Frequent and brief temporal lobe seizure or perisylvian seizure
  - Frequent EEG seizures with temporal lobe or perisylvian onset

Limbic Encephalitis



Diverse autoantibody associations

- Memory, mood, personality changes, seizures: limbic encephalitis
  - ANNA-1, 2 (anti-Hu, Ri)
  - CRMP-5 IgG
  - Lgi1, CASPR2 IgGs
  - GAD65 Ab (High titer)
  - AMPA, GABA-B receptor Abs
  - mGluR5 Ab
  - Seronegative



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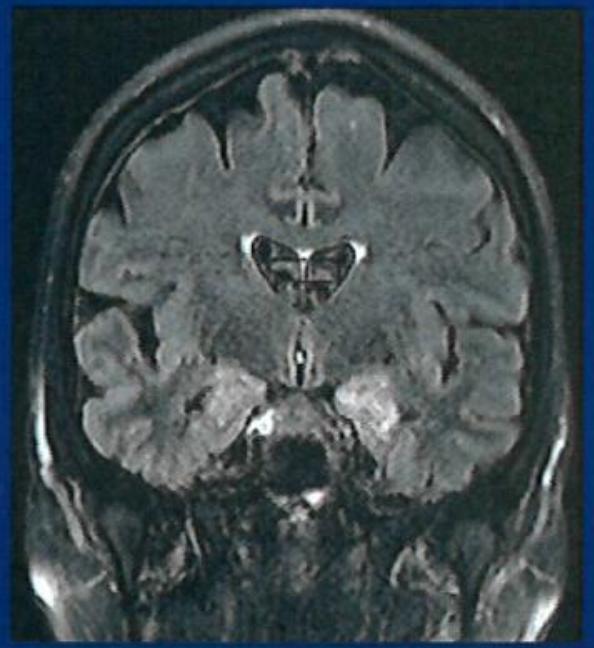
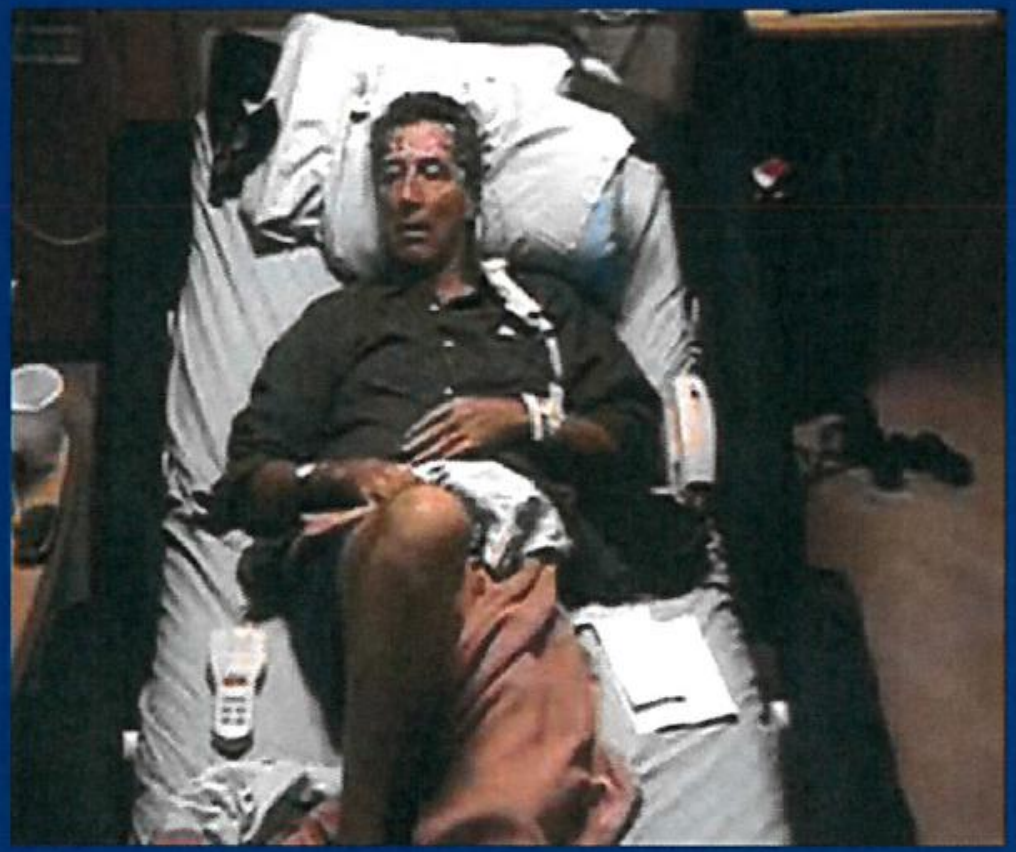
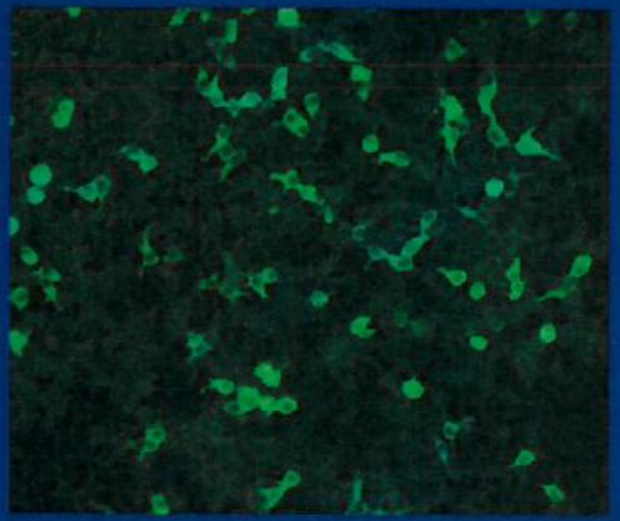


Arm and face posturing spells



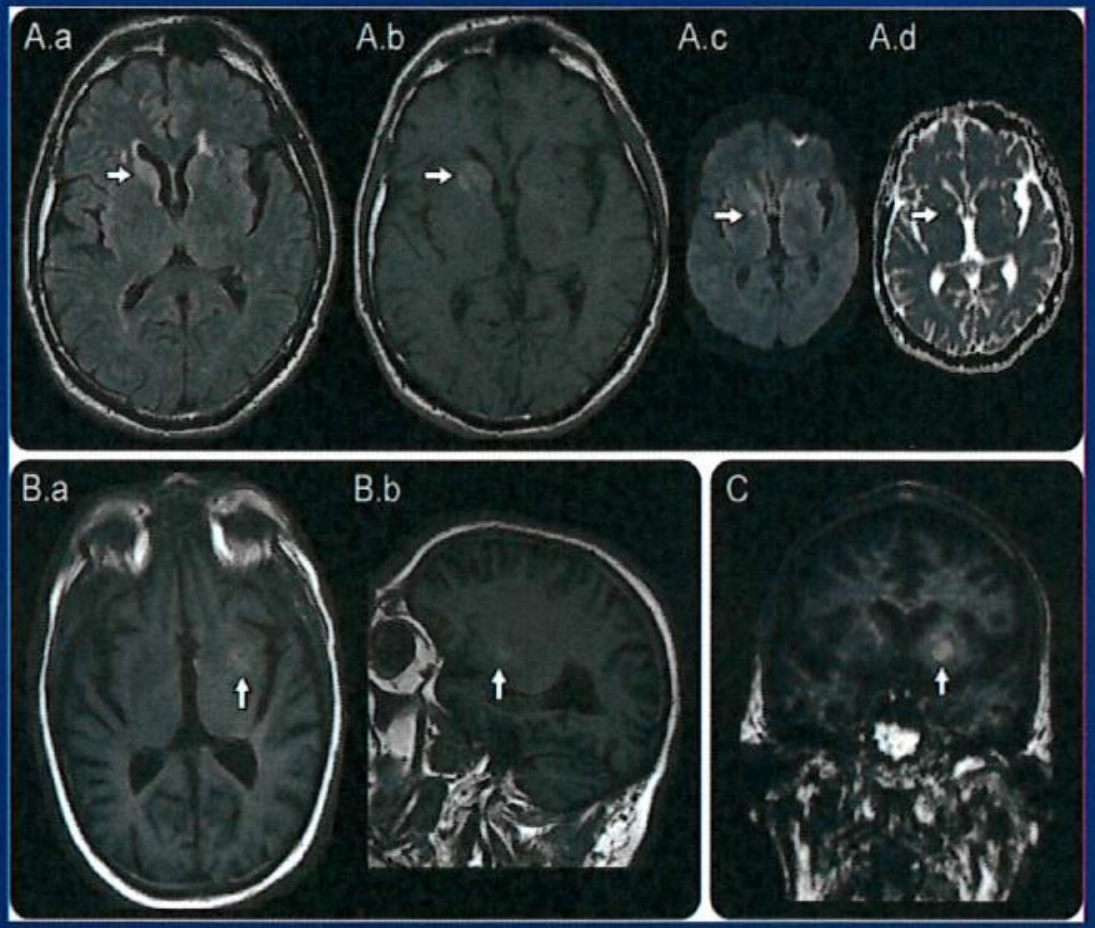
Lgi1 Encephalitis

- Seizures
- Encephalopathy
- Mood disturbance
- Steroid/IVIg-responsive
- Thymoma (rare)



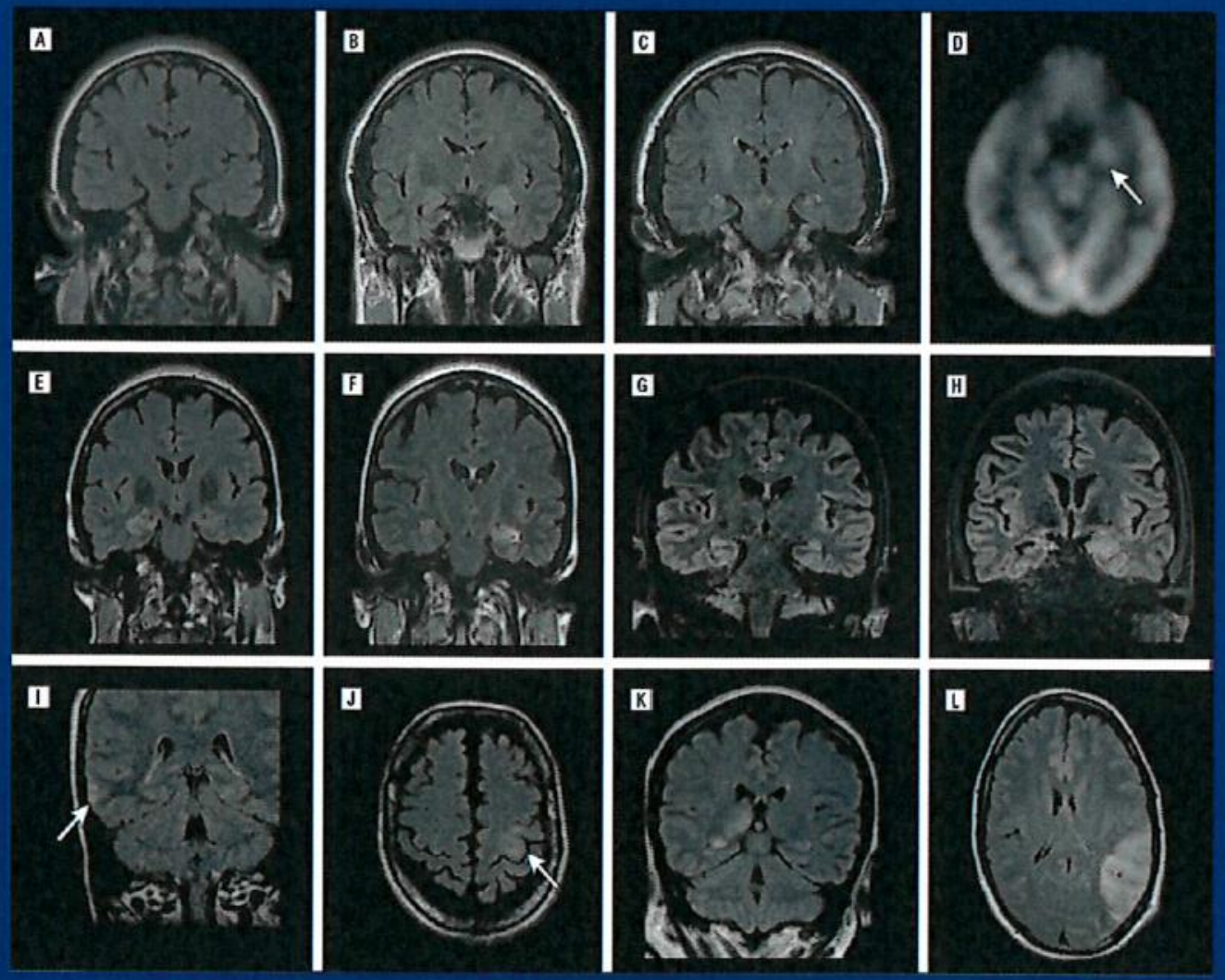
Irani et al, Ann Neurol 2011
Gadoth et al, Ann Neurol 2017

Lgi1 Encephalitis



Flanagan et al. Neurol Neuroimmunol Neuroinflamm 2015

Not Just Limbic!



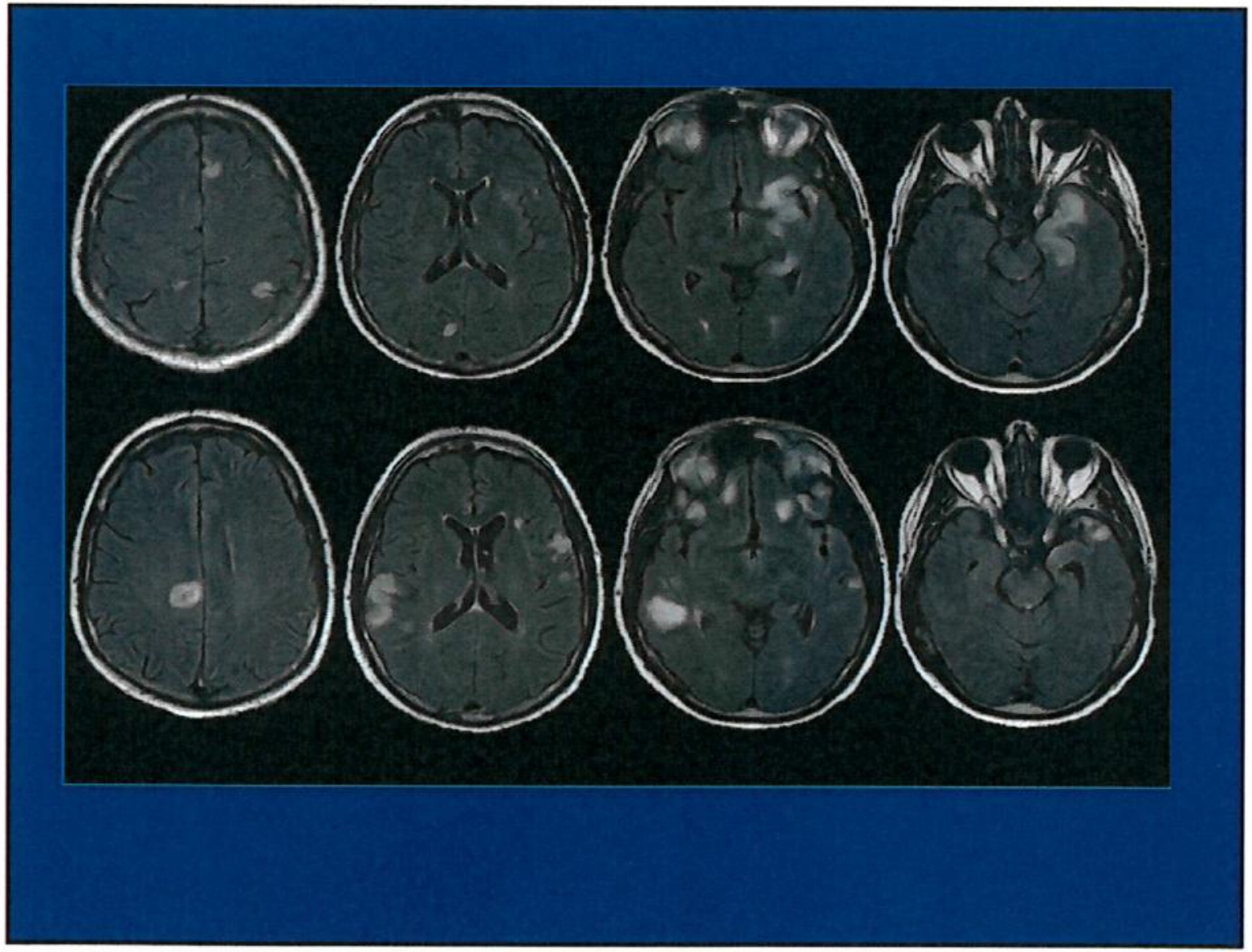
NMDA-R Encephalitis

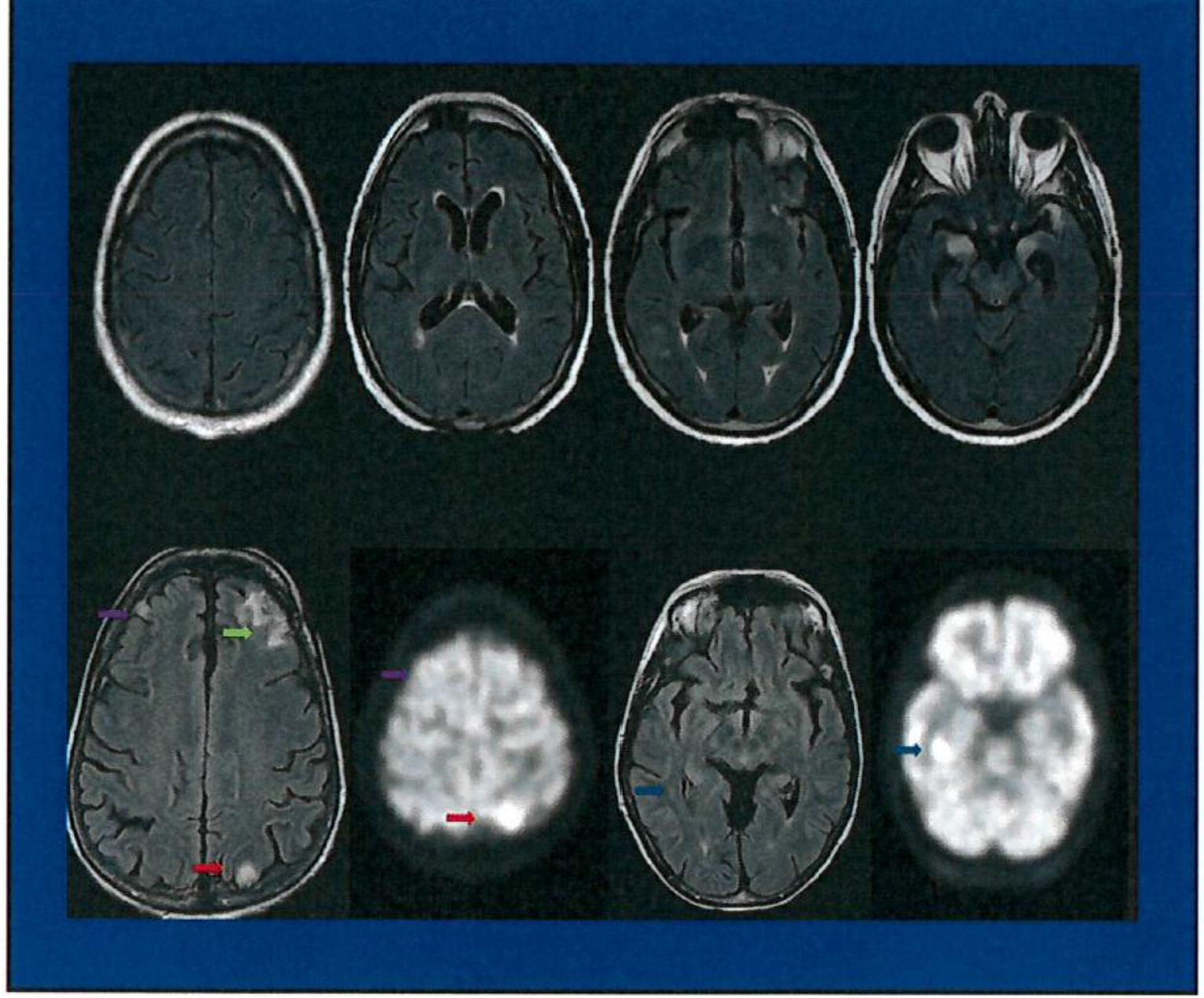
- Stereotyped course:

Psych ⟶ seizures, encephalopathy
⟶ movement disorder, dysautonomia
⟶ hypoventilation+coma

- F>M
- 50% have ovarian teratoma
- CSF testing: more sensitive and specific
- Treatment: steroids/IVIg or PLEX/rituximab/cyclophosphamide
- 80% get to mild or no disability

Titulaer, Lancet Neurology 2013





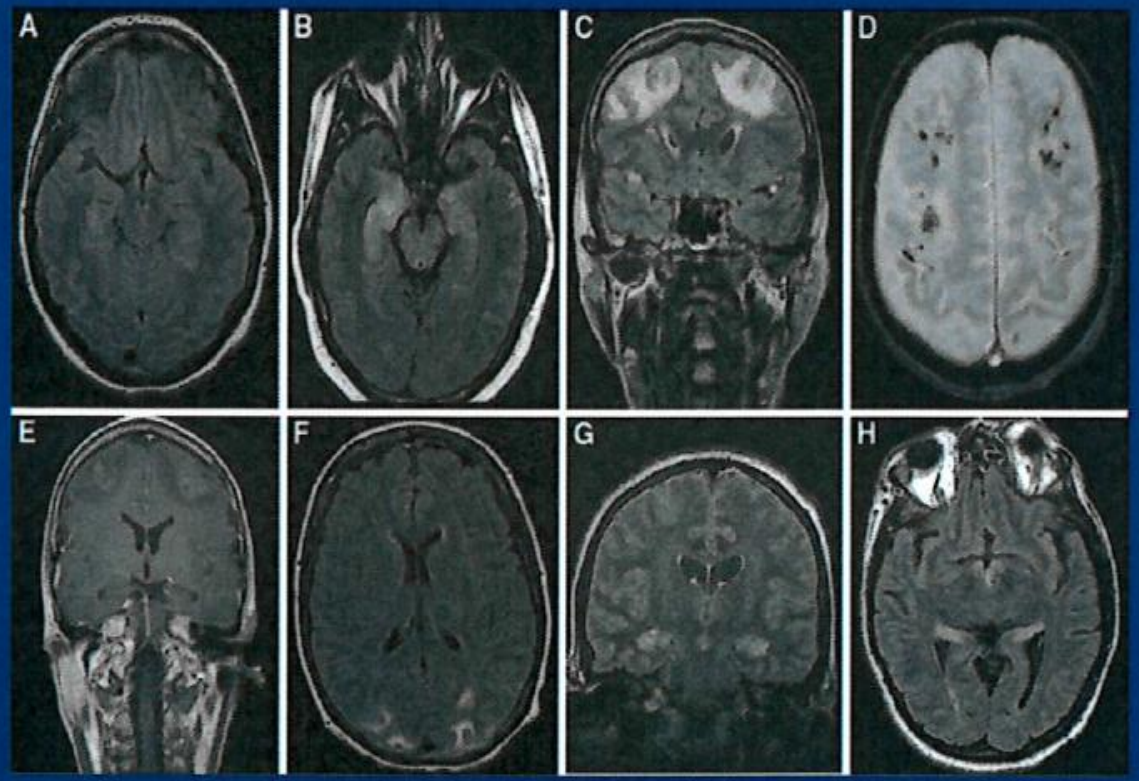
$GABA_A$ Receptor Encephalitis

- Multifocal encephalitis
- Seizures
- May occur in children ('NMDA-R Ab negative')
- Thymoma or other cancer association in adults
- Immune therapy responsive (steroids, IVIg, plasma exchange, rituximab)
- May relapse

Spatola et al, Neurology,2017

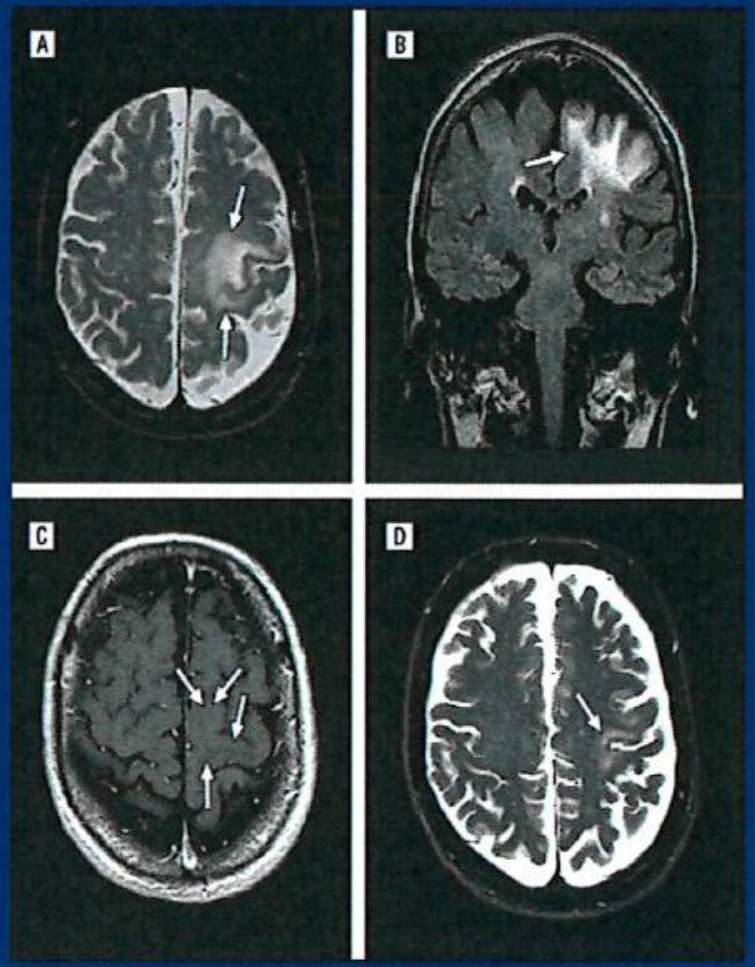
O'Connor et al, N2, 2019

In the ICU: from normal to limbic & beyond



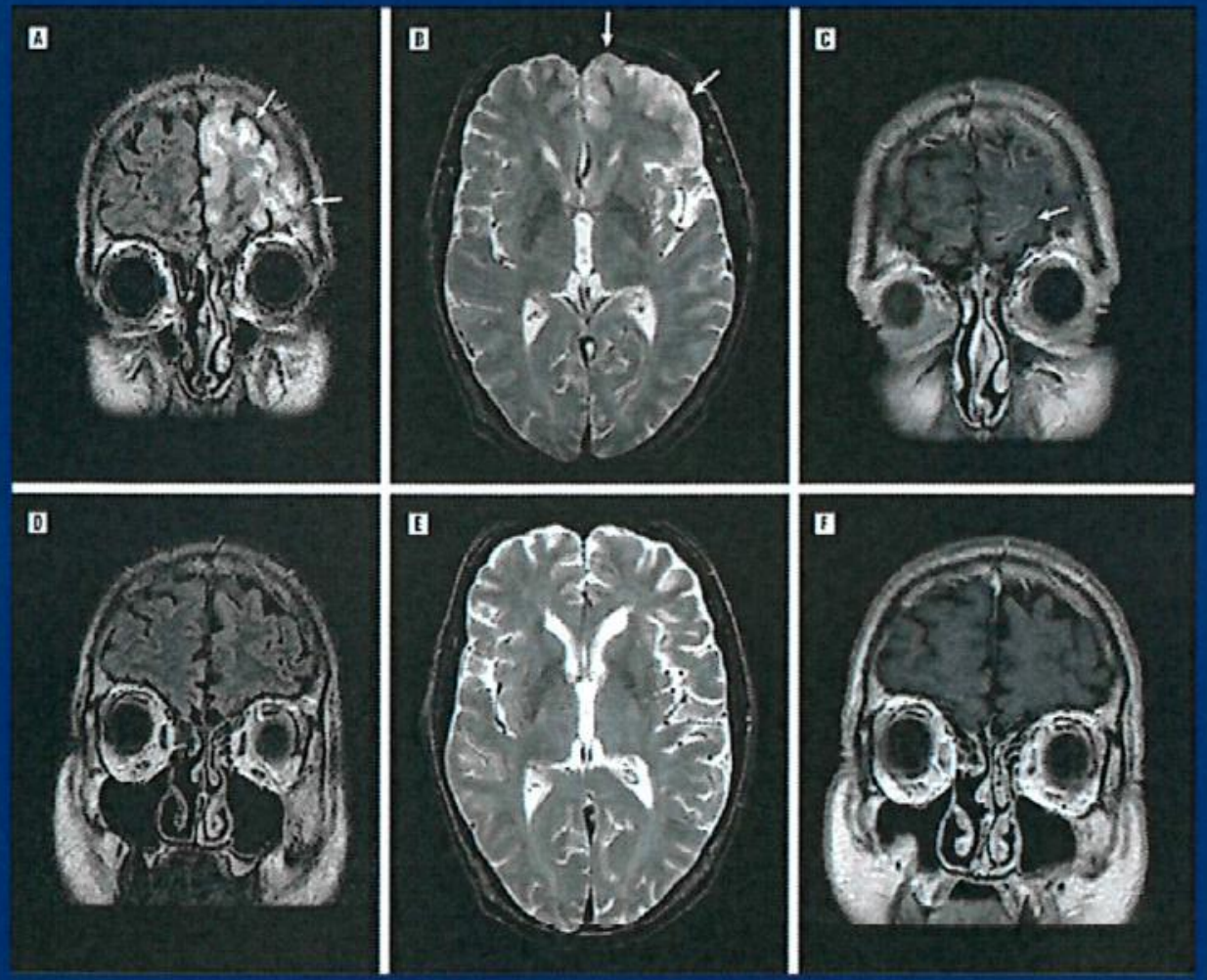
Mittal et al, Neurocritical Care 2016

EPC & Breast Cancer



McKeon et al, Arch Neurol 2009

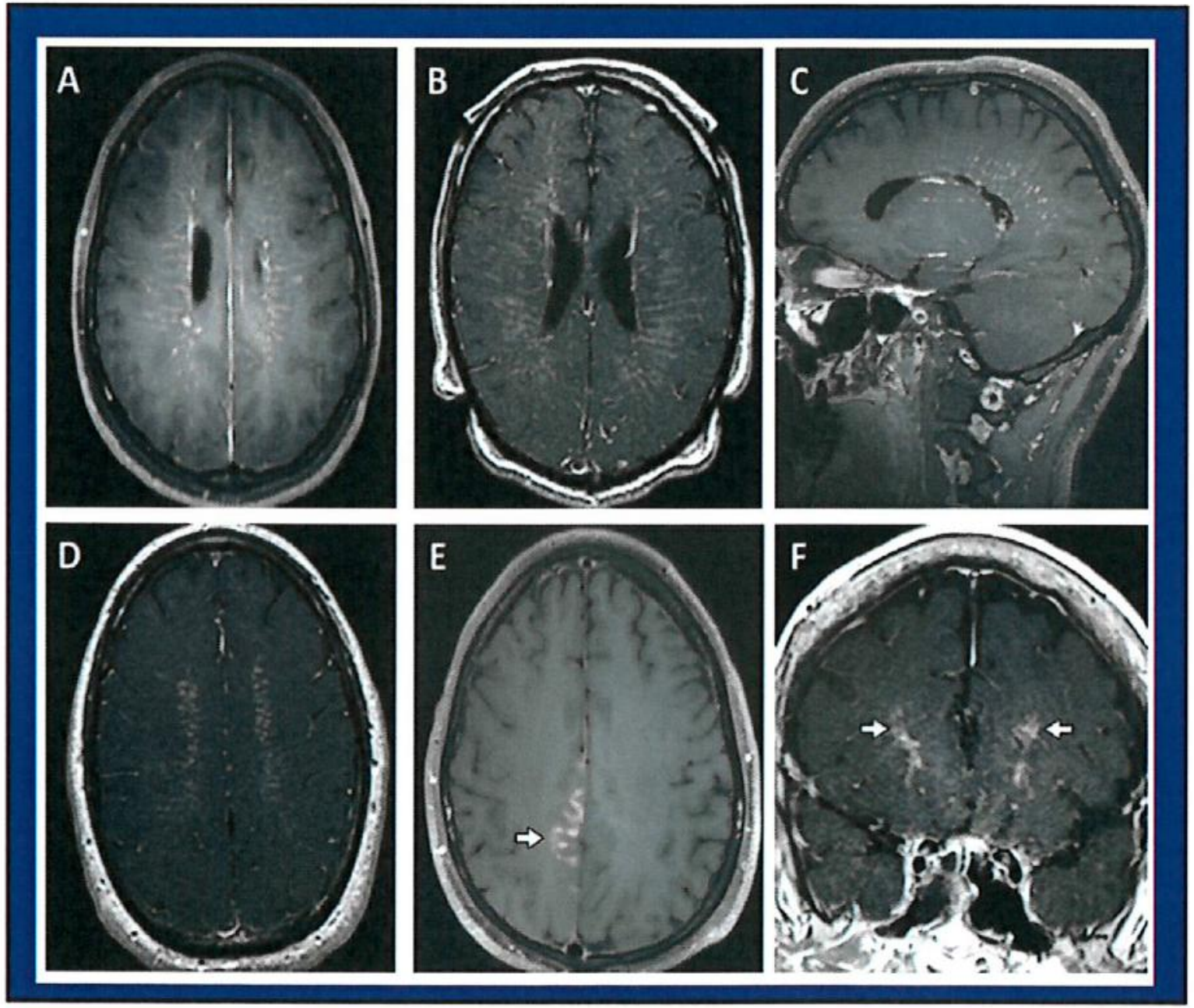
Extra-limbic paraneoplastic encephalitis with ANNA-1



Paraneoplastic Encephalitis with Seizures

- ANNA-1 (Hu), ANNA-2 (Ri), Ma1/Ma2, MAP1B (PCA-2), Amphiphysin-IgG, CRMP-5 IgG, SOX-1 (AGNA)
- Search for cancer
- Do not have good responses to steroids, IVIg or plasma exchange
- General approach:
- Oncological therapy (surgery, chemotherapy, radiation therapy)
- Cyclophosphamide

McKeon, Curr Treat Options Neurol, 2013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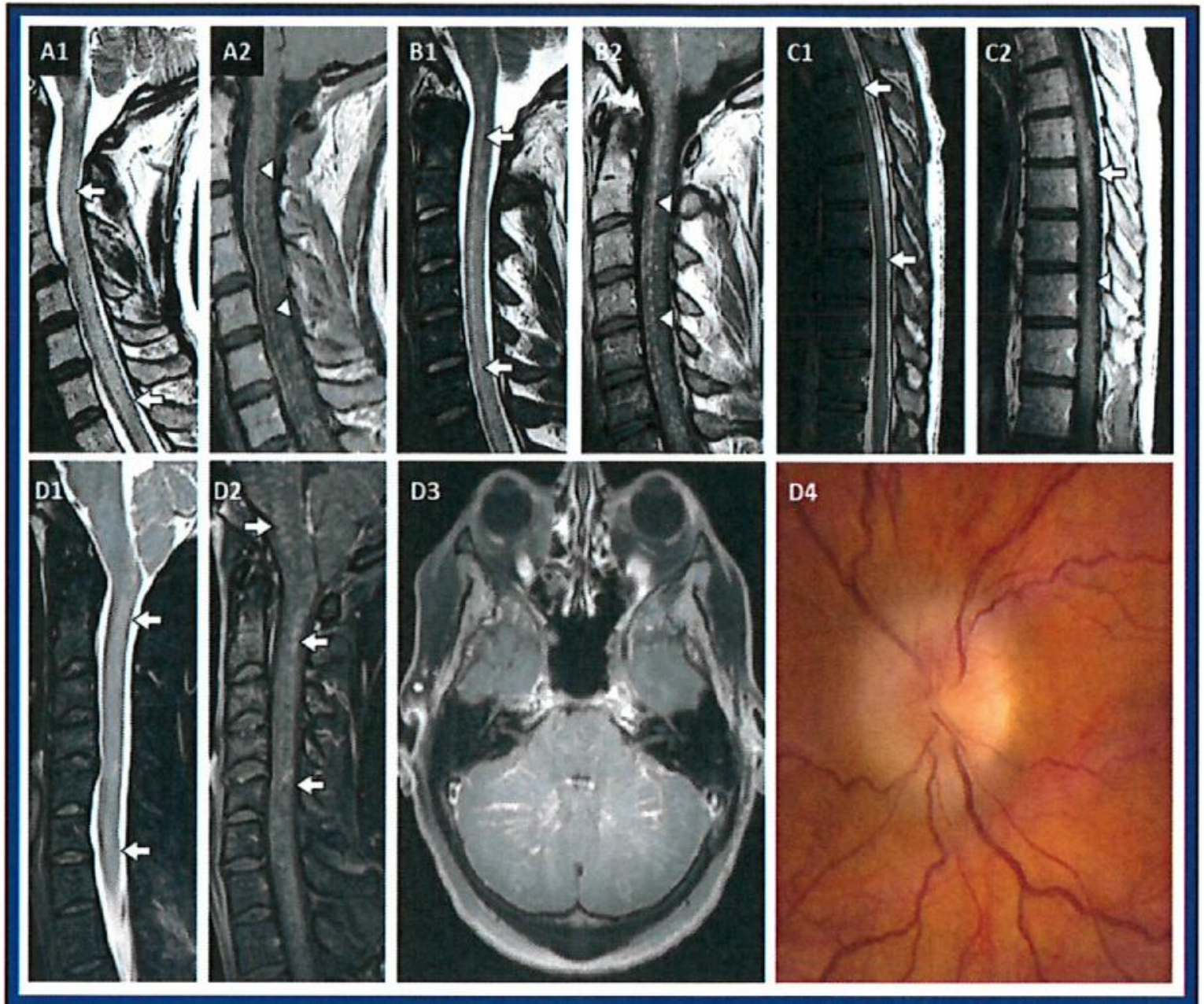
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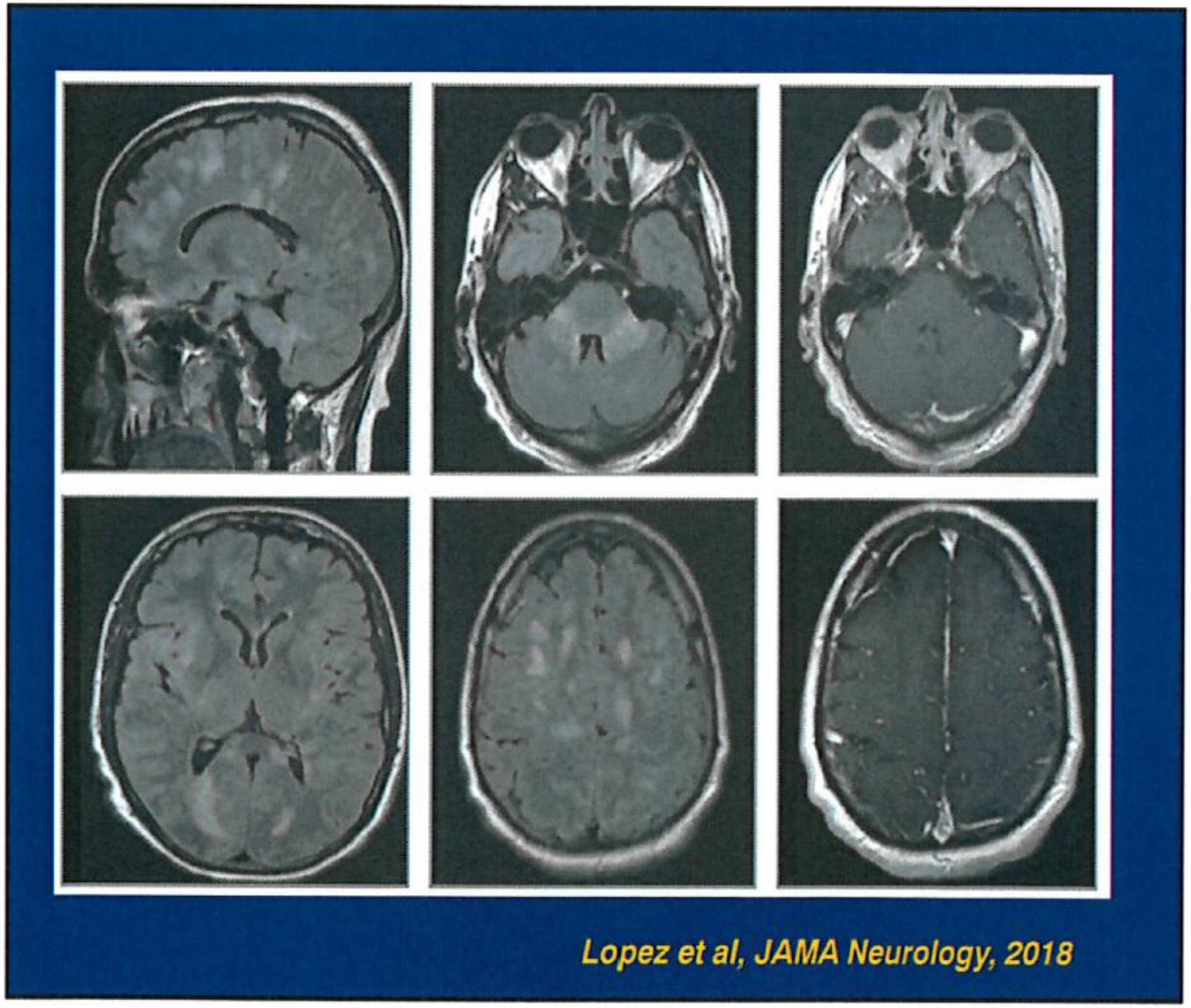
Autoimmune GFAP astrocytopathy

- Meningoencephalomyelitis
- 11% have seizures
- Inflammatory MRIs and CSF
- GFAP-IgG optimally detected in CSF
- 25% have neoplastic association (most commonly teratoma)
- NMDA-R-IgG coexists in 15%
- Steroid responsive (relapse in 20%)

Fang et al, JAMA Neurology, 2016
Dubey et al, Journal of Neuroimmunology, 2018



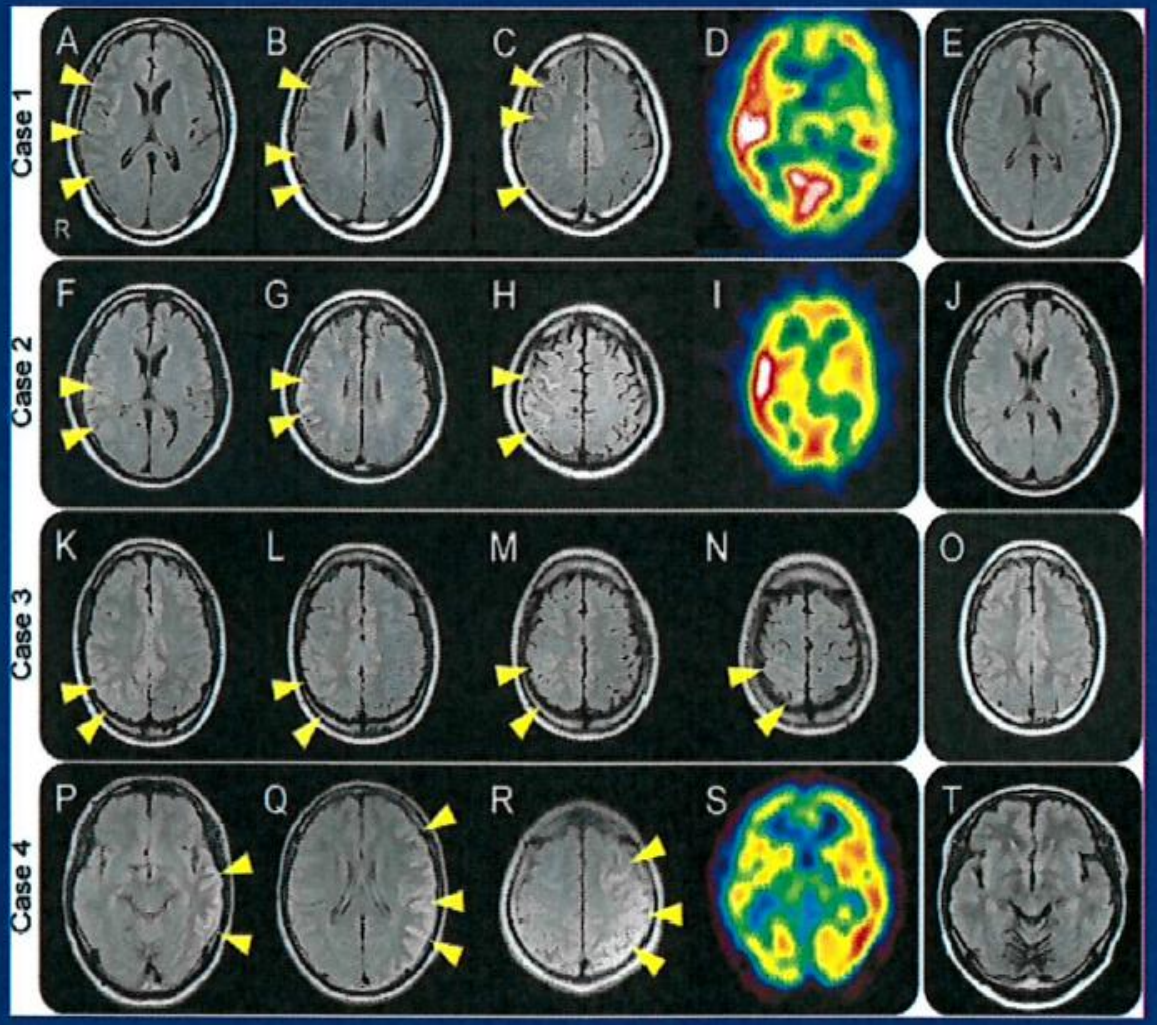
Lopez et al, JAMA Neurology, 2018

MOG Autoimmunity

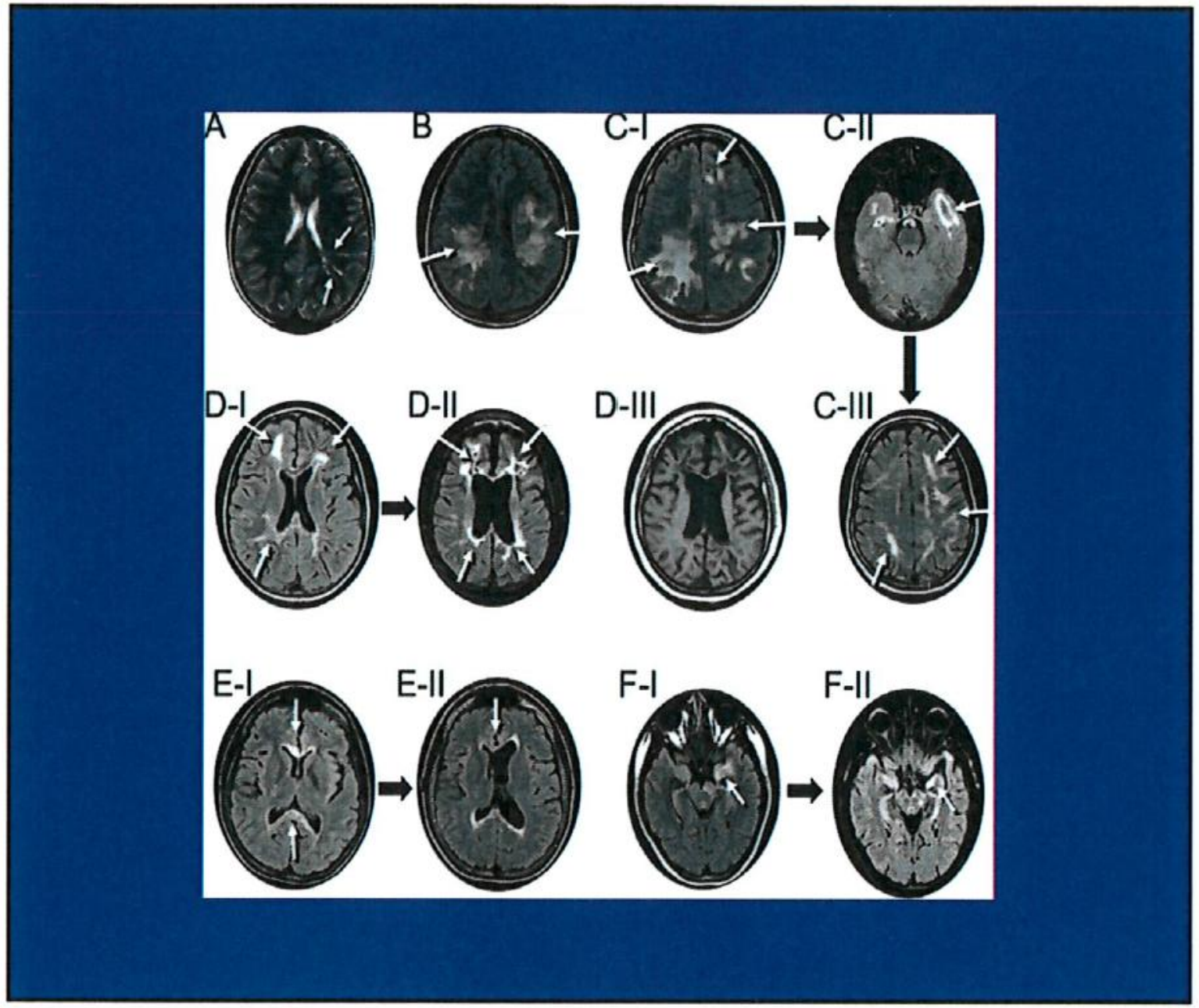
- ON, TM, ADEM
- Children > adults
- Monophasic or relapsing
- Steroid responsive
- Some steroid-dependent
- Azathioprine, mycophenolate, rituximab or IVIg maintenance (not MS drugs)

Hacohen et al, JAMA Neurology, 2018

MOG-IgG +
Benign, unilateral, cerebral cortical encephalitis with epilepsy



Ogawa et al, N2, 2017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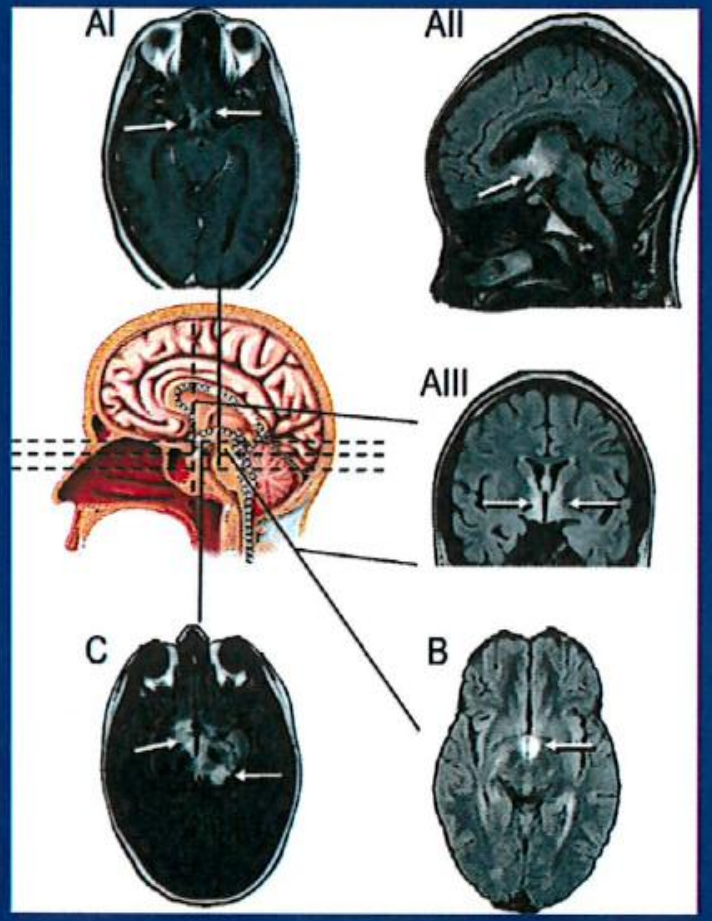
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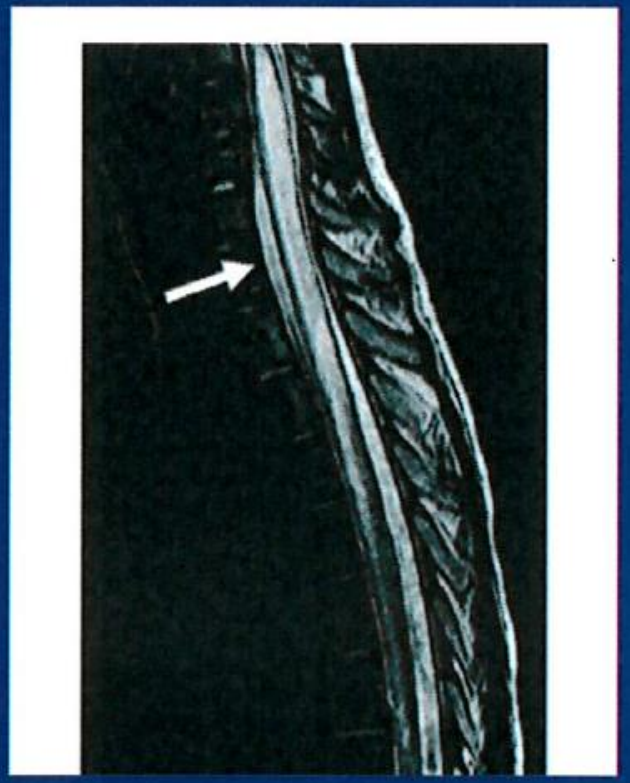
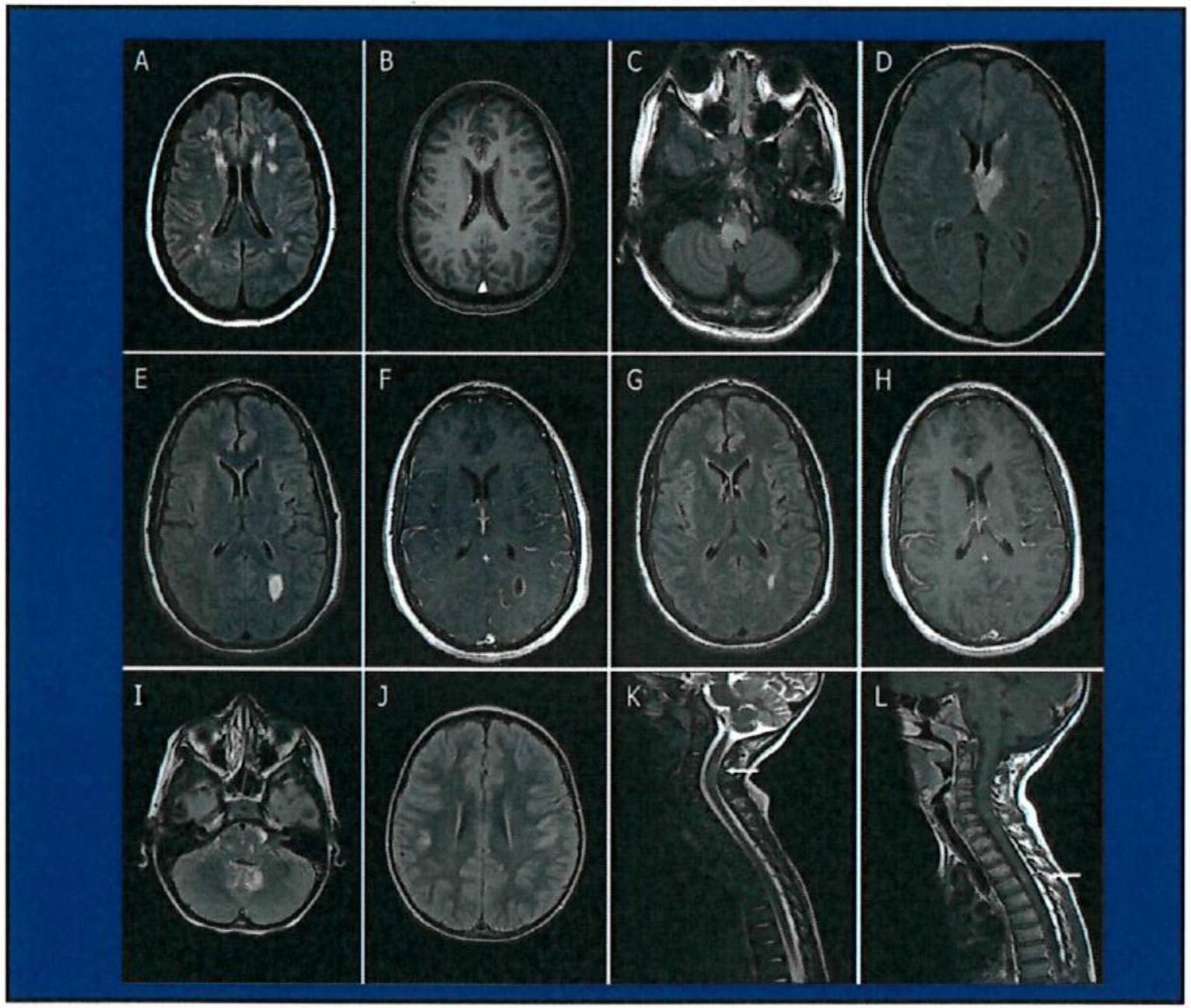


AQP4 Autoimmunity in Children

- 50%: cerebral symptoms (encephalopathy, ophthalmoparesis, ataxia, seizures, intractable vomiting, hiccups)
- 68%: brain MRI abnormal
- Medulla > white matter > midbrain, > cerebellum >thalamus, & hypothalamus

McKeon et al, Neurology, 2008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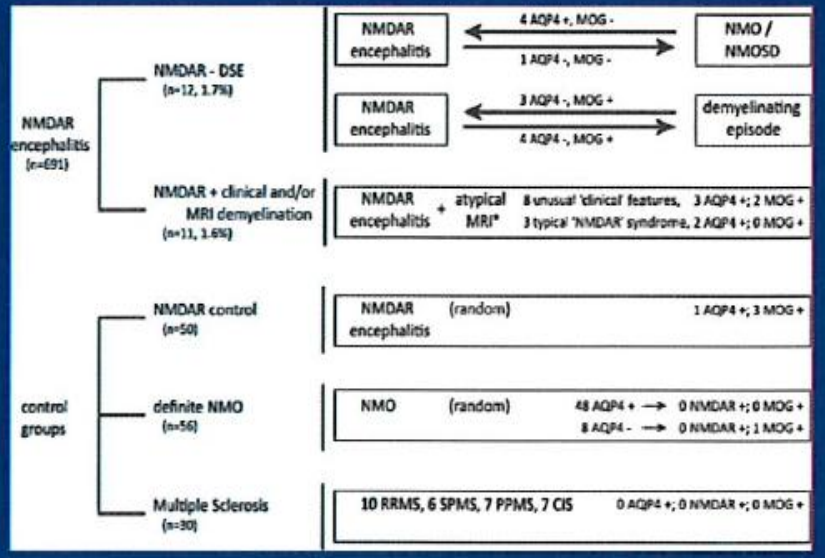
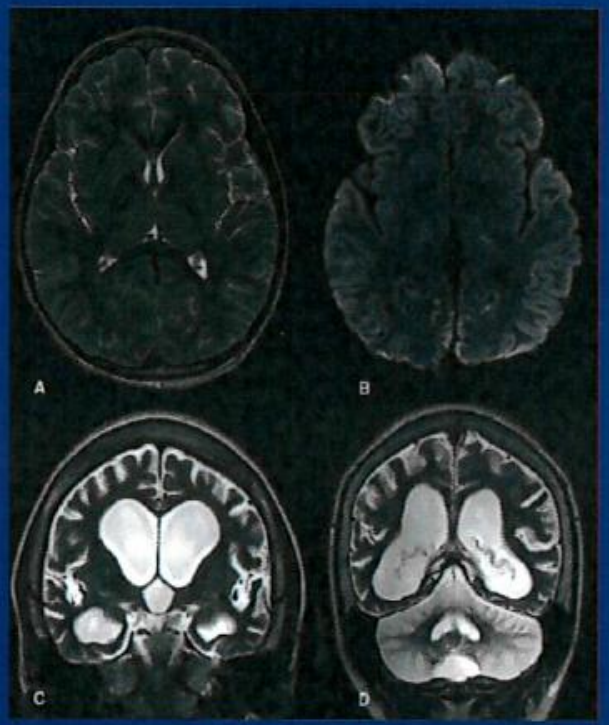
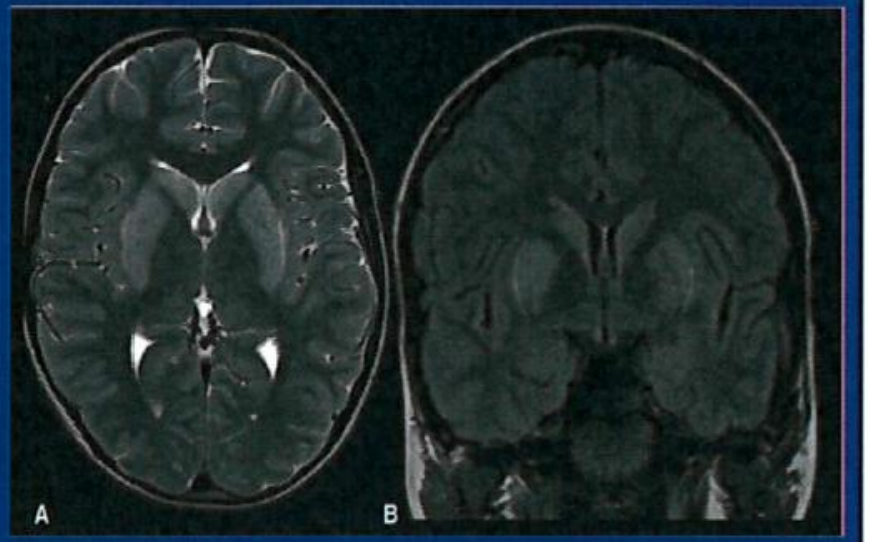
NMDA-R Encephalitis: Coexisting MOG/AQP4-IgGs..?Others

- 23/691 patients with anti-NMDAR encephalitis with MRI and/or demyelination either simultaneous or separate episodes.
- 18/23 coexisting AQP4-IgG (9) or MOG-IgG (9)

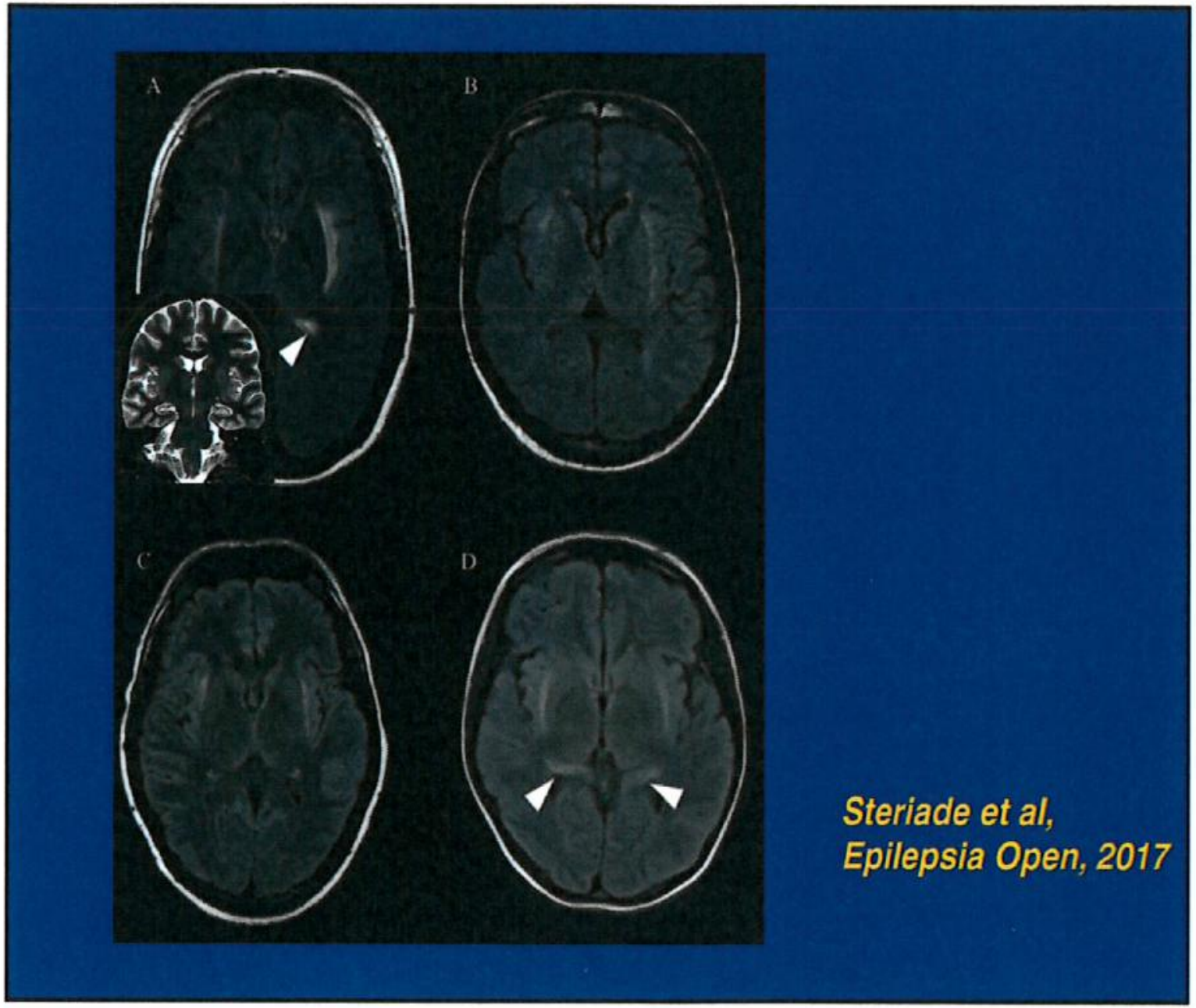


Titulaer et al, Annals Neurology, 2014





Culleton et al, Epilepsia, 2019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Steriade et al,
Epilepsia Open, 2017

NORSE/FIRES

- NORSE = New onset refractory status epilepticus
- FIRES = fever-induced refractory epileptic encephalopathy syndrome
- Fever not apparent in all
- Not all have super-refractory status
- Most of unknown cause
- IL-1 Receptor antagonist (anakinra) effective in some

Kenney-Jung et al, Ann Neurol, 2016

Normal non-specific MRI

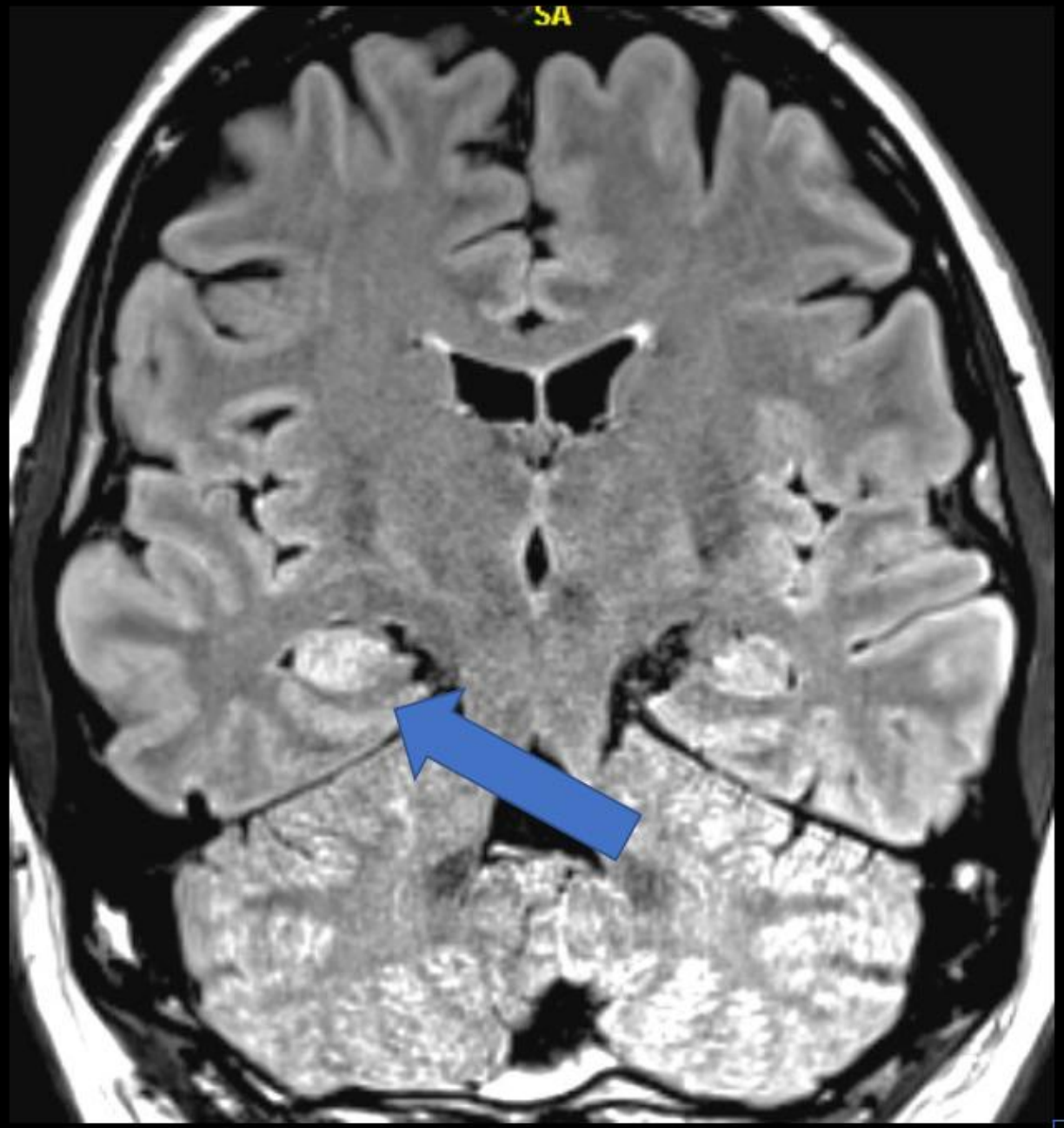
- 40% Lgi1
- 50% NMDA
- 30-50% of autoimmune encephalitis cases: antibody negative

Whats the score

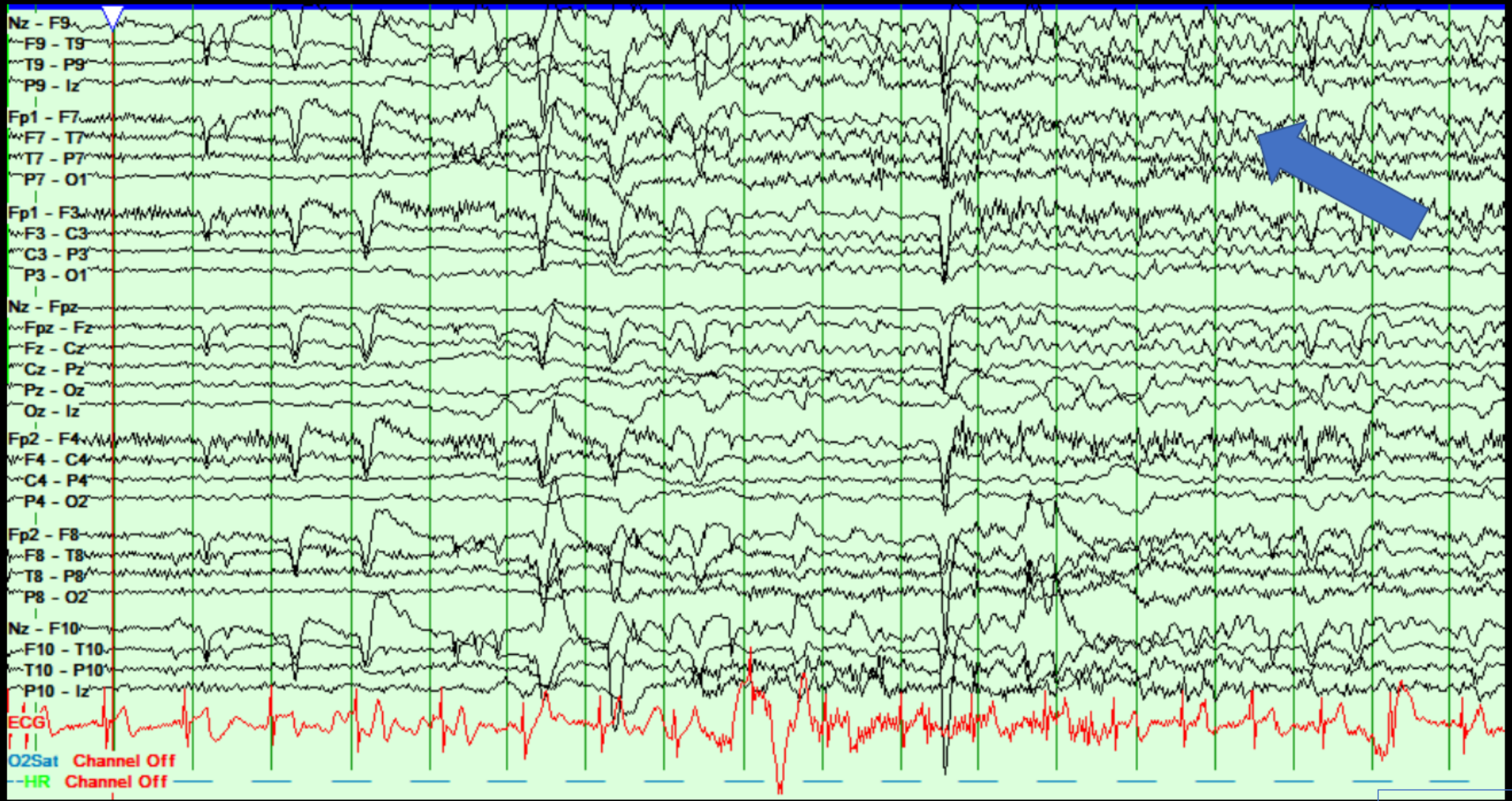
AIDS TO TREATMENT AND DIAGNOSIS

Case 1 - 46 year old male attorney

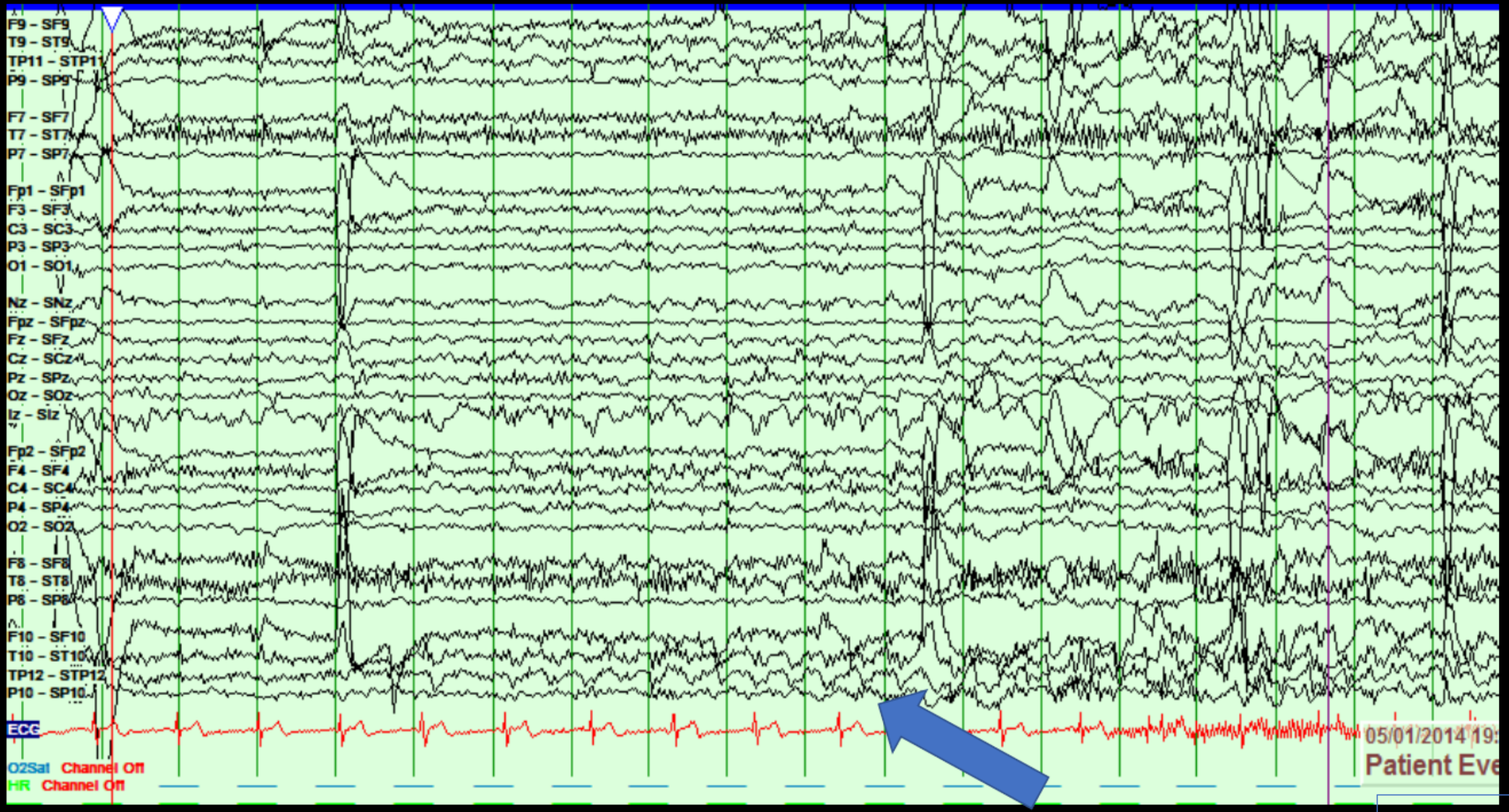
- 1 month ago - found in stopped car, confused, repeating the word “ball”
- Sensory “waves”, piloerection; more than 40 per day
- Memory impairment, irritability, weight gain
- EEG – non-diagnostic, seizures still suspected
- Levetiracetam → valproate → oxcarbazepine
- Spinal fluid – protein 65 mg/dL (15-35 mg/dL), cells=0



1 month post onset


Nz - F9
F9 - T9
T9 - P9
P9 - Iz
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Nz - Fpz
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Oz - Iz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
Nz - F10
F10 - T10
T10 - P10
P10 - Iz
ECG
O2Sat Channel Off
HR Channel Off

Sz # 8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C3 – SC3
P3 – SP3
O1 – SO1
Nz – SNz
Fpz – SFpz
Fz – SFz
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Iz – SIz
Fp2 – SFp2
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C4 – SC4
P4 – SP4
O2 – SO2
F8 – SF8
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P8 – SP8
F10 – SF10
T10 – ST10
TP12 – STP12
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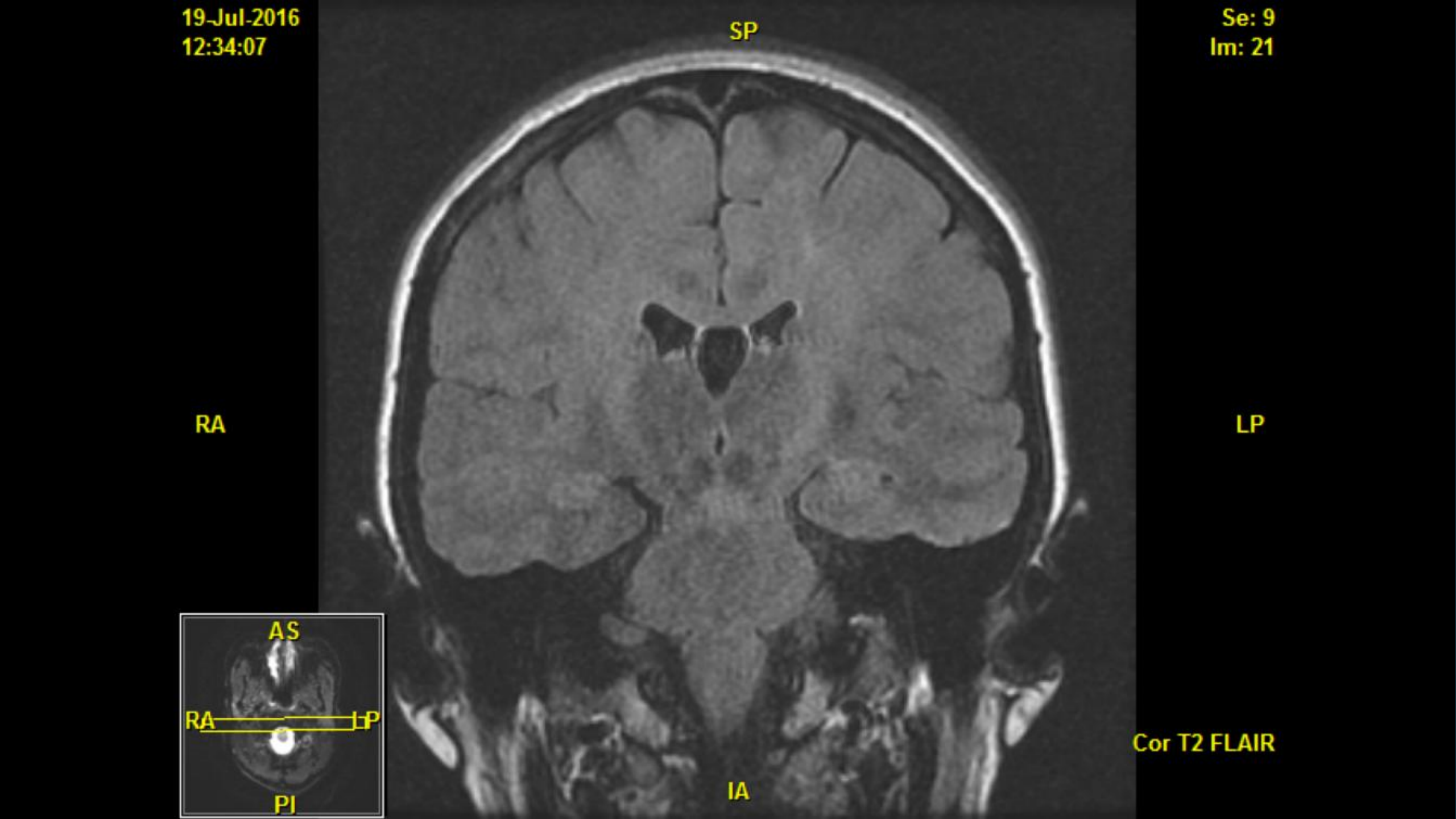
ECG
O2Sat Channel Off
HR Channel Off
05/01/2014 19:
Patient Eve

Sz # 14

Should this patient be tested for neural antibodies?

Case 2: 35 year old woman, customer service

- 6 year history focal seizures with impaired awareness, occasional bilateral convulsive seizures
- funny feeling in chest, dyspnea, warmth/flushing left chest, rising to left neck, arm, face ➔ aphasia
- Variable frequency: up to 10 days without - 5 per day
- EMU x 5 days off meds –6 left temporal onset focal seizures on final day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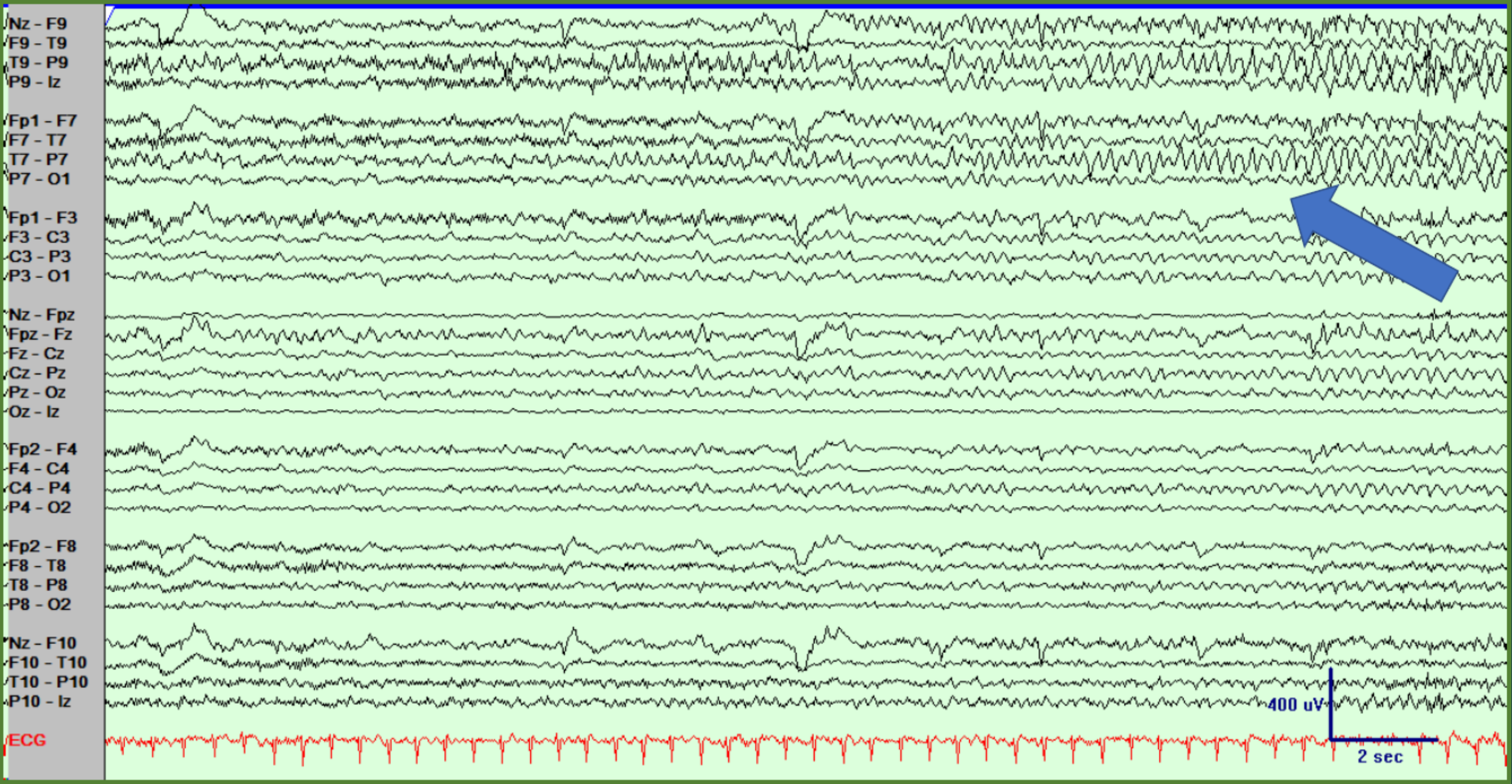
Nz - F9
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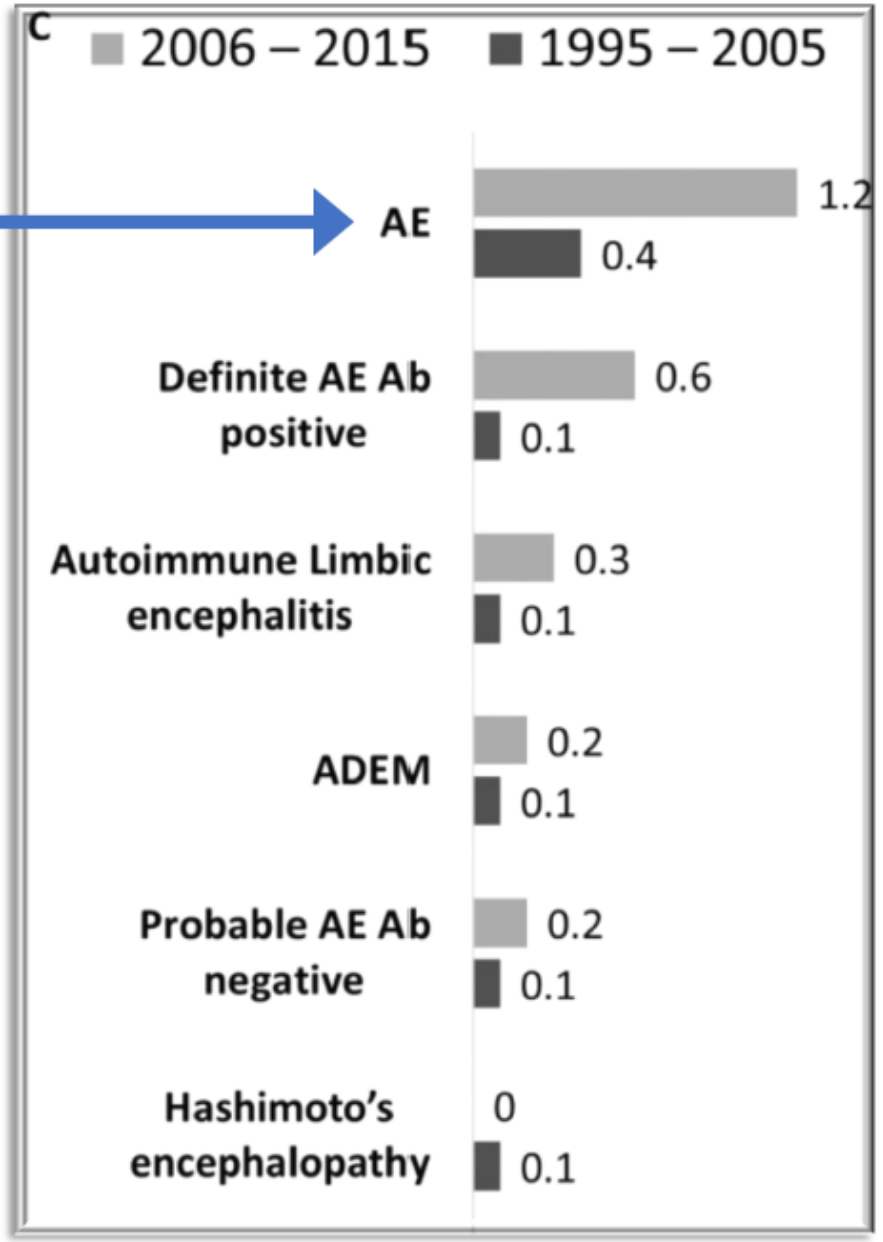
T9 - P9
P9 - Iz
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Nz - Fpz
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Oz - Iz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
Nz - F10
F10 - T10
T10 - P10
P10 - Iz
ECG
400 uV
2 sec

Who to test for neural antibodies?

- Don’t want to miss a case
- False positives
- Costs and availability of testing
- Test results lag time for clinical decision-making

Autoimmune encephalitis epidemiology

- Encephalitis: ~ 5 to 8 per 100,000 persons, 40 to 50% idiopathic[1]
- Autoimmune 3rd most common; NMDA surpasses any single infectious agent[2]
- NMDA 1% all young adult ICU admissions[3]
- LGI1 incidence 0.83 per million/year[4]
- Autoimmune incidence increasing with increased detection



1. Granerod et al. Lancet Inf Dis 2010; 10:835-44; 2.Gable MS et al. Clin Inf Dis 2012;54:899-904; 3. van Sonderen, A., et al. Neurol 2016; 87: 1449-56; 4. Prüss H et al. Neurol 2010;75:1735-1739; 5. Dubey et al. Ann Neurol 2018;83:166–177 (Permission granted for use of Fig 2 by John Wiley & Sons)

Neural Ab prevalence in patients with epilepsy

- N=124 children, focal epilepsy - 5 (4%)[1]
- N=66 adults > age 55, new onset epilepsy - 4 (6%)[2]
- N=112 epilepsy unknown cause - 39 (34.8%)[3]
- N=82 with DRE unknown cause, 17 (22%) Ab+[4]
- GAD-65+ in 5.9% epilepsy, 1.5% controls (p=0.026)[5]
- In 416 with epilepsy, 8% neural Ab+[6]

1. Borusiak et al. Paed Neurol. 2016; 20:573-9; 2. Von Podewils et al. Epilepsia 2017; 58: 1542-50; 3. Dubey et al. JAMA Neurol. 2017; 74:397-402; 4. Tecellioglu et al. Irish J Med Sci. 2018; doi:10.1007/s11845-018-1777-2; 5. Liimatainen S et al. Epilepsia. 2010; 51(5): 760-7; 6. Brenner et al. Epilepsia 2013; 54: 1028–1035

Clinical features suggesting autoimmune cause

- Recent seizure onset
- Focal epilepsy
- High seizure frequency (up to several per day)
- Seizure types (faciobrachial, paroxysmal dizzy)
- Certain EEG findings (extreme delta brush)
- Characteristic imaging
  - Medial temporal FLAIR/T2 hyperintensity
  - FDG-PET hypermetabolic foci
  - others

Criteria: *Definite* autoimmune encephalitis

Diagnosis can be made when all four* have been met:

1. Subacute onset (rapid progression < 3 mos) working memory deficits, altered mental status, psychiatric symptoms
2. Bilateral brain abnormalities on T2/FLAIR MRI or fdg-PET highly restricted to the medial temporal lobes
3. At least one of the following:
   - CSF pleocytosis (WBC > 5 cells per mm^3)
   - EEG with temporal epileptic or slow-wave activity
4. Reasonable exclusion of alternative causes

What about seizures?

** = if neural Ab positive, only 2 of first 3 required*

Graus, Titulauer, Dalmau et al. Lancet Neurology 2016; 15: 391–404

Criteria: *Possible* autoimmune encephalitis

Diagnosis can be made when all three met:

1. Subacute onset (rapid progression < 3 mos) working memory deficits, altered mental status, psychiatric symptoms
2. *At least one* of the following:
   - New focal CNS findings
   - Seizures not explained by previous seizure disorder
   - CSF pleocytosis (WBC > 5 cells per mm^3)
   - MRI features suggestive of encephalitis
3. Reasonable exclusion of alternative causes

Seizures 2nd tier

Graus, Titulauer, Dalmau et al. Lancet Neurology 2016; 15: 391–404

Who to test, who to treat? APE2 and RITE2 scores

- APE2 – Antibody Prevalence in Epilepsy
  - Score ≥ 4: specificity 85%, sensitivity 98% [1]
  - Score ≥ 7: specificity 100%
- RITE2 – Response to Immunotherapy in Epilepsy
  - = APE2 plus (1) *initiation of immunotherapy within 6 months* and (2) *plasma membrane-specific autoantibody* detected
  - Score ≥ 7: specificity 84%, sensitivity 88% [1,2]

1. Dubey et al. Epilepsia 2019; 60(2): 367-9; https://doi.org/10.1111/epi.14649

2. Dubey D et al. Epilepsia 2017; 58(7): 1181-9; https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.13797

Antibody Prevalence in Epilepsy[2] Score Abnl >= 4

APE 2	Yes/No (Y/N)	
New onset, rapidly progressive (1-6 weeks) mental status changes or seizures, within 1 year of eval = **1 pt**		
Neuropsychiatric (agitation, aggression, emotion lability) = **1 pt**		
Autonomic dysfunction (sustained supra/bradycardia, OH, hyperhidrosis, labile BP, VTach, asystole) if no prior hx = **1 pt**		
Viral prodrome (in absence Ca history last 5 yrs) = **2 pts**		
Facial dyskinesia in absence FBD seizures = **2 pts**		
Faciobrachial dystonic (FBD) seizures = **3 pts**		
Seizures refractory 2 or more AEDs = **2 pts**		
CSF inflammatory (protein > 50 mg/dL, WBC > 5 cells/µL = **2 pts**		
MRI findings of limbic encephalitis (T2/FLAIR hyperintensity one or both medial temporal lobes, or multifocal grey/white matter or both c/w demyelination/inflammation) (no MRI="n") = **2 pts**		
Underlying malignancy < 5 yrs neurologic onset = **2 pts**		
Total	0	Abnl >= 4

Dubey D et al. Epilepsia 2019; 60(2): 367-369; https://doi.org/10.1111/epi.14649

APE2: should Case 1 get tested?

- 1 month hx seizures
- Irritability, memory ↓
- Refractory to 3 medications
- CSF protein ↑
- MRI abnormal

APE 2	Yes/No (Y/N)	
New onset, rapidly progressive (1-6 weeks) mental status changes or seizures, within 1 year of eval = **1 pt**		
Neuropsychiatric (agitation, aggression, emotion lability) = **1 pt**		
Autonomic dysfunction (sustained supra/bradycardia, OH, hyperhidrosis, labile BP, VTach, asystole) if no prior hx = **1 pt**		
Viral prodrome (in absence Ca history last 5 yrs) = **2 pts**		
Facial dyskinesia in absence FBD seizures = **2 pts**		
Faciobrachial dystonic (FBD) seizures = **3 pts**		
Seizures refractory 2 or more AEDs = **2 pts**		
CSF inflammatory (protein > 50 mg/dL, WBC > 5 cells/µL = **2 pts**		
MRI findings of limbic encephalitis (T2/FLAIR hyperintensity one or both medial temporal lobes, or multifocal grey/white matter or both c/w demyelination/inflammation) (no MRI="n") = **2 pts**		
Underlying malignancy < 5 yrs neurologic onset = **2 pts**		
Total	0	Abnl >= 4

Application of APE2 to our cases – Case 2

- Several year history
- Memory
- Refractory to 6 medications
- Negative MRI

APE 2	Yes/No (Y/N)	
New onset, rapidly progressive (1-6 weeks) mental status changes or seizures, within 1 year of eval = **1 pt**		
Neuropsychiatric (agitation, aggression, emotion lability) = **1 pt**		
Autonomic dysfunction (sustained supra/bradycardia, OH, hyperhidrosis, labile BP, VTach, asystole) if no prior hx = **1 pt**		
Viral prodrome (in absence Ca history last 5 yrs) = **2 pts**		
Facial dyskinesia in absence FBD seizures = **2 pts**		
Faciobrachial dystonic (FBD) seizures = **3 pts**		
Seizures refractory 2 or more AEDs = **2 pts**		
CSF inflammatory (protein > 50 mg/dL, WBC > 5 cells/µL = **2 pts**		
MRI findings of limbic encephalitis (T2/FLAIR hyperintensity one or both medial temporal lobes, or multifocal grey/white matter or both c/w demyelination/inflammation) (no MRI="n") = **2 pts**		
Underlying malignancy < 5 yrs neurologic onset = **2 pts**		
Total	0	Abnl >= 4

SUMMARY

- Several clinical and radiologic features suggest probability of autoimmune etiology
- Testing for antibodies in appropriate patients may identify specific etiology-directed therapy
- Awareness of diagnostic criteria for autoimmune encephalitis and APE2 score help identify appropriate patients for testing
- Nonselective testing ill-advised

Neural Abs Overview
IgG Antibodies targeting

Neural cell surface antigens channels,receptors ,synapses

--Lgl1/CASPR2 Abs,NMDA-R-Ab,GABA-AA/B R Abs

Immunotherapy

Neuronal nuclear, cytoplasmic antigens

e.g. ANNA-1 (Hu),CRMP-5,Ma

Oncological therapy

Acute treatment

- IV methylprednisolone 1 g IV daily for 3-5 days , then weekly for 6-8 weeks

OR

- IVIg , 0.4 g/ kg IV daily for 3-5 days, then weekly for 6-8 weeks

OR

- Plasma exchange: 7 exchanges over 14 days (sever attacks, incomplete response to steroids)

Further treatment

- Plasma Exchange : treatments , every other day ×5 day
- Prednisone: 60 mg/day ×3 months, taper by 10 mg per month to 10 mg , then by 1 mg/ month to zero

- Azathioprine: 2.5 mg / Kg / day for 3-5 years
- TPMT 16.6 (>17.0 is normal)
- Citalopram
- Calcium, Vitamin D, trimethoprim- salfamethoxazole
- Monitored CBC,LFTS, creatinine weekly for 1 month, every other week for 2months, then monthly

Azathioprine

- Elevated ALT (119) and AST (77)
- Elevated thiopurine metabolites
- Discontinued azathioprine (no relapse)
- LFTs normalized within 1 month
- Started mycophenolate mofetil (target dose 1000mg bid)
- Same blood monitoring

Chronic treatment

- Initiate" infusion sparing" medication
- Need to overlap for a period with acute treatment
- Patient may relapse when steroids/ IVIg withdrawn
- Patient may require ongoing low oral does or infrequent infusion of steroids

Paranoplastic Encephalistis with Seizure

- ANNA-1 (Hu) , ANNA -2 (Ri), Ma1/ Ma2, MAP1B(PCA-2) , Amphiphysin-IgG, CRMP-5 IgG, SOX-1(AGNA)
- Search for cancer

-Do not have good responses to steroids, IVIg or plasma exchange

- General approach:

- Oncological therapy (surgery , chemotherapy, radiation therapy)
- Cyclophosphamide

Extra –limbic paraneoplastic encephalitis (ANN-1, anti – Hu)

Rassmusen encephalitis

- Hemispherectomy: Standard
- Histology:CD8 +T cells , Microglial activation
- Steroids, IVIg , Plassma exchange
- Mitoxantrone
- Intrathecal methotrexate
- Alemtuzumab

NORSE/FIRES

- NORSE=New onset refractory status epilepticus
- FIRES= fever – induced refractory epileptic encephalophaty syndrome
- Fever not apparent in all
- Not all have super – refractory status
- Most of unknown cause
- IL-1Receptor antagonist (anakinra) effective in some

Prednisone

- Dose: 1 mg/ Kg / day or 60 mg / day
- Duration: 3 Months, taper slowly
- Side effects:
- Immediate: insomnia , Altered mood, hyperglycemia, hypertension, tremor avascular necrosis
- Longer term: Cataracts , diabetes, osteoporosis, opportunistic infection
- Cautions:
- Diabetes, agitation, psychotic symptoms

Prednisone

- Prophylaxis:

  Pneumocystis

  Trimethoprim-sulfamethoxazole DS 1 tab 3 / Week PO

  Atovaquone 1500 mg / day PO

- Osteoporosis

  Calcium 1500 mg / day , Vitamin D, 1000 u / day consider prophylactic alendronate

- Monitoring: Glucose , blood pressure , electrolytes, bone density

- **Levetiracetam:** 1000 mg bld
- **IV methylprednisolone:** 1000 mg daily for 5 days -weekly for 6 weeks: initial improvement
- **Every other week for 6 weeks:** Worse memory , new mood disorder, right hippocampus worse on MRI

IV methylprednisolone

- **Dose:**1g daily×3-5
- weekly×6-12
- **Taper:**

Every other week×12weeks

Every 3 rd week×12weeks ,

Every 4 th week × 12 weeks

stop

IVIg

- **Side effects :** headache, allergic ,Reactione, DVT, renal failure(very rare)

-Cautions: Ig hypersensitivity

-Prophylaxis:

antlhlstamlne+/-IV sterold

Monitoring:check IgA level,creatinine at baseline

Plasma exchange

- **Dose:**5-7 exchanges,volume of plasma, alternate day
- **Side effects:** pneumothorax,line infetion/thrombosis,orthostatic Hypotension,nausea
- **Monitoring:**electrolytes,clinical volume status, blood pressure

Azathioprine

- **Dose:**2.5-3mg/kg/day,2divided doses.
- **Side effects:** nausea , fatigue, liver dysfunction, cytopenias, opportunistic infection lymphoma,
- Cautions:pregnancy, TPMT edficiency, liver dysfuntion
- **Contraindication:**undetectable TPMP
- **Monitoring:** CBC, LFTs

Mycophenolate mofetil

- **Dosing:**1g bid
- **Side effects:** fatigue, opportunistic infection, cytopenias,lymphoma
- **Cautions:** teratogenic(eggs and sperm)(2 forms of contraception)
- **Monitoring :**CBC

Rituximab

- **Dose:**1g , 2doses , 2 weeks apart or 375mg/m2 weekly×4
- **Side effects:** allergic reaction, reactivation of TB/chronic hepatitis,opportunistic infection
- **Cautions:** Ig infusion reactions , ig deficiencies, infection
- **Monitoring:**Igs if opportunistic infection

Cyclophosphamide

- **Dose:**IV 1g/m2 monthly×6 PO 2mg/ kg/day
- **IV:** hydrate, mesna pre and post , Dosing adjusted for renal, hepatic dysfunction and nadir of white cells
- **Side effects :** nausea,vomiting, alopecia, cytopenias, bladder hemorrhage,infertility,infection , malignancy,
- Contraindications:pregnancy ,lactation , infection

Monitoring

- Objectify
- Clinical history and exam
- Beware of" feelling great" with steroids
- MRI
- EEG
- Neuropsychometric testing
- ? Antibody titers

Seizure freedom with AEDs

- Levetirasetam 0.53
- Carbamazepine 3.16 (18 %)
- Lacosamide 3.18(17%)
- Phenytoin 1.8(13%)
- Oxcarbazepine 2.11 (18 %)

  (select cases , sodium Channel Blockers)

Don’t forget …

- Mood disorders: Psychiatry, Psychotropics
- Behavioral change: CBT
- Chronic Cognitive dysfunction: Rehab
- Sleep Disorders: Overnight oximetry, sleep medicine
- Sedation: taper medication

Conclusion

- Assess likelihood of response
- Treat early
- Immune treatment trails
- Review antiepileptic drug regimen
- Maintenance treatment if relapsing course
- Management of Long-term outcomes