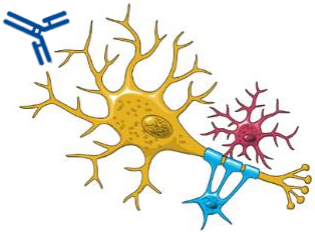
Inflammation & Epilepsy II

Metha Apiwattanakul MD.
Neuroimmunology Unit
Department of Neurology
Prasat Neurological Institute

Scope

- Seizure in systemic autoimmune disease & autoimmune neurological disease (focus on adult presentation)
- General approach to autoimmune epilepsy
- Immunotherapy

Seizure in systemic autoimmune disease



Antibody to neuronal antigens

Neuronal inflammation

Altering physiologic function → decreased seizure threshold

Immune process to systemic organ → seizure as the complication

- Lupus nephritis → renal HT → PRES (seizure)
- Antiphospholipid syndrome → cerebral venous thrombosis

Immune suppression from drugs → complication from treatment

- CNS infection → abscess
- Secondary malignancy → lymphoma

SLE

- One of NPSLE (seizure, headache, cognitive deficits, depression & psychosis)
- No characteristic seizure type
- ANA is sensitive, but *not* specific
  - High titer of anti-cardiolipin, anti-Smith & antiribosomal-P increase risk of seizure in SLE
- CSF: mildly ↑ mononuclear cell & protein

Vasculitis is *NOT* typical finding in NPSLE presenting with seizure

Seizure from SLE

Main mechanism	Etiology
Disease active	• NPSLE (also had other CNS manifestation) • Skin rash, oral ulcer • Anticardiolipin, anti-Sm, anti-ribP
Disease complication	• Libman-Sacks endocarditis → cerebral embolism • TTP • ***Vasculitis is rare*** • HypoNa, PRES
Treatment complication	• Opportunistic infection • Secondary malignancy • Drug induce seizure due to lower threshold

Other CNT diseases

- Sjögren's disease: salivary & lacrimal glands dysfunction with seizure
- Linear scleroderma (Perry-Romberg syndrome): localized facial scleroderma as well as brain (facial lesion) → refractory to antiepileptic drugs
- CNS vasculitis: seizure in 16%
- Not typical to have seizure in RA or myositis

VGKC-complex Ab LE

- New onset seizures, confusion & memory deficits
- Seizure: brief & high frequency
- Seizure semiology:
  - Faciobrachial dystonic seizure
  - Simple partial autonomic seizures
  - Hypersalivation
- Highly response to immunotherapy

FBDS

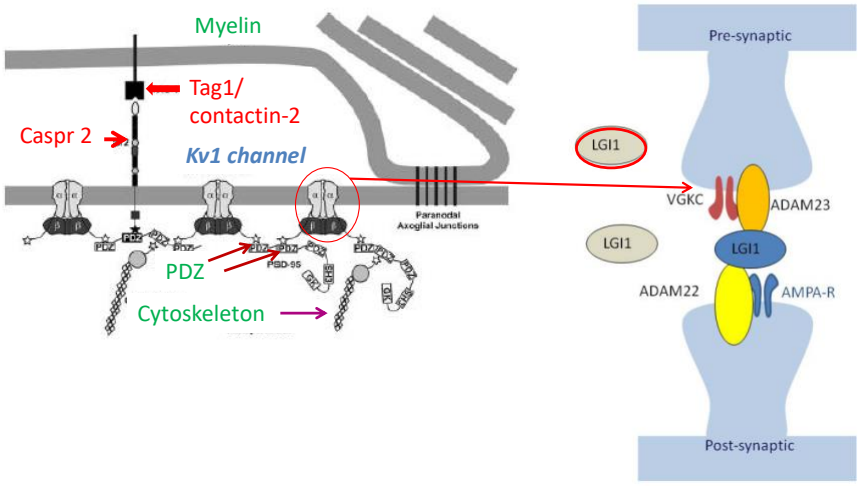
- Sudden onset of flexion contraction of one upper extremity, accompanied by contraction of the face, head & neck ipsilaterally
- Duration: seconds, multiple times/d
- May have vocalization
- Present in 25% of VGKC-Ab LE

FBDS

Other seizure

- Simple partial autonomic:
  - Unilateral piloerection or palpitation
  - "Wave" ascend or descend passing through body
  - Last in seconds, multiple times/d
- Complex partial seizure or complex partial status epilepticus
- Hypersalivation

Molecular biology of VGKC-complex



Differential diagnosis

- Infectious encephalitis (HSV-1,6)
- Vascular disease
- Acute amnestic syndrome without seizure → Wernicke's encephalopathy

Anti-GAD LE

- ***Seizures***, ataxia, EPS symptoms, stiff-person syndrome
- Anti-GAD prevalence:
  - 70% in DM type 1
  - 1.5% in normal subjects
  - 6% in epilepsy patients

Seizure in anti-GAD

- Simple partial, complex partial or secondary GTC & non-convulsive SE
- Majority: temporal lobe seizures
- Can present in *chronic epilepsy*
- High titer of anti-GAD is associated with seizure & other neurological deficits

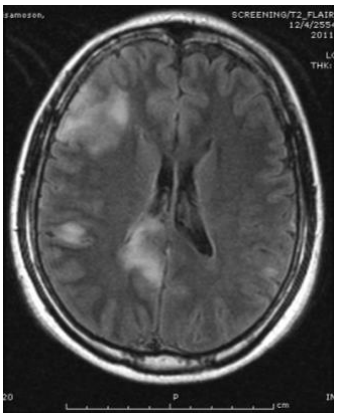
When to suspect anti-GAD

- No distinguish seizure types
- ***Should*** aware of anti-GAD in these settings:
  - DM type 1 (>50% of anti-GAD with neurologic symptoms)
  - Thyroid disease 30-40%(anti-thyroid Ab)
  - Vitiligo 15%

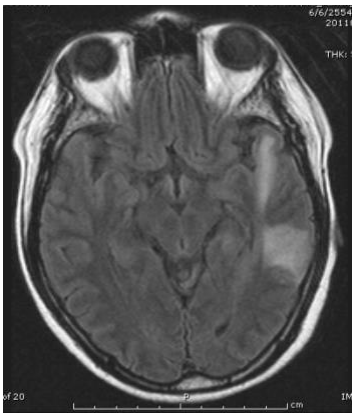
Differential diagnosis

- TLE with low-titer anti-GAD → should consider another cause
- Hashimoto's encephalopathy (coexisting anti-thyroid & anti-GAD)

GAD-Ab: chronic intractable epilepsy (M/38: duration 18 years)



EEG April, 2011: focal epilepsy arising from right fronto-temporal region



EEG May, 2011: focal epilepsy arising from left fronto-temporal region

Hashimoto's encephalopathy

- Waxing & waning mental status change
- Stroke-like episode
- Cognitive decline, dementia, ataxia, myoclonus, chorea, tremor
- Seizure (up to 66%)
  - Myoclonic epilepsy
  - New onset SE
- High titer of anti-TPO & respond to steroid

DDx: Hashimoto's encephalopathy

- Diffuse toxic-metabolic
- Vascular
- Infection
- Should be suspected in…
  - Unexplained subacute dementia
  - New onset SE
  - LE

Anti-$GABA_B$ LE

- Seizure is the main clinical symptom; may develop to status epilepticus
- Usually have cognitive dysfunction, memory problem & confabulation
- Rare: ataxia, opsoclonus-myoclonus
- May be found co-existing with ANNA-2, Anti-amphiphysin, Anti-GAD, Anti-NMDAR or Anti-SOX1
- Paraneoplastic: SCLC

When should we suspect this seizure is immune-mediated?

JAMA Neurology | Original Investigation

Neurological Autoantibody Prevalence in Epilepsy of Unknown Etiology

Divyanshu Dubey, MD; Abdulradha Alqallaf, MD; Ryan Hays, MD; Matthew Freeman, MD; Kevin Chen, MD; Kan Ding, MD; Mark Agostini, MD; Steven Vernino, MD, PhD

- Prospectively study
- Detected potential autoimmune etiology 34.8%
- Most common Ab finding:
  - Anti-TPO 13.4%
  - Anti-GAD65 12.5%
  - Anti-VGKC 10.7%
  - Anti-NMDAR 3.6%

Result

- Presence of antibody: good seizure outcome (65.2% vs 27%)
- Patient with autoantibody seropositive: reduction of seizures is depend on immunotherapy
- APE ≥ 4 → select patient for Ab testing

APE score

Table 1. Components of the APE Score

Clinical Feature	Value[a]
New-onset, rapidly progressive mental status changes of 1-6 weeks, or new-onset seizure activity	1
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	1
Autonomic dysfunction (presenting as labile blood pressure, labile heart rate, persistent tachycardia, postural hypotension)	1
Viral prodrome (runny nose, sore throat, low-grade fever), only to be scored in the absence of underlying malignancy	2
Facial dyskinesias or faciobrachial dystonic movements	2
Seizure refractory to at least 2 antiseizure medications	2
CSF findings consistent with inflammation (elevated CSF protein level >50 mg/dL and/or lymphocytic pleocytosis >5 cells/dL, if the total number of CSF RBCs is <1000 cells/dL)[b]	2
Brain MRI showing signal changes consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)[b]	2
Presence of underlying malignancy (excluding cutaneous squamous cell or basal cell carcinomas)	2
Total	15

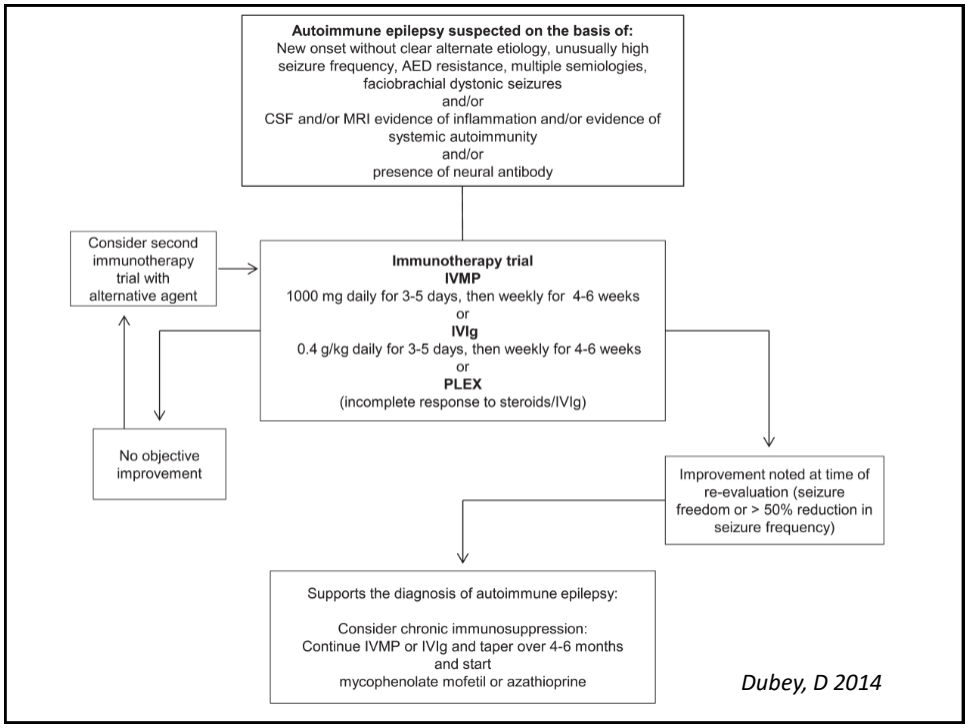
Clinical features suggested autoimmune epilepsy

- 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

Add on : autonomic dysfunction, neuropsychiatric symptoms & facial dyskinesia

Toledano, M 2014 & Dubey, D 2017

General Treatment


Autoimmune epilepsy suspected on the basis of:
New onset without clear alternate etiology, unusually high seizure frequency, AED resistance, multiple semiologies, faciobrachial dystonic seizures
and/or
CSF and/or MRI evidence of inflammation and/or evidence of systemic autoimmunity
and/or
presence of neural antibody
Consider second immunotherapy trial with alternative agent
Immunotherapy trial
IVMP
1000 mg daily for 3-5 days, then weekly for 4-6 weeks
or
IVIg
0.4 g/kg daily for 3-5 days, then weekly for 4-6 weeks
or
PLEX
(incomplete response to steroids/IVIg)
No objective improvement
Improvement noted at time of re-evaluation (seizure freedom or > 50% reduction in seizure frequency)
Supports the diagnosis of autoimmune epilepsy:
Consider chronic immunosuppression:
Continue IVMP or IVIg and taper over 4-6 months and start
mycophenolate mofetil or azathioprine
Dubey, D 2014