Autoimmune epilepsy: A new cause of seizure & status epilepticus

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Objective

• How to identify autoimmune epilepsy, are there any clues that help the physician to differentiate from other causes of epilepsy?
• Clinical summary of autoimmune epilepsy, regarding of specific autoantibody
• How to approach the patients when you encounter these diseases?
• General immunotherapy

Clinical characteristic

• Seizure: one manifestation of autoimmune neurologic disorder esp. LE
• Usually resist to AED, but well response to additional immunosuppressive Rx
• May be detected up to 14% of epilepsy patient
• Perivascular chronic inflammatory cell infiltrates (T cells)

The scope of EEG interpretation & anti-epileptic drugs will not be discussed in depth.

2 Categories of autoimmune epilepsy

1. Autoantibody recognize transmembrane protein: pathogenic antibody
   Anti-NMDAR, Anti-VGKC complex (Lgi1 > Caspr2), Anti-GABAβ, Anti-AMPAR, Anti-Glycine

2. Autoantibody recognize intracytoplasmic organelle: T-cell mediated cytotoxicity
   ANNA-1, ANNA-2, Anti-CRMP-5, Anti-GAD, Anti-Ma2

Case 1: M/70

• 12 days PTA, he developed generalized tonic clonic seizure. He was received phenytoin 300 mg/day. Four days later, he developed fever and decreased level of consciousness.
• 3 days PTA, he was admitted in one hospital and developed multiple episodes of focal (alternate hand fumbling left and right) → generalized seizure. He was unconscious during episode of seizure.
M/70

- EEG monitoring:
- He was treated with levitiracetam, sodium valproate, but could not control his seizure.

Right fronto-temporal

Laboratory investigation

- CSF WBC 21 (mononuclear cells 100%), Protein 76 mg%, Sugar 81 mg%
- PCR for herpes: Negative
- Paraneoplastic screening:
  - Anti-GABA$_B$ receptor antibody
Anti-\textit{GABA}_B Ab

This case has 2 characteristics of autoimmune epilepsy

1. Multifocal lesions, intraindividual variability
2. Refractory to AED

\textbf{Anti-\textit{GABA}}_B

- \textbf{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

\textbf{GABA}_B receptor

- If there is another autoantibody (higher in titer) co-exist with anti-\textit{GABA}B (lower titer); the prognosis of LE will depend on the main autoantibody
- From evidence of 2 case series, 60-80\% of cases that received immunotherapy +/- oncologic Rx (if indicated) improved clinical outcome. >50\% had nearly complete recovery
Case 2: M/73

- 2 weeks PTA, he had memory impairment with multiple episode of jerking (3-5 sec per episode, > 10 per days) predominately on face and arm. He also had difficulty in calculation and could not do ADL as usual.
- He was received phenytoin, valproate and topiramate, but could not control his symptoms.
- At the time of admission, he had hyponatremia with refractory to treatment.

M/73

- EEG showed generalized, intermittent slow.
- Left arm tonic/clonic (VDO) → right arm tonic/clonic event: No EEG change
- Serum Na++: 125 mmol/l (refractory to Rx)
- CSF: No cell, protein 41 mg%, sugar 48 mg%
- Paraneoplastic screening: Anti-Lgi1 positive

Abnormal signal at bilateral medial temporal and insular lobes

VGKC-complex autoantibody encephalopathy

- Lgi1 & Caspr2
- Lgi1: secreted protein interact with presynaptic ADAM23 & postsynaptic ADAM22); mutation in Lgi1 → ADLTE
- Caspr2: neurexin, mediates cell-cell interaction & clustering VGKC in juxtanodal region of myelinated axon. Also high expression in hippocampus & cerebellum

Molecular biology of VGKC-complex

Immunohistochemistry of KC-complex AutoAb

Hippocampus

Cerebral cortex

Axon hillock: Clustering of VGKC
This case has 3 characteristics of autoimmune epilepsy

1. Seizure with cognitive decline + hyponatremia
2. Refractory to AED
3. High frequency seizure

Clinical feature of Lgi1
- Seizure 82%, clinical LE > 70%
- Faciobrachial dystonic seizure (multiple brief (<3s) episodes of simultaneous facial grimacing & ipsilateral arm dystonia.
- 77% FBDS precede amnesia or confusion
- Only FBDS presentation: serum sodium & MRI were normal.
- In contrast, if FBDS + LE → 88% had hyponatremia, 54% had abnormal MRI (medial temporal)

Clinical feature of Lgi1
- Interictal EEG: diffuse mild slowing (35%), bilateral frontotemporal slowing (23%), temporal sharp wave (7%), normal (35%)
- CSF: 19% mild pleocytosis/or elevated protein
- PET/SPECTs increase sensitivity of detecting brain abnormality
- Other features: sleep disturbance, dysautonomia, pain, cerebellar ataxia

Faciobrachial dystonic seizure
- Ictal EEG (24%): 2-4 Hz spike-wave activity over frontotemporal region
- AEDs alone reduce (>20% from baseline) frequency of seizure in only 10% of cases.
- Additional corticosteroids achieved cessation of seizure nearly 100% usually respond within 7 days in 30% and additional 60% within 60 days
- Relapse in 40% (no steroid) → absolute response within 2-7 days after increased steroid dosage.

FBDS: EEG

Rx response to AED vs AED + IT

Irani S, et al Brain 2013
Immunotherapy may prevent progression from faciobrachial dystonic seizure to cognitive impairment

Clinical feature of Caspr2

• Responsible for 14% of LE in VGKC-complex Ab
• Other manifestation: Peripheral nerve hyperexcitability spectrum disorder, painful neuropathy
• Can co-exist with other Ab (Lgi1-Ab, AChR-Ab, MuSK-Ab, GAD-Ab)

Case 3: F/15

• 3 weeks PTA, her mother noticed that she had unusual aggressive behavior and also had an argument with her friends with inappropriate reason.
• 1 week PTA, she developed generalized tonic clonic seizure. She was treated with anti-epileptic drug. Her consciousness was deteriorated and developed chewing with myorhythmia of limbs. No seizure was detected at the time of clinical deterioration.

Abnormal movement

Autonomic dysfunction

Investigation

• EEG showed diffuse slow wave at the time of abnormal movement
• CSF WBC 0 Protein 17 mg% Sugar 67 mg%
• Paraneoplastic screening:
  Anti-NMDA receptor Ab
Course of disease

• She was treated with IV methylprednisolone & 5 cycles of plasmapheresis
• Her autonomic dysfunction and abnormal movement were improved after 3 weeks of treatment
• She developed 2 episodes of generalized seizure with well response to anti-epileptic drug → antibody titer was decreased as compared to before plasmapheresis
• Her behavior was recovery after 3-4 months

This case has 2 characteristics of autoimmune epilepsy

1. Seizure preceded or followed by abnormal behavior
2. Seizure may disappear when other clinical deteriorate, and may re-emerge when clinical improved.

Molecular basic of NMDA-receptor

Anti-NMDA encephalopathy

Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma
Roberto Vecchioni, MD,1* Watanabe Max, MD,1 Bruce Anson, MD, PhD,1 Thorensic Zwindling, MD,1 Zhiling Jiang, PhD,1 and Joseph Chiosis, MD, PhD1

Paraneoplastic Anti–N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

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Kalia, LV, et al. 2008

Kalia, LV, et al. 2008

Ann Neurol 2005

Ann Neurol 2007

Anti-NMDA Ab

MRI brain (F/15)
**Tumor association**

- 38% had tumor
- 97% were female (predominantly age 12-45 yrs)
- Age ≤ 12 yrs; 6% had tumor
- 94% of all tumor → ovarian teratoma, 2% extra-ovarian teratoma, 4% other tumors (breast, testicular, ovarian, thymic and pancreatic carcinoma)
- Asian & black patients were more likely to have teratoma

**Clinical manifestation**

**Within 4 weeks of symptom onset → most patients developed a similar spectrum of symptoms irrespective of their age**

**Clinical spectrum**

- Flu-like symptom
- Short-term memory loss or *seizure*
- Psychiatric symptom
- Dystonia
- Orofacial dyskinesia,
- Choreaathetoid of extremities,
- abdomen, pelvis
- Abnormal posture
- Autonomic instability
- Hypoventilation & coma

**Uncommon presentations**

- Cerebellar ataxia or hemiparesis: more common in younger age
- Memory deficit or central hypoventilation: more common in older age
Laboratory investigation

- Abnormality in MRI (33%), EEG (90%), CSF (79%)
- Compared sera & CSF for NMDAR-Ab (IgG) detection → Sensitivity CSF (100%) & Serum (85%)

EEG

- Diffuse slow wave (39%)
- Focal slowing (frontal, temporal)
- Electrographic seizure (60%)
- Normal EEG (8.7%)

F/39:

Over all patients (including non-treatment group)
- 97% mRS ≤ 2
- Patients who responded to 1st line Rx
- Early treatment & no need for ICU admission

Additional factor for good outcome: the use of 2nd line therapy

Relapses: tumor & treatment

- 12% had clinical relapses, one-third had multiple relapses
- Compared with initial episode, most relapses were less severe, more often monosymptomatic
- Patients without a tumor had a higher frequency of relapses than those with a tumor
Relapses: tumor & treatment

The use of immunotherapy in the initial episode of encephalitis was associated with lower frequency of relapses. 2nd line immunotherapy was associated with fewer relapses in patients without tumor and decreased occurrence of subsequent relapses.

Outcome in children

- Overall outcome in children was the same as in adults.
- Multivariate risk factors are the same as adults: early treatment, no need for ICU admission & the use of 2nd line therapy.
- Beneficial of 2nd line Rx was similar to the entire cohort.

Rx suggestion

- Acute encephalopathy
  - Infectious cause
    - Anti-NMDAR positive
      - 1st line: Plasmapheresis or IVIg + high dose steroid
        - Not response
        - Response
      - 2nd line: cyclophosphamide or rituximab
        - Consider long term immunosuppressant especially tumor negative group
  - Anti-NMDAR negative
    - Consider long term immunosuppressant especially tumor negative group

Tumor screening

- NMDAR-Ab positive
  - Screening for ovarian teratoma
    - Teratoma positive
    - Teratoma negative
    - Tumor removal
      - Female ≥ 12 yrs
      - Female < 12 yrs, male patients
    - MRI of abdomen & pelvis every 6 months for 4 years
      - Repeat screening is unclear

Does Ab disappear after recovery?

Persistent Intrathecal Antibody Synthesis 15 Years After Recovering From Anti-N-methyl-D-aspartate Receptor Encephalitis

- The antibody titer will decrease during the recovery and usually elevated at the time of relapse.
- The antibody may persist even patients had complete recovery.
- This may be due to other effector(s) play a role in pathogenesis. (complement??)

The relationship between infection & autoimmunity

N-Methyl-D-Aspartate Receptor Antibodies in Herpes Simplex Encephalitis

- The antibody titer will decrease during the recovery and usually elevated at the time of relapse.
- The antibody may persist even patients had complete recovery.
- This may be due to other effector(s) play a role in pathogenesis. (complement??)
Anti-NMDAR in Herpes simplex encephalitis

Rational:
1. Observation of a more severe disease course in immunocompetent than in immunocompromised host → 2nd immune response
2. Beneficial effect on outcome when combining acyclovir with steroids
3. Some clinical aspects (e.g. choreoathethosis) are not explained by viral cytotoxicity

Anti-NMDA & infection

- NMDAR-Ab (IgA, M, G) are common in HSE: can be found up to 30%
- Virus-induced destruction of neurons → initiate primary immune response against NMDAR
- CNS inflammation in the course of HSE → immunological activation → polyspecific B-cell activation

2 Categories of autoimmune epilepsy

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2. Autoantibody recognize intracytoplasmic organelle: T-cell mediated cytotoxicity
   - ANNA-1, ANNA-2, Anti-CRMP-5, Anti-GAD, Anti-Ma2

Antibody to intracytoplasmic organelle

- ANNA-1: LE 20%, almost with SCLC
- ANNA-2: seizure rare → lung & breast cancer
- Anti-CRMP5: LE rare → SCLC, thymoma
- Anti-Ma2: LE → CA testes

Case 4: 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
This case has 3 characteristics of autoimmune epilepsy

1. Multifocal lesions, intraindividual variability
2. Refractory to AED
3. Seizure can persist >15 years (esp GAD encephalopathy)

GAD-Ab encephalopathy

- Glutamic acid decarboxylase: synthesis inhibitory NT (GABA)
  - Low level: 60-70% of type 1 DM
  - High level: cerebellar ataxia, SPS, seizure (temporal lobe)
  - Clinical feature similar to VGKC-complex-Ab, but with the younger age of onset
  - Can present as chronic intractable epilepsy (especially high titer) → range of epilepsy duration 2-16 years

Seizure characteristic

- Seizure type:
  - Simple partial/aura = 84%
  - CPS = 81%
  - CPS w 2nd generalized = 53%

- 38% Seizure semiologies were variable or changed over time
- 81% had received ≥ 2 AEDs at presentation
- 81% had daily seizure

EEG characteristic

- 50% interictal epileptiform discharge
- 40% electrographic seizures
- 32% focal slowing
- 18% generalized slowing

Other neuropsychiatric

- 63% memory & cognitive disorder
- 25% personality changes
- 19% depression or anxiety

Summary of autoimmune epilepsy
MRI

- Half were MRI abnormalities
- 50% → amygdalohippocampal complex,
  20% → extramedial temporal lobe

CSF profiles

- More than half had protein elevation, only
  20% found pleocytosis

Immunotherapy & response

- 81% had improved clinically after initiation
  of immunotherapy
- Time from seizure onset to receiving
  immunotherapy: major determinant of
  responder or non-responders
- Cognitive & memory problem may persist
  up to 44%

Recommend autoimmune investigation

1. Unusual high seizure frequency
2. Intraindividual seizure variability or
   multifocality
3. AED resistance
4. Seizure preceded or followed by cognitive
   or behavior problem
5. Personal or family history of autoimmunity
   or recent or past neoplasia

Keep in mind that...

- Normal brain MRI or CSF profile does not
  exclude autoimmune epilepsy
- Seizure may disappear when clinical
  deteriorate & re-emerge when clinical
  improve
- Seizure may be the manifestation of
  complication of disease rather than
  disease active itself

Treatment

- Immunotherapy should be started as well
  as anti-epileptic drugs
- Should be aware of drug interaction
- Seizure that emerges during treatment
  may caused by disease active, disease
  improvement, complication from the
disease or complication from treatment
For autoimmune epilepsy caused by pathogenic antibody

- Early immunodepletion therapy (plasmapheresis or IVIG + high dose steroid) followed by immunosuppressive drugs yield good outcome.
- Tumor screening is recommended according to type of antibody

For autoimmune epilepsy caused by cytotoxic T cell

- Tumor screening & oncologic therapy along with immunosuppressive drugs are the mainstay of therapeutic process
- Outcome of disease is depend on type of tumor, time at adequate tumor & immunosuppressive therapy