AUTOIMMUNE ENCEPHALITIS
In children
Clinical Round 20/09/2022

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Group of non-infectious, immune-mediated inflammatory disorders of the brain parenchyma often involving the cortical or deep grey matter, with or without involvement of the white matter, meninges or the spinal cord.
Polysymptomatic syndrome

Seizure
Movement disorders
Psychiatric features
Gait disturbances
Autonomic disturbances
## Classification

### Table 1: Anatomical-clinical syndromes of autoimmune encephalitis

<table>
<thead>
<tr>
<th>Anatomical-clinical syndromes of autoimmune encephalitis</th>
<th>Corresponding clinical syndromes</th>
<th>Possible associated antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic encephalitis</td>
<td>Cognitive presentation</td>
<td>Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65, GABAergic, DPPX, mGlur5, AOKs, Neurexin-3x antibodies</td>
</tr>
<tr>
<td>Cortical/subcortical encephalitis</td>
<td>Cognitive presentation</td>
<td>PCA-2 (MAP1B), NMDAR, GABA A/B R, DPPX, MOG antibodies</td>
</tr>
<tr>
<td>Striatal encephalitis</td>
<td>Movement disorder presentation</td>
<td>CRMP5/CV2, DR2, NMDAR, LGI1, PO16A antibodies</td>
</tr>
<tr>
<td>Dienephalic encephalitis</td>
<td>Autonomic presentation</td>
<td>Ma 1–2, IgLON5, DPPX, AQP4 antibodies</td>
</tr>
<tr>
<td>Brainstem encephalitis</td>
<td>Cognitive presentation</td>
<td>R1, R1–2, KLHL11, IgLON5, DPPX, AQP4, MOG, GQ1b antibodies</td>
</tr>
<tr>
<td>Cerebellar or cerebellar degeneration</td>
<td>Dystonic presentation</td>
<td>Hu, R1, R1, R1-C, CASPR2, KLHL11, NIF, IgR1, GAD65, VGCC antibodies</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>Cognitive presentation</td>
<td>GFAP antibody or sereonegative AE</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Movement disorder presentation</td>
<td>GAD65, amphi, glycin receptor, PCA-2 (MAP1B), GABA A/B R, DPPX, CRMP5/CV2, AQP4, MOG antibodies</td>
</tr>
</tbody>
</table>

### Table 2: Proposed classification concepts in autoimmune encephalitis

<table>
<thead>
<tr>
<th>Anatomical classification</th>
<th>Serological classification</th>
<th>Aetiological classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic</td>
<td>Antibodies to intracellular antigens (classical convulsing antibodies).</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Cortical/subcortical</td>
<td>Antibodies to surface antigens and other antigens with high clinical relevance (eg, NMDAR, AMPAR, LGI1, CASPR2, GABA A/B, DPPX, glycin receptor, AQP4, MOG, GFAP).</td>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Striatal</td>
<td>Antibodies to surface antigens with low clinical relevance (eg, VGKC, VGCC).</td>
<td>Postinfectious</td>
</tr>
<tr>
<td>Dienephalic</td>
<td>Seronegative autoimmune encephalitis.</td>
<td>Iatrogenic (eg, in the setting of immune checkpoint inhibitors or other immune-modulating agents).</td>
</tr>
</tbody>
</table>
**A clinical approach to diagnosis of autoimmune encephalitis**

1. Rapid progression (less than 3 months) of working memory deficits, psychiatric symptoms, altered mental status.
2. At least two of the following:
   - MRI findings suggestive of encephalitis.
   - Brain biopsy showing inflammatory infiltrates and excludes other disorders
   - GOF, pleocytosis, GOF-specific oligoclonal bands and/or elevated GOF IgG Index.
3. Exclusion of well-defined syndromes of autoimmune encephalitis (e.g., ADEM, Bickerstaff’s encephalitis).
4. Reasonable exclusion of alternative causes.

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**Table: Antibodies against intracellular antigens**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Syndrome</th>
<th>Diagnostic assay</th>
<th>Frequency of cancer</th>
<th>Main type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu (ANNA1)</td>
<td>Limbic encephalitis</td>
<td>Western blot</td>
<td>&gt;95%</td>
<td>Small-cell lung carcinoma</td>
</tr>
<tr>
<td>Ma2</td>
<td>Limbic encephalitis</td>
<td>Western blot</td>
<td>&gt;95%</td>
<td>Testicular seminoma</td>
</tr>
<tr>
<td>GAD</td>
<td>Limbic encephalitis</td>
<td>Radioimmunoassay</td>
<td>25%</td>
<td>Thymoma, small-cell lung cancer</td>
</tr>
</tbody>
</table>

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**Table: Antibodies against synaptic receptors**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Syndrome</th>
<th>Diagnostic assay</th>
<th>Frequency of cancer</th>
<th>Main type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor</td>
<td>Anti-NMDA receptor encephalitis</td>
<td>Cell-based assay</td>
<td>Varies with age and sex</td>
<td>Ovarian teratoma</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Limbic encephalitis</td>
<td>Cell-based assay</td>
<td>65%</td>
<td>Thymoma, small-cell lung carcinoma</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>Limbic encephalitis</td>
<td>Cell-based assay</td>
<td>50%</td>
<td>Small-cell lung carcinoma</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>Ependymitis</td>
<td>Cell-based assay</td>
<td>&lt;5%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Ependymitis</td>
<td>Cell-based assay</td>
<td>70%</td>
<td>Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

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**Table: Antibodies against ion channels and other cell-surface proteins**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Syndrome</th>
<th>Diagnostic assay</th>
<th>Frequency of cancer</th>
<th>Main type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGI1</td>
<td>Limbic encephalitis</td>
<td>Cell-based assay</td>
<td>5–10%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>CASPR2</td>
<td>Limbic encephalitis</td>
<td>Cell-based assay</td>
<td>20–50%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>DPPX</td>
<td>Ependymitis</td>
<td>Cell-based assay</td>
<td>&lt;10%</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>MOG</td>
<td>Acute disseminated encephalomyelitis</td>
<td>Cell-based assay</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Aquaporin-4</td>
<td>Encephalitis</td>
<td>Cell-based assay</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>GQ1b</td>
<td>Bickerstaff’s brainstem encephalitis</td>
<td>ELISA</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
## Diagnosis

### A. Initial investigations for patients with possible AE

<table>
<thead>
<tr>
<th><strong>Diagnostic imaging</strong></th>
<th>Brain MRI with gadolinium (including T1, T2, FLAIR, and diffusion-weighted sequences)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood tests</strong></td>
<td>Consider adding spine MRI if neurologic abnormalities potentially mediated by spinal cord involvement</td>
</tr>
<tr>
<td></td>
<td>Complete blood cell count and differential</td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate, Creative protein, and ferritin</td>
</tr>
<tr>
<td></td>
<td>Vitamin B12 level and vitamin D level</td>
</tr>
<tr>
<td></td>
<td>Serum albumin</td>
</tr>
<tr>
<td></td>
<td>Thyroid-stimulating hormone, free thyroxine, and thyroid autoantibodies (e.g., antithyroid peroxidase, antithyroglobulin, and anti-thyroid-stimulating hormone receptor)</td>
</tr>
<tr>
<td></td>
<td>Serologic testing for infectious causes (dependent on regional epidemiology)</td>
</tr>
<tr>
<td></td>
<td>Consider antinuclear antibodies and specific antinuclear antibodies (e.g., anti-double-stranded DNA and anti-Smith) if indicated by clinical presentation</td>
</tr>
<tr>
<td><strong>Urine tests</strong></td>
<td>Consider serum complement and immunoglobulin levels if personal or family history of autoimmunity or immune deficiency</td>
</tr>
<tr>
<td><strong>Lumbar puncture</strong></td>
<td>Testing for recreational drugs (e.g., marijuana, cocaine, and opioids)</td>
</tr>
<tr>
<td><strong>Respiratory tests</strong></td>
<td>Opening pressure</td>
</tr>
<tr>
<td></td>
<td>CSF cell counts, protein, lactate, oligoclonal bands, and neopterin (if available)</td>
</tr>
<tr>
<td></td>
<td>Infectious testing dependent on regional epidemiology, but often includes PCR for enterovirus, herpes simplex virus, and varicella zoster viruses</td>
</tr>
<tr>
<td></td>
<td>Save 5-10 mL of CSF for future testing</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Nasopharyngeal swab for respiratory viruses and mycoplasma PCR</td>
</tr>
<tr>
<td><strong>CT chest, abdomen, and pelvis</strong></td>
<td>Assess for focal or generalized seizures, epileptiform discharges, and changes in background activity</td>
</tr>
</tbody>
</table>

### B. More specific investigations for patients with possible AE

<table>
<thead>
<tr>
<th><strong>Blood tests</strong></th>
<th>Serum testing for antibodies associated with AE*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar puncture</strong></td>
<td>CSF testing for antibodies associated with AE*</td>
</tr>
<tr>
<td><strong>Neurocognitive tests</strong></td>
<td>Assess for cognitive deficits affecting memory, attention, problem solving, language, and cognitive processing</td>
</tr>
<tr>
<td><strong>Other tests</strong></td>
<td>Consider using symbol digit modalities test to screen for cognitive dysfunction</td>
</tr>
<tr>
<td><strong>PET and SPECT</strong></td>
<td>Consider if available and/or if required based on initial investigations: PET and SPECT</td>
</tr>
</tbody>
</table>

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**Autoimmune Encephalitis in Children: An Update**

Vulval Garg, Krishna S. Mohindra, and Sharmi Sharma

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Autoimmune Encephalitis in Children: An Update

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Therapy

Mild To Moderate Disease

- No ICU

Severe Disease

- ICU/Dysautonomia/Intractable seizures

First Line Therapy

- IV methylprednisolone, 30mg/kg/day (max 1g/day) divided q6 hrs, for 5 days, then transition to Prednisone 2mg/kg (max dose 60mg/day)
- IVIG 2g/kg over 48 hrs

Additional Therapeutic Management

- Rituximab for continued treatment and relapse prevention after thorough discussion of risk vs benefits with family
- Obtain (quantiFERON Gold, hepatitis B, screening, IgG, IgM, ECE) cell subset panel prior to giving

Symptomatic Treatment

- On going supportive management of symptoms after diagnosis
- O2 prophylaxis while on steroids
- Anti-seizure medication for seizure management
- Trazodone, clonidine, benzodiazepines for sleep and psychiatric symptoms as needed; caution with anti-psychotic use
- Close monitoring of dysautonomia
- Physical, occupational, speech therapies
- Consider involvement of behavioral health, rehab, education consultant, integrative medicine, child life therapies

Autoimmune encephalitis: proposed best practice recommendations for diagnosis and management

Rasmussen
Encephalitis
Definition

CHRONIC, PROGRESSIVE ENCEPHALOPATHY WITH UNIHEMISPHERIC INVOLVEMENT AND FEATURED BY:

- DRUG-RESISTANT FOCAL SEIZURES/ EPC
  - HEMIPARESIS
  - PROGRESSIVE COGNITIVE DECLINE

Epidemiology
2,4 cases/ 10^7 under 18
No sex or ethnic predominance
Median age of onset 6yo
Diagnostic criteria

Clinical application and evaluation of the Bien diagnostic criteria for Rasmussen encephalitis


Table 2. Clinical criteria for Rasmussen encephalitis

<table>
<thead>
<tr>
<th>Part A</th>
<th>Need 3/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical</td>
<td>Focal seizures (+/− EPC) and unilateral cortical deficit(s)</td>
</tr>
<tr>
<td>2. EEG</td>
<td>Unihemispheric slowing +/− epileptiform activity and unilateral seizure onset</td>
</tr>
<tr>
<td>3. MRI</td>
<td>Unihemispheric focal cortical atrophy and at least one of the following: Grey or white matter T2/FLAIR hyperintense signal, Hyperintense signal or atrophy of the ipsilateral caudate head</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part B</th>
<th>Need 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical</td>
<td>EPC or Progressive† unilateral cortical deficit(s)</td>
</tr>
<tr>
<td>2. MRI</td>
<td>Progressive† unihemispheric focal cortical atrophy</td>
</tr>
<tr>
<td>3. Histopathology</td>
<td>T-cell-dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules and reactive astrogliosis) Numerous parenchymal macrophages, B cells, or plasma cells or viral inclusion bodies exclude the diagnosis of RE</td>
</tr>
</tbody>
</table>

Patients need to meet either A or B criteria.
*Progressive means that at least two sequential clinical examinations or MRI studies are required to meet the respective criteria. Adapted from Bien et al. (2005)
### International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions

<table>
<thead>
<tr>
<th></th>
<th>Mandatory</th>
<th>Alert</th>
<th>Exclusionary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Focal/hemispheric seizures that often increase in frequency over weeks to months</td>
<td>Focal onset independently in both hemispheres (only 2% of RS is bilateral)</td>
<td>Generalized onset seizures</td>
</tr>
<tr>
<td>EEG</td>
<td>Hemispheric slowing and epileptiform abnormality</td>
<td>Generalized spike-and-wave</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td>Adolescence or adulthood</td>
<td></td>
</tr>
<tr>
<td>Development at onset</td>
<td></td>
<td>Abnormal development prior to seizure onset</td>
<td></td>
</tr>
<tr>
<td>Neurological exam</td>
<td>Imaging</td>
<td>Imaging shows Sturge–Weber syndrome</td>
<td></td>
</tr>
</tbody>
</table>
• Disturbance of the background activity
• Asimmetry
• Focal slow activity
• Multifocal ictal discharges

• Normal at the beginning (unilateral enlargement of ventricular system)
• Cortical and subcortical increased signal T2
• Progressive unilateral cortical atrophy (F-T lobe or Insula)
Brain $^{18}$F-FDG PET for the diagnosis of autoimmune encephalitis: a systematic review and a meta-analysis

Manon Bordonne 1 - Mohammad B. Chawki 1 - Matthieu Doyen 1,3 - Aurelie Kas 3 - Eric Guedj 4 - Louise Tyvaert 4 - Antoine Verger 2,5
Clinical features: 3 stage disease

Prodromal stage
- Non-specific, low seizure frequency, and mild hemiplegia

Acute stage
- Frequent seizures, often epilepsy partialis continua (EPC); progressive hemiparesis, hemianopia, cognitive deterioration, and aphasia (if dominant hemisphere affected)

Residual stage
- Permanent and stable neurological deficits and continuing seizures
The Pathology of Rasmussen Syndrome: Stages of Cortical Involvement and Neuropathological Studies in 45 Hemispherectomies

Carlos A. Pardo, Eileen P. G. Vining, Liping Guo, Richard L. Skolasky, Benjamin S. Carson, and John M. Freeman
Pathophysiology

- Immune-mediated disease
- Cortical inflammation, lymphocytic infiltration, microglial activation
- (T CD8+)
- Both humoral and innate immunity
Caso clinico

**Storia famigliare:** sorella con patologia disimmune (Tiroidite hashimoto), e cugina in linea paterna con disabilità intellettiva.

**Decorso Neonatale:** ittero neonatale (fototerapia), lagoftalmo destro.

**Sviluppo neuropsicomotorio:** nella norma.

19 yo
**Semeiologia critica:** perdita di coscienza, fissità di sguardo e clonie agli arti superiori. Aura anticipatoria con nausea e parestesie retro-oculari. Sonno e nausea post-critico

**Storia personale:**

**Primo episodio critico 9/10/2017 (14aa)**
- TC encefalo: nella norma
- EEG basale: Onde lente anteriori post HP e dubbie punte-onda atipiche

**Secondo episodio critico 19/10/2017**
- Posta indicazione a ricovero presso nostro Istituto

**Ricovero**
- RMN: alterazione della diffusione alla sequenza ASL
- Livello cognitivo adeguato
- Iniziata terapia con Ox-CBZ 20 mg/Kg
- Diagnosi: EP. Focale temporale

Benessere 8 mesi
Da maggio 2018: crisi in addormentamento e/o al risveglio con variazione nella sintomatologia critica:
- Crisi minori (30s): scialorrea, stiramento rima orale verso sinistra, non perdita di consapevolezza ma sguardo vacuo.
- Crisi maggiori (2min): parestesie orali, deviazione capo, occhi e rima orale a sinistra, mioclonie orali, agitazione, afasia e disartria post-critica.
• EEG: incremento delle anomalie focali temporali destra con tendenza alla diffusione -> incremento terapia ox-carbazepina e introduzione perampanel.
• Valutazione cognitiva: stabilità del funzionamento cognitivo, ma evidenza di fragilità a carico delle funzioni esecutive

Follow-up ambulatoriale: crisi a semiologia nota, frequenza quindicinale. Numerosi tentativi terapeutici con ASMs.

Febbraio 2019, nuovo ricovero:
• EEG: anomalie a tipo punta e punta-lenta sulle regioni temporo-occipitali destra in veglia e scariche di sharp-waves generalizzate in sonno.
• RMN: quadro stabile, non segni di atrofia.
Novembre 2019: PET encefalo con «diffusa riduzione del metabolismo cerebrale di glucosio in sede emisferica destra. Il pattern metabolico appare suggestivo per epilessia emisferica (Encefalite di Rasmussen)>>.

Dicembre 2019 ricovero:
• RMN: nella norma. Alla ASL minimo incremento della perfusione cerebrale a livello fronto-opercolare sinistra.
• LCR: normalità
• EEG: attività diffusamente più lenta con anomalie punta e punta lenta sulle regioni temporo-occipitali di destra.
• Valutazione NPS: nella norma (fragilità funzioni esecutive).
• Psicopatologia: ansia sociale, senso di inadeguatezza, senso di colpa e anedonia

2020: follow-up ambulatoriale e telemedicina: persistenza crisi a frequenza quindicinale e stabilità del quadro elettrico

Marzo 2021: Ripetizione PET (sovrapponibile alla precedente: netta asimmetria della distribuzione del farmaco a destra).
Anomalie lente e puntute posteriori destre (temporali o temporo-occipitali)

**Neuroimaging:**
- RMN (2017): focale iperperfusione in sede temporale posteriore destra estesa anche in regione temporo-insulare.
- RMN (2021): iperperfusione insulare e temporale posteriore destra.
- PET (2021): asimmetria di distribuzione del radiofarmaco in sede corticale emisferica con minore captazione a destra.

**EEG**

**ASM**
- OXC
- PER
- LTG
- VPA
- LCS
- LEV

**LCR**
- negativo

**Cognitivo:**
- Deficit funzioni esecutive
- QI nella norma
- Difficoltà emotivo-relazionali
- irritabilità
Differential Diagnosis

- Unihemispheric epileptic syndromes
- Metabolic disorders
- Degenerative progressive neurological diseases
- Infectious diseases
Unihemispheric epileptic syndromes

- Rasmussen Encephalitis
- Tuberous sclerosis
- Cortical dysplasia
- Hemimegalencephaly
- Sturge-Weber-syndrome
- Stroke
- Hemiconvulsion-hemiplegia-epilepsy-syndrome
Prodromal stage not clearly identified
Slower evolution (3-9 years)
Favourable outcome

23% fulfill part a criteria
77% fulfill part B criteria
What to do next?

- **Neuroimaging?**
- **Stereo-EEG?**
- **Try add-on immunotherapy?**
ANY SUGGESTIONS?