Inflammation & Epilepsy II

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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
  - Lupus nephritis → renal HT → PRES (seizure)
  - Antiphospholipid syndrome → cerebral venous thrombosis
- Immune process to systemic organ → seizure as the complication
  - CNS infection → abscess
  - Secondary malignancy → lymphoma
- Immune suppression from drugs → complication from treatment

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

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

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?

• 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

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Value*</th>
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<tbody>
<tr>
<td>New-onset, rapidly progressive mental status changes of 1-6 weeks, or new-onset seizure activity</td>
<td>1</td>
</tr>
<tr>
<td>Neuropsychiatric changes; agitation, aggressiveness, emotional lability</td>
<td>1</td>
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<tr>
<td>Autonomic dysfunction (presenting as labile blood pressure, labile heart rate, persistent tachycardia, postural hypotension)</td>
<td>1</td>
</tr>
<tr>
<td>Viral prodrome (runny nose, sore throat, low-grade fever), only to be scored in the absence of underlying malignancy</td>
<td>2</td>
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<tr>
<td>Facial dyskinesias or faciobrachial dystonic movements</td>
<td>2</td>
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<tr>
<td>Seizure refractory to at least 2 antiseizure medications</td>
<td>2</td>
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<tr>
<td>CSF findings consistent with inflammation (elevated CSF protein level &gt;50 mg/dL and/or lymphocytic pleocytosis &gt;5 cells/dL, if the total number of CSF RBCs is &lt;1000 cells/dL)²⁶</td>
<td>2</td>
</tr>
<tr>
<td>Brain MRI showing signal changes consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)²⁶</td>
<td>2</td>
</tr>
<tr>
<td>Presence of underlying malignancy (excluding cutaneous squamous cell or basal cell carcinomas)</td>
<td>2</td>
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<tr>
<td><strong>Total</strong></td>
<td>15</td>
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</table>
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

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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
- IVlg
  - 0.4 g/kg daily for 3-5 days, then weekly for 4-6 weeks
  - or
- PLEX
  - (incomplete response to steroids/IVlg)

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 IVlg and taper over 4-6 months and start mycophenolate mofetil or azathioprine

Dubey, D 2014