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Teaching Course 2

Autoimmune causes of epilepsy - Level 3

Autoimmune-like epilepsy without detectable antibodies

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Aim of this teaching presentation

To understand

1. the definition of “antibody negative autoimmune encephalitis/epilepsy”

2. potential shortcomings of diagnostics leading to an erroneous diagnosis of “antibody negative autoimmune encephalitis/epilepsy”

3. therapeutic approaches to true antibody-negative autoimmune epilepsies.

Definition “Antibody-negative autoimmune encephalitis”/ “autoimmune-like epilepsy without detectable antibodies”

- Requires clinical/paraclinical features to be fulfilled for making this diagnosis.[1, 2]

- Can only be defined in relation to the range of antibodies that are tested in a given laboratory (compare to “cryptogenic epilepsy” - may say more about quality of imaging than about the epilepsy)

- Overview over presently testable neural antibodies
“Ab negative autoimmune encephalitis/epilepsy” may erroneously be diagnosed:

First possibility
- 4 cases from Univ of Bonn, Dept. of Epileptology: Not only non-paraneoplastic but also negative for well-defined antibodies at that time.[3]
- But on closer look: one patient had atypical Hu antibodies
- Another one was recently (2017) re-tested and turned out to be Ma2 ab positive. These antibodies were not in regular test batteries when this study was performed. The index publication appeared only in 1999.[4]

➢ Take home message 1: Ab negative patients may - by time - turn out to be ab positive (newly detected antibodies)

Second possibility
- Doctor asks the lab for the “wrong” antibody. The patient has another antibody.[5]

➢ Take home message 2: A very sensitive approach is that with antibody panels and/or a sensitive rodent brain assay as first step

Third possibility
- Patient from hospital X with clear-cut clinical diagnosis of temporal lobe seizures due to limbic encephalitis: Laboratory A said “antibody negative”. The responsible doctor sent the material to another lab, which found LGI1 antibodies.
- If we have negative findings on the panel with cell based assays and the VGKC complex ab RIA gives a high concentration, we repeat LGI1 and CASPR2 antibodies. In rare instances, we then identified LGI1 antibodies.

  ➢ **Take home message 3:** Ab negative can be sensitivity problem of the laboratory/assay

**Fourth possibility**


  ➢ **Take home message 4:** Antibodies may not be found in all cases in CSF and serum alike

**Fifth possibility**

- Rasmussen encephalitis: no or inconsistently found autoantibodies

  ➢ **Take home message 5:** Autoimmune encephalitides do not need to have specific antibodies with them, they may be T cell driven diseases. Cf. Multiple sclerosis.

**Sixth possibility**

- The condition appears like “autoimmune encephalitis/epilepsy” but finally turns out to have a different cause. E.g., Creutzfeldt-Jakob disease[9]

  ➢ **Take home message 6:** not every case that looks like “autoimmune epilepsy” is really autoimmune in origin; one may have missed the real, no-encephalitic cause

  ➢ **Take home message 7:** tba
If by all intents and purposes a case remains suggestive of “autoimmune epilepsy” and is indeed antibody-negative with the available testing options, and if there are symptoms of the disease that ask for improvement beyond traditional symptomatic approaches with antiepileptics of psychotropic substances:

**Therapeutic approach (in house scheme Epilepsy Centre Bethel, The Mara):**

1. Establish a 3-month baseline on stable symptomatic medication (AED, psychotropic drugs)

2. Perform comprehensive evaluation: seizure diary, 48-h-EEG, neuropsychology testing, psychiatric examination. In addition, if abnormal: brain MRI, CSF (potential surrogate markers)

3. Define the target parameters of the immunological intervention (e.g.: a ≥50% reduction in seizure frequency; a “meaningful improvement” on neuropsychology testing)

4. Then a 3-4-month trial of a first line compound: steroids or IVIG. Symptomatic treatment needs to be hold at constant dosage.

5. Then re-evaluation as under #1. Was at least one aim achieved?

6. Plan further immunological treatment:
   a. Continuation of running therapy (when good response)
   b. Azathioprine to spare steroids (when good response but steroid side effects)
   c. Escalation with rituximab[10] (if insufficient response)
   d. Stop of immuno-tx (if no sufficient response and the risk-benefit ratio or the cost speak against rituximab)
References


