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

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

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)

2 Categories of autoimmune epilepsy

1. Autoantibody recognize transmembrane protein: pathogenic antibody
   Anti-NMDAR, Anti-VGKC complex (Lgi1 > Caspr2), Anti-$GABA_B$, Anti-AMPAR, Anti-Glycine
2. Autoantibody recognize intracytoplasmic organelle: T-cell mediated cytotoxicity
   ANNA-1, ANNA-2, Anti-CRMP-5, Anti-GAD, Anti-Ma2

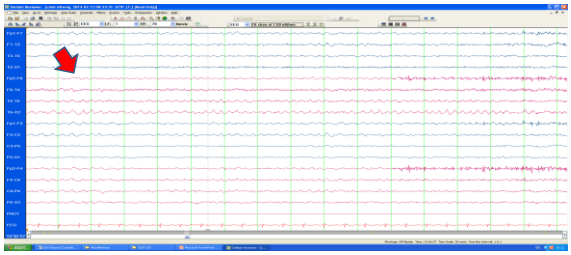
Case 1: M/70

- 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 fumbing left and right) → generalized seizure. He was unconscious during episode of seizure.

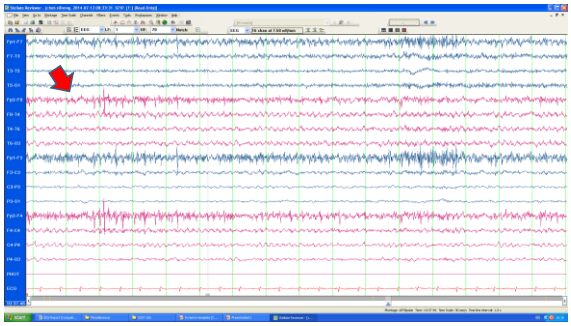
M/70

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

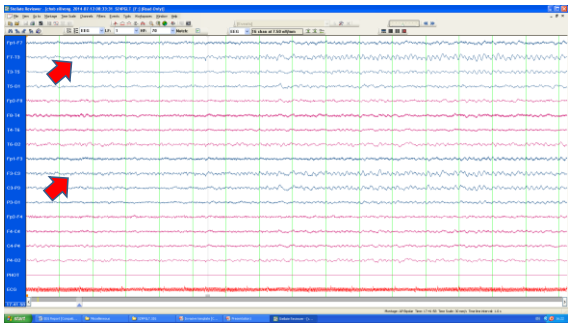
Right fronto-temporal



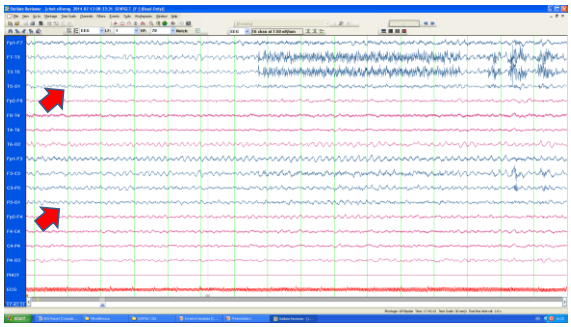
Right fronto-temporal



Lateralized left hemisphere



Lateralized left hemisphere

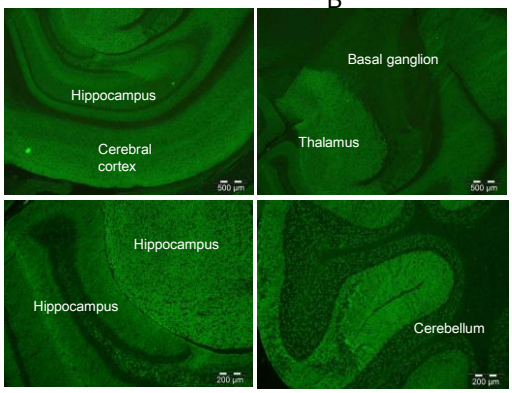


Laboratory investigation

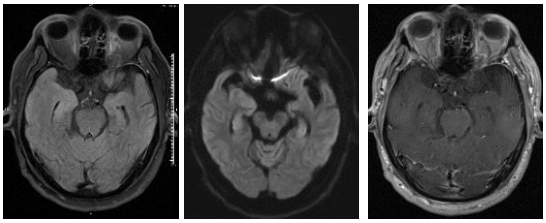
- CSF WBC 21 (mononeurclear cells 100%), Protein 76 mg%, Sugar 81 mg%
- PCR for herpes: Negative
- Paraneoplastic screening :

  Anti-$GABA_B$ receptor antibody

Anti-$GABA_B$ Ab



MRI brain: Abnormal signal at bilateral hippocampus with more edema on the right side

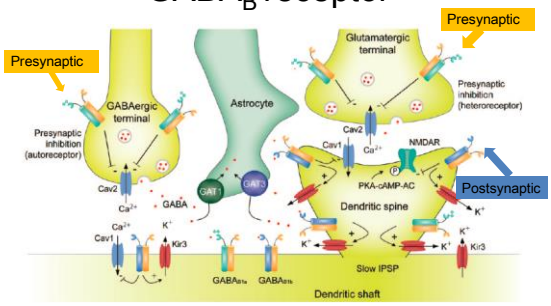


FLAIR DWI T1 w Gd

This case has 2 characteristics of autoimmune epilepsy

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

$GABA_B$ receptor



Benarroch EE, 2012

Anti-$GABA_B$

- 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

Anti-$GABA_B$

- If there is another autoantibody (higher in titer) co-exist with anti-GABAB (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

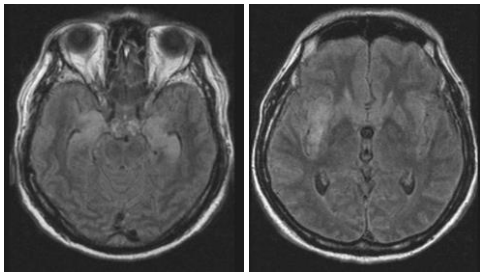
Case 2: M/73

- 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

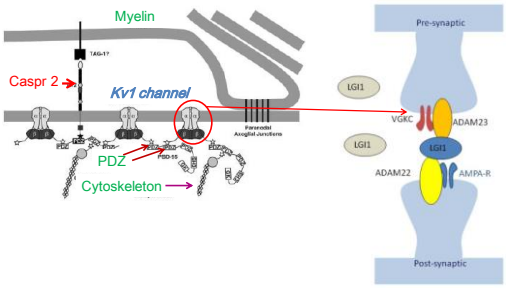
Abnormal signal at bilateral medial temporal and insular lobes



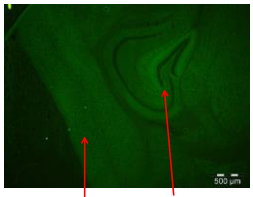
VGKC-complex autoantibody encephalopathy

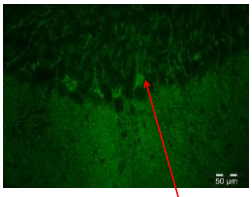
- ***Lgi1 & Caspr2***
- ***Lgi1*** : secreted protein interact with presynaptic ADAM23 & postsynaptic ADAM22); mutation in Lgi1 → ADLTE
- ***Caspr2***: neurexin, mediates cell-cell interaction & clustering VGKC in juxtanodal region of myelinated axon. Also high expression in hippocampus & cerebellum

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)

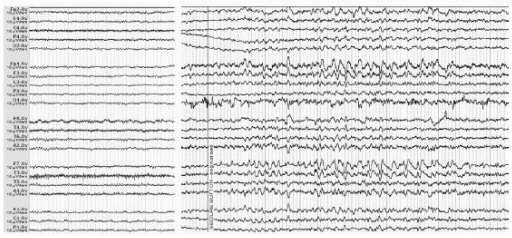
Clinical feature of Lgi1

- 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.

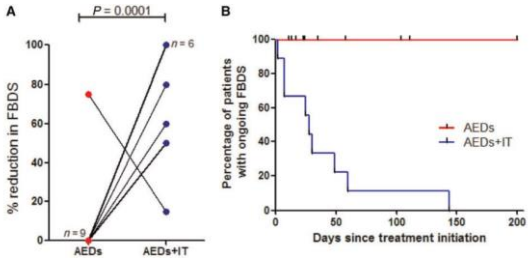
FBDS: EEG



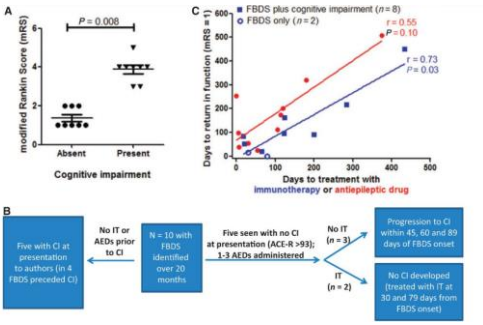
Interictal

Ictal: 2-4 Hz spike wave activity at frontotemporal region

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

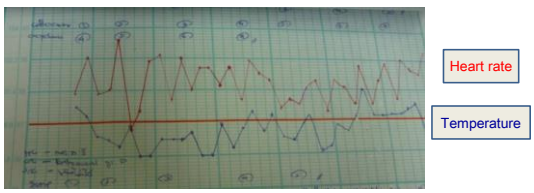
- Responsible for 14% of LE in VGKC-complex Ab
- Other manifestation: Peripheral nerve hyperexcitability spectrum disorder, painful neuropathy
- Can be co-exist with other Ab (Lgi1-Ab, AChR-Ab, MuSK-Ab, GAD-Ab)

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

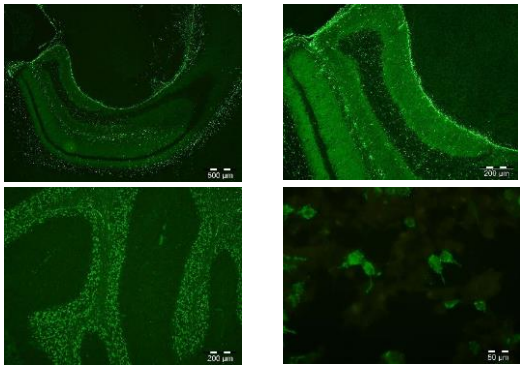


Investigation

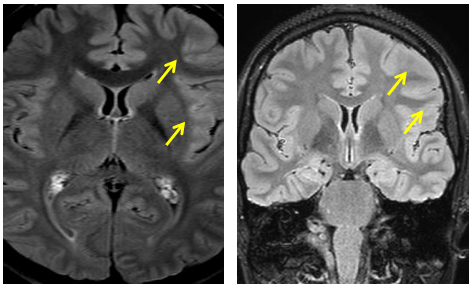
- EEG showed diffuse slow wave at the time of abnormal movement
- CSF WBC 0 Protein 17 mg% Sugar 67 mg%
- Paraneoplastic screening :

  Anti-NMDA receptor Ab

Anti-NMDA Ab



MRI brain (F/15)



Course of disease

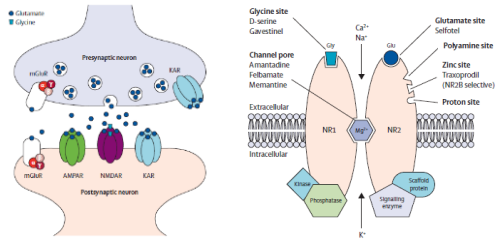
- She was treated with IV methylprednisolone & 5 cycles of plasmapheresis
- Her autonomic dysfunction and abnormal movement were improved after 3 weeks of treatment
- She developed 2 episodes of generalized seizure with well response to anti-epileptic drug → antibody titer was decreased as compared to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



Kalia, LV, et al. 2008

Anti-NMDA encephalopathy

Ann Neurol 2005

Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma

Roberta Vitaliani, MD,[1] Warren Mason, MD,[2] Beau Ances, MD, PhD,[1] Theodore Zwerdling, MD,[3] Zhilong Jiang, PhD,[1] and Josep Dalmau, MD, PhD[1]

Ann Neurol 2007

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

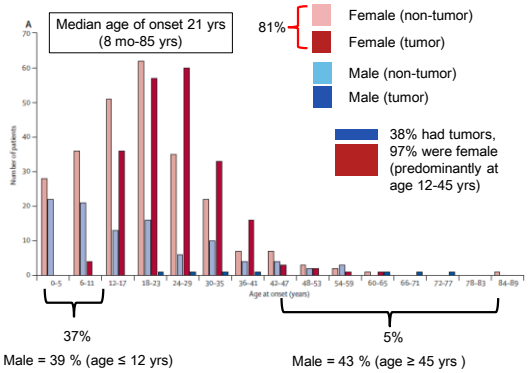
Josep Dalmau, MD, PhD,[1] Erdem Tüzün, MD,[1] Hai-yan Wu, PhD,[1] Jaime Masjuan, MD,[2] Jeffrey E. Rossi, BA,[1] Alfredo Voloschin, MD,[3] Joachim M. Baehring, MD,[4] Haruo Shimazaki, MD, PhD,[5] Reiji Koide, MD,[6] Dale King, MD,[7] Warren Mason, MD,[8] Lauren H. Sansing, MD,[1] Marc A. Dichter, MD, PhD,[1] Myrna R. Rosenfeld, MD, PhD,[1] and David R. Lynch, MD, PhD[1]

Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

Maarten J Titulaer, Lindsey McCracken, Iñigo Gabilondo, Thais Armangué, Carol Glaser, Takahiro Iizuka, Lawrence S Honig, Susanne M Benseler, Izumi Kawachi, Eugenia Martinez-Hernandez, Esther Aguilar, Núria Gresa-Arribas, Nicole Ryan-Florance, Abiguei Torrents, Albert Saiz, Myrna R Rosenfeld, Rita Balice-Gordon, Francesc Graus, Josep Dalmau

Lancet Neurol 2013

Total 501 patients



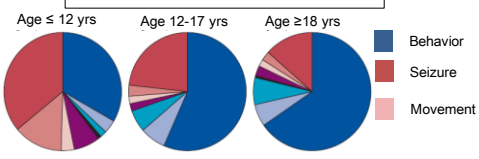
Male = 39 % (age ≤ 12 yrs)

Male = 43 % (age ≥ 45 yrs)

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

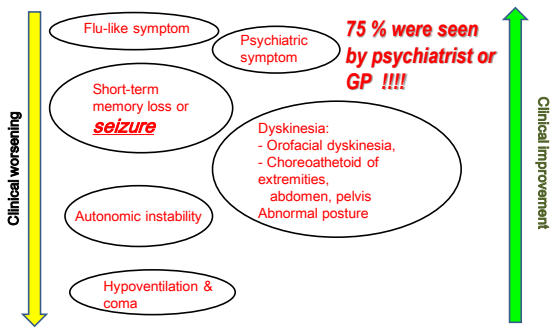


Age ≤ 12 yrs:
50% presented with seizure or movement disorder

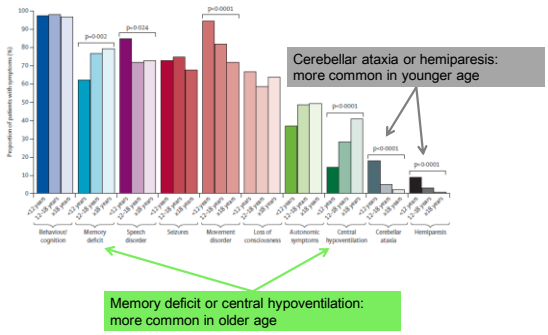
Adult:
65% presented with behavioral problems

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

Clinical spectrum



Uncommon presentations



Laboratory investigation

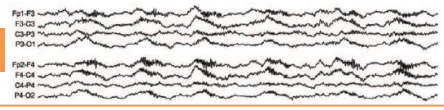
- Abnormality in MRI (33%), EEG (90%), CSF (79%)
- Compared sera & CSF for NMDAR-Ab (IgG) detection → Sensitivity CSF (100%) & Serum (85%)

EEG

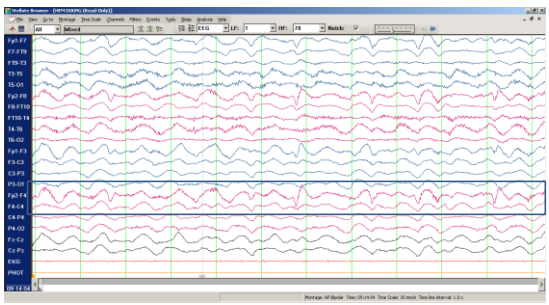
- Diffuse slow wave (39%)
  Focal slowing (frontal, temporal)
- Electrographic seizure (60%)
- Normal EEG (8.7%)

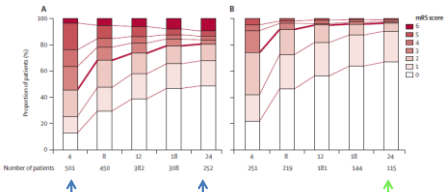
Extreme delta brush : A unique EEG pattern in adults with anti-NMDA receptor encephalitis
Sarah E. Schmitt, Kimberly Pargeon, Eric S. Frechette, et al.
Neurology 2012;79;1094; Published online before print August 29, 2012;

30%

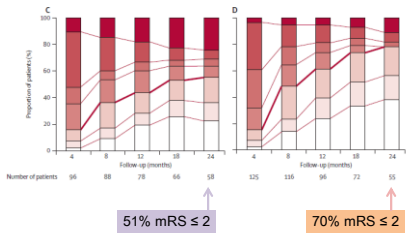


F/39:



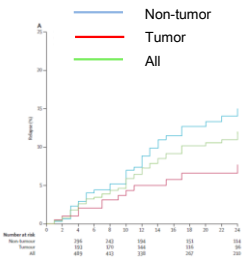


Multivariable analysis factors associated with good outcome: early treatment & no need for ICU admission



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

Relapses: tumor & treatment

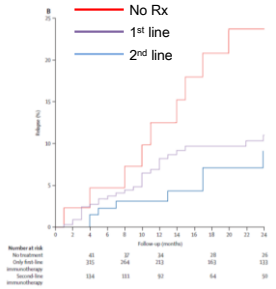


12% had clinical relapses, one-third had multiple relapses

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



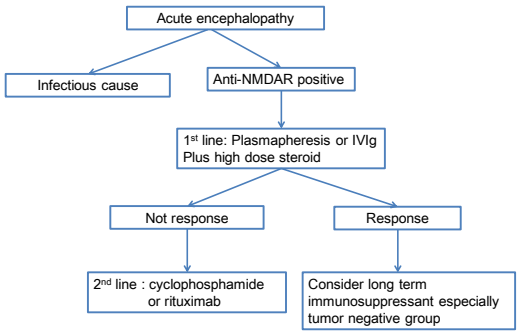
The use of immunotherapy in the initial episode of encephalitis was associated with **lower** frequency of relapses.

2nd line immunotherapy was associated with fewer relapses in patients without tumor and decreased occurrence of subsequent relapses

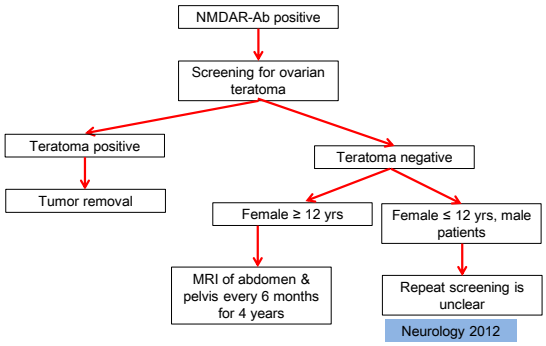
Outcome in children

- 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



Tumor screening



Neurology 2012

Does Ab disappear after recovery?

JAMA Neurol 2013

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

Hans-Christian Hansen, MD; Christine Klingbeil; Josep Dalmau, MD, PhD; Wenhan Li, MD; Benedikt Weißbrich, MD; Klaus-Peter Wandinger, MD

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

Ann Neurol 2012

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

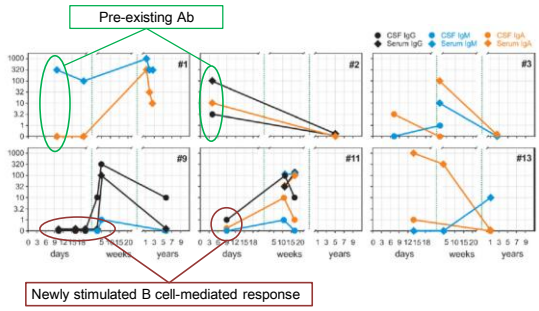
Harald Prüss, M.D.,[1] Carsten Finke, M.D.,[1] Markus Höltje, Ph.D.,[2] Joerg Hofmann, M.D.,[3] Christine Klingbeil,[4] Christian Probst, Ph.D.,[4] Kathrin Borowski,[4] Gudrun Ahnert-Hilger, Ph.D.,[2] Lutz Harms, M.D.,[1] Jan M. Schwab, M.D., Ph.D.,[1] Christoph J. Ploner, M.D.,[1] Lars Komorowski, Ph.D.,[4] Winfried Stoecker, M.D.,[4] Josep Dalmau, M.D., Ph.D.,[5,6] and Klaus-Peter Wandinger, M.D.[4,7]

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 (eg. choreoathethosis) are not explained by viral cytotoxicity

Kinetic of NMDAR-Ab: development of Ab during the disease course



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

1. Autoantibody recognize transmembrane protein: pathogenic antibody

   Anti-NMDAR, Anti-VGKC complex (Lgi1 > Caspr2), Anti-$GABA_B$, Anti-AMPAR, Anti-Glycine

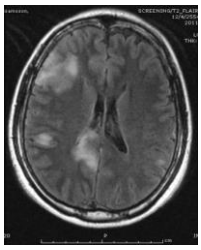
2. Autoantibody recognize intracytoplasmic organelle: T-cell mediated cytotoxicity

   ANNA-1, ANNA-2, Anti-CRMP-5, Anti-GAD, Anti-Ma2

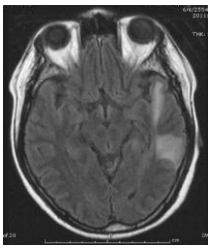
Antibody to intracytoplasmic organelle

- 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)

Summary of autoimmune epilepsy

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

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-responder
- 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