Teaching Course 2

Autoimmune causes of epilepsy - Level 3

Treatment of autoimmune epilepsies

Andrea Rossetti
Lausanne, Switzerland

Email: andrea.rossetti@chuv.ch
The treatment of autoimmune epilepsies

Andrea O. Rossetti
Service de neurologie
Lausanne
Switzerland

Disclosures

None
Aim

To learn the principles of pharmacological management of epilepsy and status epilepticus in patients with autoimmune etiologies

Case study 1: Mrs. CF, 25 yo

Subacute onset of
- drowsiness
- cognitive impairment (teacher)
- unusual behavior, irritability.

After admission
- stuporous, episodes of blank staring
- dysautonomic features, athetotic movements
Case study 1: Mrs. CF, 25 yo

Case study 2: Mr. MP, 47 yo

2 nocturnal GTC within 3 weeks

Slight, subacute
- emotional changes (wife)
- memory impairment (work)
Case study 2: Mr. MP, 47 yo
Case study 3: Mrs GR, 49 yo

At 28 yo:
-L arm convulsions, then throat constrictions

Evolution over 20 years:
-several episodes of L focal Status epilepticus, progressive
L corticospinal signs, then dystonia
-cognitive slowing, tilt to the R
Case study 3: Mrs GR, 49 yo

Operational epilepsy definition
Fisher Epilepsia 2014

• ≥ 2 seizures not due to reversible factors, or
• 1 seizure and >60% recurrence risk /10yrs, or
• one defined epileptic syndrome
Operational epilepsy definition

Fisher Epilepsia 2014

- ≥ 2 seizures not due to reversible factors,
- 1 seizure and >60% recurrence risk /10yrs,
- one defined epileptic syndrome

Epilepsies: treatment approach

- Is it epilepsy?
  - NO
    - 1st monotherapy
      - Efficacious treatment
        - 2nd monotherapy
          - Polytherapy (2 AEDs)
            - Efficacious treatment
              - Polytherapy (2-3 AEDs)
                - Efficacious treatment
                  - "in extremis"
                    - Surgery, Palliative treatments
AED: pearls and pitfalls
After Rossetti Rev Med Suisse 2010

<table>
<thead>
<tr>
<th>Situation</th>
<th>to favour</th>
<th>to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>LTG, VPA, CBZ, OXC</td>
<td>LEV, TPM, VGV, PER</td>
</tr>
<tr>
<td>Anxiety</td>
<td>PGB, GBP</td>
<td>LEV</td>
</tr>
<tr>
<td>Overweight</td>
<td>TPM, ZNS</td>
<td>VPA, CBZ, PGB</td>
</tr>
<tr>
<td>Elderly / polymedicated</td>
<td>LTG, LEV, PGB, GBP</td>
<td>PB, PHT, PRM, CBZ, OXC</td>
</tr>
<tr>
<td>Childbearing age</td>
<td>VPA, PB, TPM</td>
<td></td>
</tr>
</tbody>
</table>

Mostly for chronic treatment, CAVE:
- PHT and steroids
- LEV and hallucinosis / irritability

Operational Status epilepticus definition
Trinka Epilepsia 2015

Table 1. Operational dimensions with $t_1$, indicating the time that emergency treatment of SE should be started and $t_2$ indicating the time at which long-term consequences may be expected

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Operational dimension 1</th>
<th>Operational dimension 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic SE</td>
<td>Time ($t_1$) when seizure is likely to be prolonged leading to continuous seizure activity</td>
<td>Time ($t_2$) when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)</td>
</tr>
<tr>
<td>Focal SE with impaired consciousness</td>
<td>5 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Absence status epilepticus</td>
<td>10 min</td>
<td>&gt;60 min</td>
</tr>
</tbody>
</table>

*Evidence for the time frame is currently limited and future work may lead to modifications.

Guides treatment start
Guides treatment aggressiveness
Status epilepticus: tt approach
Rossetti & Bleck Int Care Med 2014

Immunosuppressants
Titulaer Lancet Neurol 2013

First line:
• corticosteroids; IVIG, PEX

Second line
• cyclophosphamide, rituximab, methotrexate, tacrolimus, alemtuzumab, adalimumab, …
Immunosuppressants: targets

<table>
<thead>
<tr>
<th>Compound</th>
<th>Humoral (AB)</th>
<th>Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>IV Immunoglobulins</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rituximab (anti CD20)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Alemtezumab (anti CD52)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Adalimumab (anti TNα)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

• Immunologic treatment → good prognosis! Bien Epilepsia 2013

Treatment with MP ± IVIG, PEX correlates with excellent prognosis in 60-90%
Titulaer Lancet Neurol 2013

Not all abnormal movements are epileptic!
→ (continuous)EEG
Dericioglu Epil Disord 2013
AB vs surface AG (NMDA-R, **LGI-1**, AMPA-R)

- Immunologic treatment → good prognosis!

![Graph showing percentage of patients with ongoing FADs](image)

MP ± IVIG, PEX
Irani *Brain* 2013

Outcome better for seizures than memory
Malter *J Neurol* 2014

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AB vs surface AG (NMDA-R, **LGI-1**, **AMPA-R**)

- Immunologic treatment → moderate prognosis!

Survival better for pts w/o associated onconeural AB
Höffberger *Neurology* 2015

![PET images](image)

PET to disentangle inflammation vs. seizures?
Spatola *J Neuroimmunol* 2014
AB vs intracellular AG (Hu/ANNA, Ma2/Ta, Yo, GAD65)

**Attempt tumor removal!** Dalmau & Rosenfeld *Lancet Neurol* 2008

**Rituximab**
Seizures controlled in few patients (Hu) Shams’ili *J Neurol* 2006

**MP ± IVIG, rituximab, cyclophosphamide**
Better seizure response in Ma2, Yo; (55%) than GAD65 (18%) Hansen *Epilepsy Behav* 2016

**MP, IVIG, PEX, surgery**
Seizure response: fair (MP: 45% - surgery: 66%) to poor (IVIG: 20%, PEX: 13%) in GAD65 Malter *Seizure* 2015

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### Rasmussen encephalitis

**Table 1** The “two faces” of RC

<table>
<thead>
<tr>
<th>Progressive neurological deficit</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying cause</td>
<td>Epileptiform - not further determined pro-epileptic (immunological) factor</td>
</tr>
<tr>
<td>Duration</td>
<td>Partial seizures - duration</td>
</tr>
<tr>
<td>Additional symptoms</td>
<td>Whole epileptic seizure</td>
</tr>
</tbody>
</table>

**Therapeutic options**
Long-term immunotherapy & 423x: "Short-term high-intensity" immunotherapy

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**Bien Epilepsy Res 2009**

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**Varadkar Lancet Neurol 2014**
Rasmussen encephalitis

Tacrolimus/IVIG
Functional « survival »
No definite effect on seizures
Bien Epilepsia 2013

Anti TNFα (adalimumab)
5/11 with 12-mo effect on sz frequency (<<50%)
3/5 with functional deficit stabilization
CAVE: infections, hepatotoxicity, neutropenia, skin reactions
Lagarde Epilepsia 2016

Presumed autoimmune, intractable epilepsy

29pts.; tt with MP, IVIG, PEX; response:
• 62%; seizure free in 34%
• surface AG: 88%, intracellular AG or no AB: 33%
• More often in subacute onset: median epilepsy duration 9 months (88%)
Toledano Neurology 2014

42pts.; tt with MP, IVIG, PEX:
• neural AB in 15 (36%); with surface AG in 8
• response in 9 (60%), seizure free in 6 (40%); mostly with surface AG and
disease duration < 6 months
Iorio Eur Neurol 2014
Autoimmune Status epilepticus

570 adult episodes

• 14 (2.5%) with autoimmune etiology
• Younger pts, more refractory to treatment than infectious causes
• Mortality in 1, more often *restitutio* than infectious causes

*Spatola Neurology* 2015

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**Flow chart of treatment**

Suspected autoimmune epilepsy → clinic, serum, CSF, MRI

- Definite AB / syndrome
  - AEDs + IV MP 1g, x 5d
  - If response: Wait and see
  - If no response: continue

- No definite AB / syndrome, illness > 2-3 years: STOP

- No definite AB / syndrome, illness < 2-3 years
  - IVIG 0.4 g/kg, x 5d, or PEX 5-7d
  - If no response: STOP

- Definite AB / syndrome
  - Rituximab 1g, 2x over 14d
  - or Cyclophosphamide 500mg, every 2w for 4 mo
  - Supportive care, until delayed response (consider experimentally: alemtuzumab, intrathecal methotrexate...)

Modified after Bakpa *Seizure* 2016
Case study 1: Mrs. CF, 25 yo

St. epilepticus in NMDA-R encephalitis

Which antiepileptic strategy do you prefer, after a benzo.?

A. Levetiracetam
B. Phenytoin
C. Valproate
D. Ketamine
Case study 1: Mrs. CF, 25 yo

St. epilepticus in NMDA-R encephalitis:

• ICU
• IV load with CLZ, LEV, then PO PGB, under cEEG
• After ruling out infections: IV MP, tightly followed by IVIG
• Slow improvement (EEG, clinical) over 8 weeks

Follow-up at 6 years:

• restitutio ad integrum
• no AED, no immnosuppression

Case study 2: Mr. MP, 47 yo
Case study 2: Mr. MP, 47 yo

GTC seizures in LGI-1 encephalitis

Which therapeutic strategy do you prefer?
A. Antiepileptic prescription only
B. Left temporal lobectomy
C. Immunosuppression only
D. Antiepileptic and immunosuppression

GTC seizures in LGI-1 encephalitis:

• In-patient work-up
• VPA 2x500mg
• After ruling out infections: IV MP, then IVIG and 2x rituximab

Follow-up at 2 years:
• Slight memory impairment
• no seizures, no AED, no immunosuppression
Case study 3: Mrs. GR, 49 yo

Seizures and St. epilepticus in Rasmussen encephalitis

Which therapeutic strategy do you prefer?

A. Long-term antiepileptic prescription
B. Elective hemispherotomy
C. Short-term immunosuppression
D. Long-term immunosuppression
Case study 3: Mrs. GR, 49 yo

Seizures and St. epilepticus in Rasmussen encephalitis:

**AED**
(CBZ, BDZ, VPA, VGV, TPM, GBP, LEV, LTG, LCM, PER)
PHT (tight blood level follow-up); PB; PGB; CLBZ

**Immunological**
AZT; MP; PEX; IVIG; mycophenolate-mofetil → no improvement

Follow-up at 21 years:
• Rel. stable neurological and neuropsychological deficits
• Dependent on PHT levels (target: 20-25 mg/l)

Conclusion: autoimmune epilepsies

• Look for neuronal antibodies !

• Target the cause → **immunosuppression**

• Surface antigens: generally good prognosis

• No definite syndrome, long illness: do not treat aggressively
Literature