Autoimmune Epilepsy & Inflammation Associated with Epilepsy

The emerging concepts, diagnosis, and management

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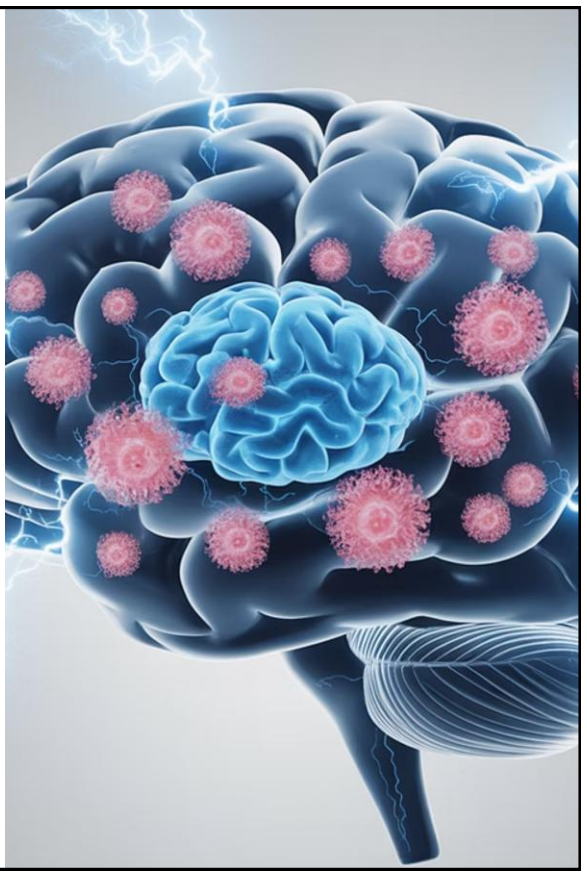

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Outlines

Introduction
Core concepts and definitions

Pathophysiology
Mechanisms of autoimmune and inflammatory epilepsy

Clinical Syndromes
Major autoimmune epilepsy syndromes

Diagnosis
Diagnostic approach and workup

Treatment
Management strategies and outcomes

Future Directions
Research priorities and emerging therapies

2

References:

- Steriade C, et al. Autoimmune encephalitis-associated epilepsy: Nature Reviews Neurology 2025
- Diprose WK, et al. Autoinflammatory syndromes in neurology: when our first line of defence misbehaves: Pract Neurol 2022
- Dalmau J, et al. Autoimmune encephalitis: NEJM 2018
- Dalmau J, et al. Immunity, Inflammation and epilepsy: Autoimmune encephalitis and related disorder of nervous system 2022

3

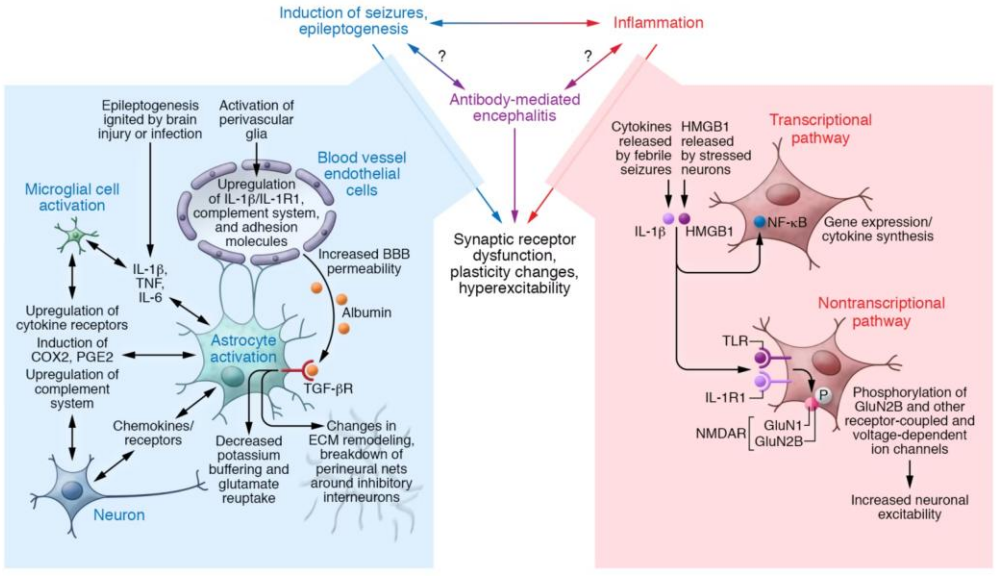
Immune System and CNS Interaction

The immune system interacts with the CNS through multiple pathways including:

- Antibody-mediated effects on neuronal surface proteins
- T cell-mediated cytotoxicity
- Cytokine-induced changes in neuronal excitability
- Microglial activation and neuroinflammation

4

Inflammation and Epilepsy



Geis C, et al. Autoimmune seizures and epilepsy: J Clin Invest 2019

5

Term & definition:

Autoimmune epilepsy

Epilepsy caused by an immune system attack on the brain.

Autoinflammation with seizure

Seizures as a symptom of a broader autoinflammatory disorder.

Autoimmune encephalitis associated with epilepsy (AEAE)

Epilepsy that develops as a consequence or long-term complication of autoimmune encephalitis.

Acute symptomatic seizure in autoimmune encephalitis

Seizures that occur during the acute phase of autoimmune encephalitis.

6

Autoimmune vs. Autoinflammatory Mechanisms

Autoimmune Mechanisms

- ***Adaptive immune*** system involvement
- Autoantibodies or autoreactive T cells
- Target specific antigens
- Examples: NMDAR, LGI1, GAD65 antibodies

Autoinflammatory Mechanisms

- ***Innate immune*** system dysregulation
- No specific autoantibodies
- Genetic mutations in inflammatory pathways
- Examples: CAPS, DADA2, MKD

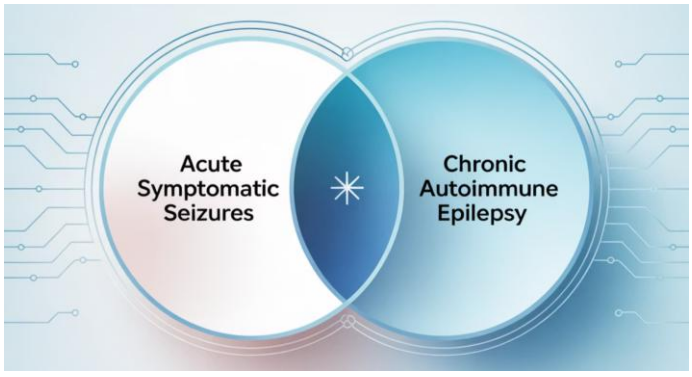
Both mechanisms can lead to epilepsy through different pathways

7

Core Concept: Autoimmune Encephalitis-Associated Epilepsy (AEAE)

AEAE is a new concept that distinguishes a subset of encephalitic conditions that present with:

- Recurrent seizures resistant to immunotherapy
- Different from acute symptomatic seizures (ASS) in autoimmune encephalitis (AE)
- ASS typically resolve with treatment for active AE
- AEAE requires a fundamentally different management approach



8

Distinguishing Autoimmune Encephalitis Associated Epilepsy from Acute Symptomatic Seizures

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Acute Symptomatic Seizures (ASS)

- Occur during active inflammation
- Typically resolve with immunotherapy
- No structural brain injury
- Temporary phenomenon

2

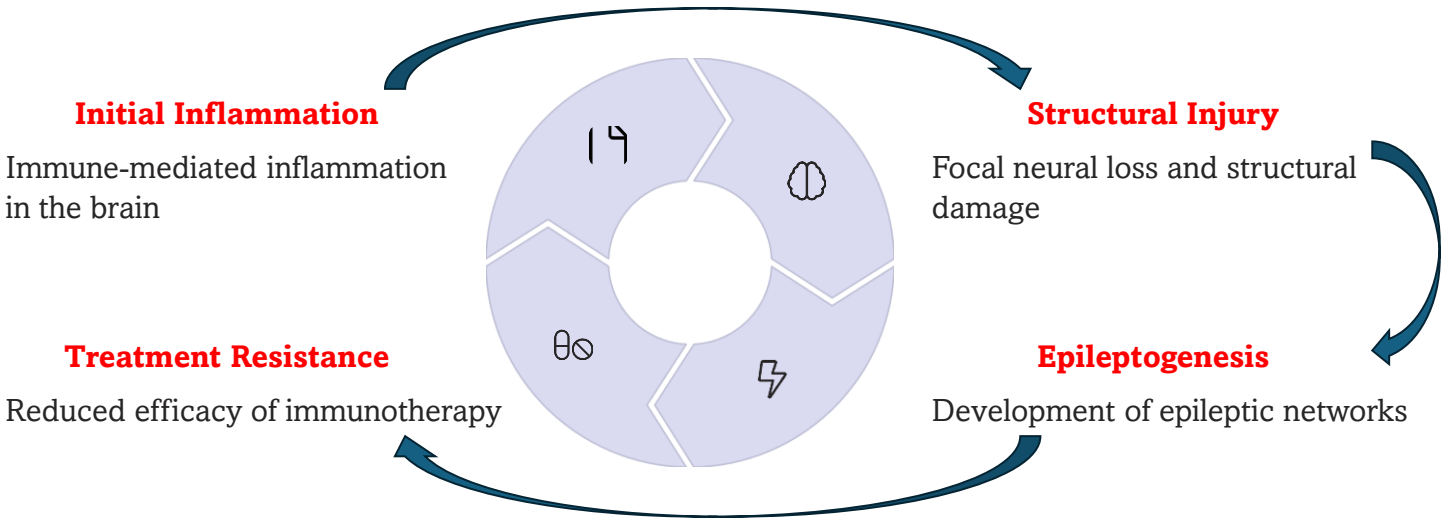
Autoimmune Epilepsy (AEAE)

- Persistent seizures despite immunotherapy
- Structural brain injury develops
- Requires chronic epilepsy management
- Often drug-resistant

The distinction is crucial for treatment planning and prognosis

9

Central Hypothesis for AEAE Development



Once structural injury is established, the likelihood of achieving seizure freedom through inflammation treatment alone significantly diminishes —> ***early treatment is the key***

10

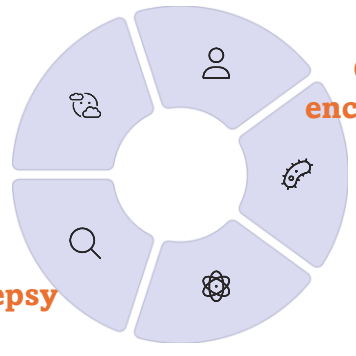
Autoimmune Epilepsy Syndromes

Hashimoto's Encephalopathy

Characterized by high anti-TPO antibodies, seizures, and rapid response to steroids

Rasmussen's Encephalitis

Asymmetric encephalitis with intractable focal seizures and progressive hemiparesis



Cell surface associated AE: NMDAR encephalitis & LGI1/CASPR2 Encephalitis

NMDAR-AE: Prominent psychosis, dyskinesias, and seizures

LGI1-AE: Limbic encephalitis with faciobrachial dystonic seizures and hyponatremia

GAD65 Antibody-Associated Epilepsy

Temporal lobe epilepsy with high GAD65 antibody titers

Intracellular Antigen associated AE

ANNA-1, CRMPS, KLHL11 AE → Related to tumors

11

Three Primary Neurological Constellations of AEAE

Temporal Lobe Epilepsy with GAD Antibodies (GAD-TLE)

Characterized by **high GAD antibody titers** and **temporal lobe epilepsy**

High-Risk Paraneoplastic Antibody-Associated Epilepsy

Associated with **antibodies recognzing intracellular antigen** indicating underlying malignancy

Epilepsy Following Treated Surface Antibody-Mediated AE

Persistent seizures after adequate treatment of LGI1, CASPR2, NMDAR, or GABABR encephalitis

12

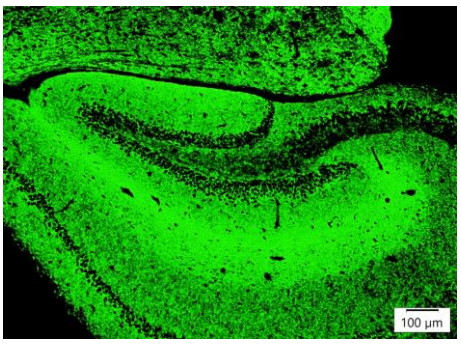
GAD-TLE: Clinical Presentation

Key Features

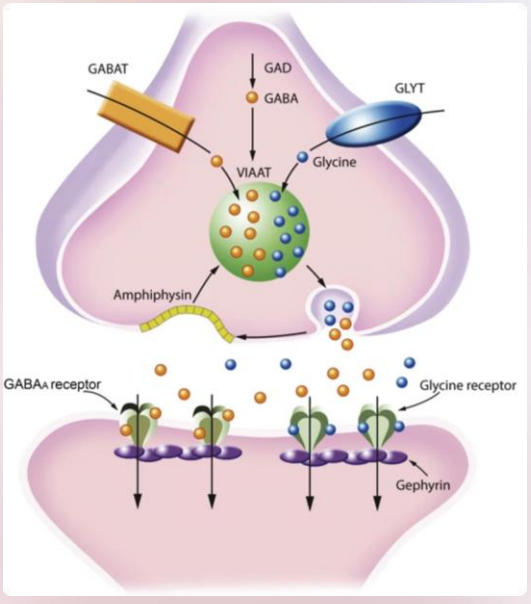
- ***High titers of GAD*** antibodies
- Temporal lobe epilepsy presentation
- Often female patients
- Associated with other autoimmune conditions
- Insidious onset leading to late diagnosis
- Peculiar semiological elements:
  - *Pilomotor seizures* (6.3% of cases associated with anti-GAD; mostly are associated with anti-LGI1)
  - *Musicogenic seizures* (56% of this seizure type associated with anti-GAD)

MRI scans may visually normal, but volumetric analyses may reveal amygdalar, frontal, and cerebellar volume abnormalities

IIF-tissue based assay identified high titer of anti-GAD



13



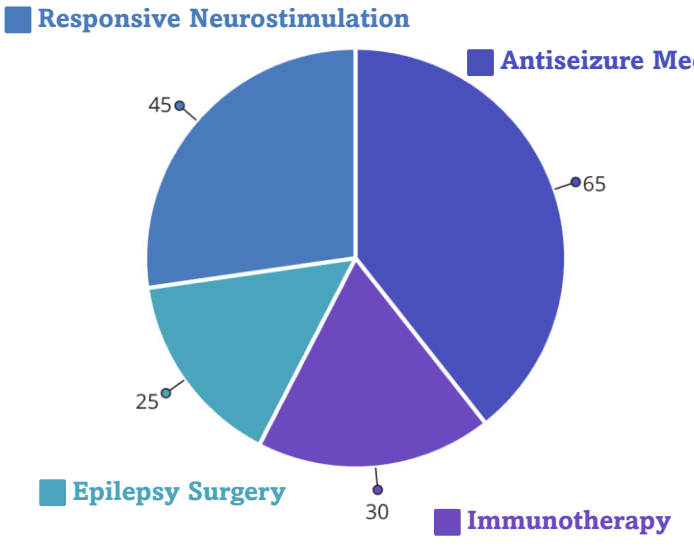
ⓘ Dalmau J et al , Physiol Rev 2017

GAD-TLE: Pathophysiology

- Strong inflammatory response in CNS parenchyma
- Dominant infiltration of CD8+ cytotoxic T cells, cytotoxic T cells with Granzyme B+ attack neurons, neuronal loss, astrocyte gliosis and activated microglia
- Degree of T-cell mediated inflammation are severe in the first few years, then gradually decrease with longer duration
- Imbalance of inhibitory and excitatory neurons induces seizures
- Genetic factors: HLA haplotypes and CTLA4 mutation noted
- Uncertain direct pathophysiological role of GAD antibodies (intracellular antigen)

14

GAD-TLE: Treatment and Outcome



- Immunotherapy has limited efficacy in achieving seizure freedom (steroid, IVIG, TPE)
- Longer disease duration before treatment —> reduces efficacy
- Cognitive improvements possible with early immunotherapy (within first two years)
- Antiseizure medications (ASMs) are the mainstay of seizure prevention with the trial of steroid over 3-6 months → substantial seizure reduction >50% support use of maintenance immunosuppression
- Poor epilepsy surgery outcomes
- Responsive neurostimulation shows promise in reducing seizure frequency

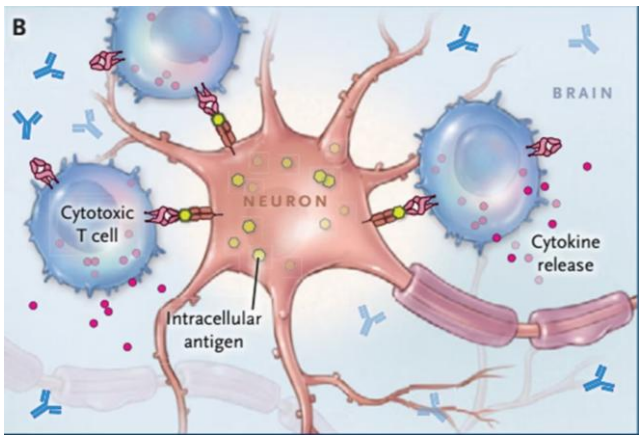
15

High-Risk Paraneoplastic Antibody-Associated Epilepsy

Clinical Presentation

- Associated with intracellular antibodies: ANNA-1/Hu, Ma2, CRMP5, ANNA-2/Ri, PCA2, KLHL11
- Frequently indicate underlying malignancy
- Recurrent seizures as core feature, can include ***extralimbic epilepsy, high seizure frequency***
- **Perisylvian semiology** common
- **Subclinical seizures** also common

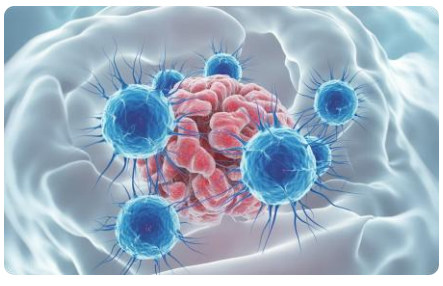
Functional imaging often shows hypermetabolism in affected regions before structural changes are evident



ⓘ Josep Dalmau, NEJM 2018

16

High-Risk Paraneoplastic Antibody-Associated Epilepsy: Pathophysiology

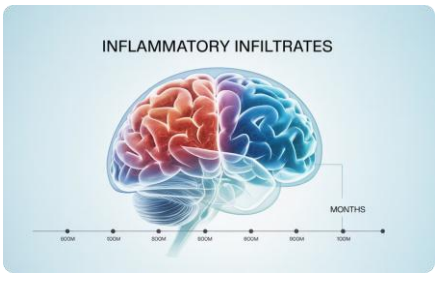


T Cell Infiltration

CD8+ cytotoxic T cells tightly appose neurons, leading to neuronophagia

Perivascular Inflammation

Inflammation in perivascular and parenchymal locations, but no Ab-mediated or complement-mediated killing



Temporal Evolution

Inflammatory infiltrates decrease over time, especially in prolonged cases

17

High-Risk Paraneoplastic Antibody-Associated Epilepsy: Treatment and Outcome

Oncological Treatment

Identification and treatment of underlying malignancy is critical

Immunotherapy

Cyclophosphamide may modulate T cells more effectively than other therapies

Antiseizure Medications

ASM adjustments are crucial, but specific data on outcomes are limited

Epilepsy Surgery

May offer palliative effects due to high seizure burden

Outcomes are generally poor, with high mortality rates and limited improvement from immunotherapy, related to rapidly destructive T-cell mediated inflammation + unfavorable prognosis of underlying malignancy

18

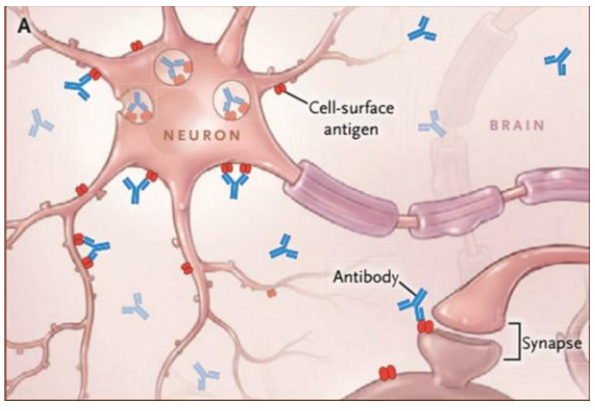
Epilepsy Following Treated Surface Antibody-Mediated AE

Key Features

- Minority of patients develop persistent seizures after acute phase treatment
- **No** latent period - seizures persist unabated
- Challenging to distinguish from active AE relapse
- Lack of reliable biomarkers for ongoing inflammation

Predictors for Ongoing Seizures

- Older age at onset
- Status epilepticus
- Elevated CSF protein
- Specific antibodies (LGI1, GABABR)
- Hippocampal sclerosis in LGI1 encephalitis



Josep Dalmau, NEJM 2018

19

Surface Antibody-Mediated AE: Pathophysiology

Genetic Associations

Strong HLA associations with LGI1 and CASPR2 antibody-mediated AE

Receptor Internalization

LGI1 and NMDAR antibodies cause receptor internalization, reducing synaptic receptors

Complement Activation

In severe LGI1/CASPR2 encephalitis, antibody-mediated complement activation contributes to neuronal cell death

Structural Changes

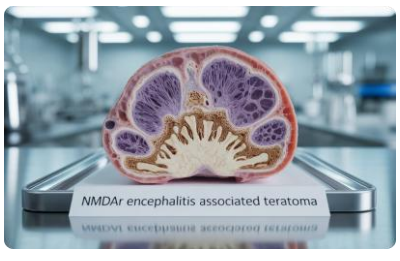
Neuronal loss and hippocampal sclerosis mostly absent in NMDAR AE but can occur in LGI1 encephalitis

20

NMDA Receptor Antibody-Associated Encephalopathy

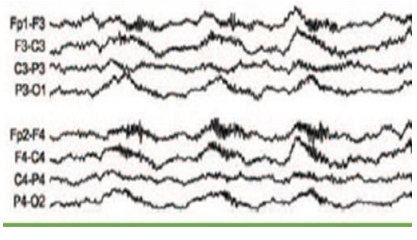
Clinical Presentation

Seizures, psychosis, dyskinesias, catatonia, and respiratory failure



Tumor Association

Highly correlated with ovarian teratoma in young women

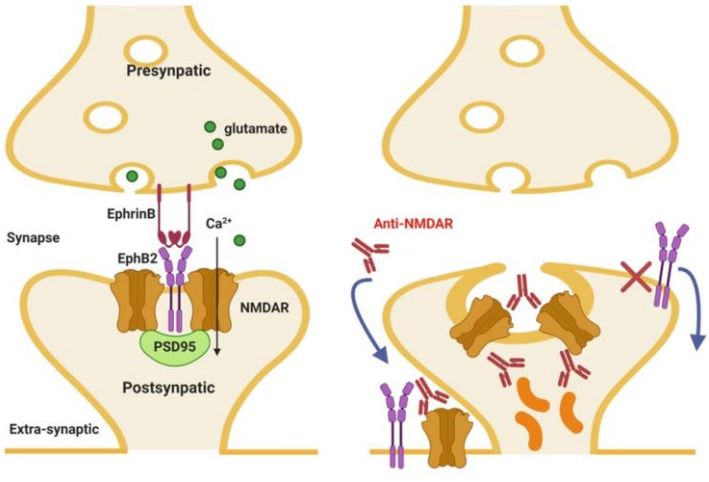


Diagnostic Features

Characteristic EEG pattern of diffuse rhythmic delta activity ("extreme delta brush")

22

NMDA Receptor Antibody-Associated Encephalopathy: Pathophysiology and Treatment



Pathophysiology

- NMDA receptor antibodies target the GluN1 subunit
- Cause reversible decrease in surface receptor density through internalization
- Autoimmune neuronal destruction does not typically occur
- Explains high potential for neurological recovery
- Often-normal MRI findings

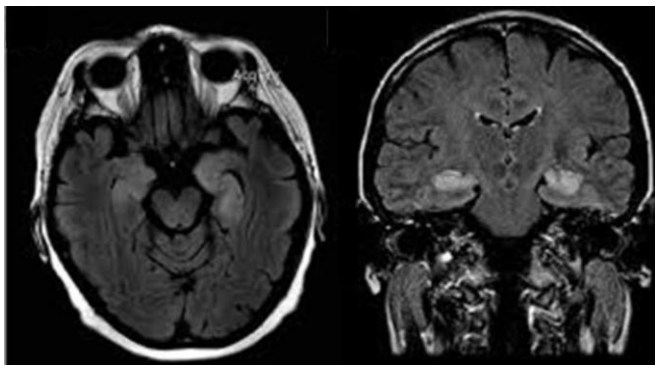
Treatment

- High dose steroid + IVIG or PLEX
- Early second line therapy with rituximab if not response with 1st line in 2 weeks
- Third line therapy include tocilizumab

22

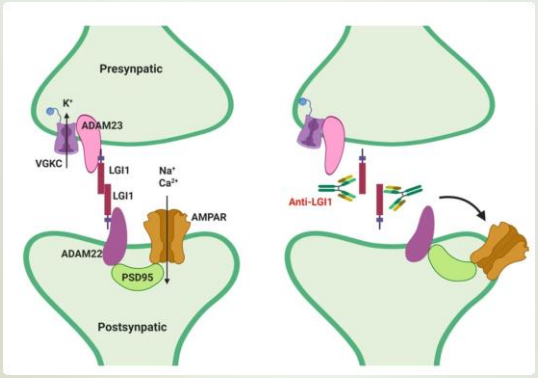
LGI1 Antibody-Associated Encephalitis

Clinical Presentation



- Temporal-lobe seizures (65%)
- ***Faciobrachial dystonic seizures*** (50%) (characteristic) are brief, frequent movements affecting the face, arm, and sometimes leg on one side of the body
- Hyponatremia or hypothermia (helpful clue)
- Favorable seizure prognosis with treatment
- Memory deficits can persist (up to 30%)

23



LGI1 and CASPR2 Antibody-Associated Encephalitis: Pathophysiology and Treatment

Antibody Mechanism

LGI1 antibodies lead to internalization of the LGI1–ADAM22 complex, reducing synaptic AMPA receptors

Complement Activation

In severe cases, LGI1 antibody-mediated complement activation contributes to neuronal cell death

Most of LGI1 (some IgG1,3) and CASPR2 are IgG4

Treatment Response

Highly responsive to immunotherapy (corticosteroids)

NOT well response to IVIG

Refractory Options

Plasmapheresis and rituximab for resistant cases

24

Other Neural Antibodies Associated with Epilepsy

Antibody	Clinical Features	Treatment Response
GABA-B Receptor	Limbic encephalitis, often with small-cell lung carcinoma	Responds to immunosuppressants
GABA-A Receptor	Refractory seizures and status epilepticus	Variable response
AMPA Receptor	Limbic encephalitis, sometimes with psychosis or tumors	Generally respond to immunotherapy
Glycine Receptor	Progressive encephalomyelitis, rigidity, and myoclonus (PERM)	Most respond to immunotherapy

25

Surface Antibody-Mediated AE: Treatment and Outcome

Diagnostic Dilemma

Deciding on further immunotherapy for persistent seizures is challenging

Seizure recurrence often represents AE relapse that may respond to treatment

Monitoring Approach

Use antibody titers, neuroimaging (MRI, FDG PET), and CSF analysis to guide decisions

Time alone is insufficient to diagnose AEAE

Treatment Strategy

ASMs are crucial when immunotherapy fails

Sodium channel blockers may be particularly effective for LGI1 antibodies

Surgical Options

Experience with epilepsy surgery in this subtype is limited

26

Detailed Comparison of AEAE Subtypes

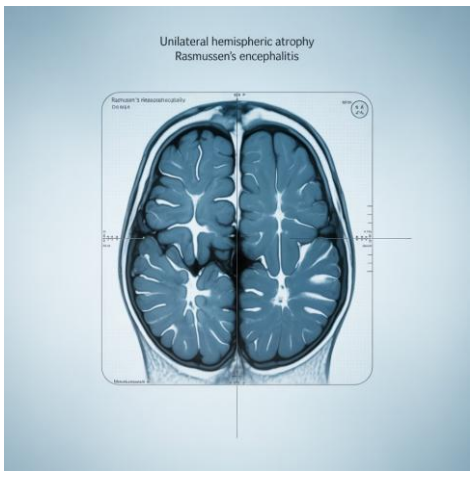
Feature	GAD-TLE	High-Risk Paraneoplastic	Post-LGI1 AEAE
Primary Mechanism	Cytotoxic T-cell mediated	Cytotoxic T-cell mediated	Complement cascade, neuronal surface antibody
Female Predominance	Strong (84-95%)	Moderate (43-52%)	Moderate (40-60%)
Cancer Association	Rare (0-6%)	Common (63%)	Rare (0%)
Autoimmune Comorbidities	Common (55-57%), e.g., Type 1 Diabetes	Uncommon	Uncommon
Immunotherapy Response	Poor (11-20%) for epilepsy	Moderate (45%)	Variable, often good for acute encephalitis
Hippocampal Sclerosis on MRI	18%	12%	50-58%
Seizure Type	Drug-resistant TLE, focal impaired awareness seizures	Focal, often drug-resistant	Facial brachial dystonic seizures (FBDS), focal impaired awareness, secondary generalized
Onset Age	Adults, often middle-aged	Variable, often older adults	Adults, often middle-aged to older
CSF Findings	Often normal or subtle changes, GAD antibodies	Inflammation (pleocytosis, elevated protein), antibodies	Often normal or mild pleocytosis, LGI1 antibodies
Prognosis	Chronic, often drug-resistant epilepsy	Variable, depends on tumor treatment	Good for encephalitis, but epilepsy can persist

27

Rasmussen's Encephalitis

Clinical Features

- Asymmetric encephalitis, Unilateral hemispheric atrophy
- Intractable focal seizures, often progressing to epilepsia partialis continua, progressive hemiparesis
- Primarily affects children, late-onset cases possible



Diagnosis

- No specific serological test
- CSF often normal in over 50% of cases
- MRI shows unilateral hemispheric atrophy
- Not considered a paraneoplastic syndrome

28

Rasmussen's Encephalitis:

Pathophysiology and Treatment

Pathophysiology

- T-cell mediated inflammation
- Microglial nodules and cytotoxic CD3+/CD8+ T lymphocytes
- Previous theories about GluR3 antibodies largely disproven
- Considered an autoimmune disorder of unknown etiology with potentially triggered by viral infection
- Transitions into chronic immune-mediated disease

Treatment

- Immunosuppressive therapy often disappointing
- Options include: Corticosteroids, Cyclophosphamide, Intravenous immunoglobulins (IVIG), Plasmapheresis,
- ***Hemispherectomy or hemispherotomy*** most effective for seizure control
- ***Surgical intervention can halt*** neurological deterioration in refractory cases

29

Hashimoto's Encephalopathy

Clinical Presentation

- Waxing and waning mental status changes
- Seizures (up to 66% of cases), Stroke-like episodes, Chronic cognitive decline, Psychiatric symptoms
- Patients typically euthyroid

Diagnosis

- Serological hallmark: high titers of anti-thyroperoxidase (anti-TPO) antibodies
- MRI often normal (74%)
- Can show mesial temporal T2 hyperintensities
- EEG shows moderate abnormalities, epileptiform discharges, generalized triphasic waves
- EEG tends to improve with treatment

Also known as Steroid-Responsive Encephalopathy Associated with Thyroiditis (SREAT) or Nonvasculitic Autoimmune Inflammatory Meningoencephalitis (NAIM)

30

Hashimoto's Encephalopathy: Pathophysiology and Treatment

Pathophysiology

- Anti-TPO antibodies considered markers rather than direct pathogenic agents
- Other neural antibodies identified but pathogenic relevance uncertain
- Histopathology shows perivenular inflammatory changes without frank vasculitis

Treatment

- Marked and relatively quick response to corticosteroids
- IVIG and plasmapheresis are options for refractory cases
- Maintenance immunotherapy may be needed for relapsing cases

31

Diagnostic Work-up for AEAE

1

Clinical Suspicion

- Adult-onset focal epilepsy
- Drug-resistant, frequent seizures
- Temporal, insular, or perisylvian involvement
- Pilomotor or musicogenic seizures highly suggestive

2

Initial Evaluation

- Check for systemic comorbidities (tumors, autoimmune conditions)
- MRI brain (hippocampal sclerosis does not rule out AEAE)
- EEG monitoring

3

Laboratory Testing

- Serum antibody testing: GAD, LGI1, CASPR2, paraneoplastic antibodies
- CSF analysis
- Consider brain biopsy in unclear, antibody-negative cases

4

Monitoring

- Serial MRI, PET, EEG, neuropsychological assessments
- Serial CSF/serum antibody tests
- Optimal frequency not yet established

32

AEAE Diagnostic Criteria

AEAE diagnosis can be considered if ongoing seizures persist for at least 2 years after immunotherapy, accompanied by decreasing antibody titers and resolution of imaging and standard CSF signs of active inflammation.

33

Management Philosophy of AEAE

1. **Multimodal Epileptological Approach**
2. **Antiseizure Medications**
3. **Consider Epilepsy Surgery**
4. **Address Cognitive, Psychological, and Social Challenges**
5. **Scale Back Immunotherapy if Structural Injury Supersedes Inflammation**

Close collaboration with a neuroimmunologist is essential

34

Autoinflammatory Diseases (AIDs) and CNS

Group of disorders characterized by:

- Dysregulated immune responses
- Chronic inflammation within the CNS
- Activation of the innate immune system
- Absence of autoantibodies or antigen-specific T cells

35

Mechanisms of Autoinflammation in CNS

Genetic Mutations

Affecting genes involved in inflammasome regulation, cytokines, and innate immune components

Inflammasome Activation

NLRP3 and NLRC4 play crucial roles in initiating auto-inflammation in the CNS

Microglial Activation

Resident immune cells become activated and release pro-inflammatory cytokines

Tissue Damage

Sustained activation leads to protein aggregation and neuronal damage

36

Clinical Manifestations of CNS Autoinflammation

Neurological Symptoms

- Recurrent fever
- Headaches
- Seizures
- Altered mental status
- Focal neurological deficits
- Developmental delays

Inflammatory Markers

- Elevated C-reactive protein
- Increased ferritin
- CSF pleocytosis
- Elevated protein levels
- Specific cytokine profiles

Imaging Findings

- Brain calcifications
- Cerebral atrophy
- White matter changes
- Meningeal enhancement
- Vascular abnormalities

37

Classification of Autoinflammatory Disorders Affecting CNS

1

Primary CNS Autoinflammatory Disorders

- Aicardi-Goutières Syndrome (AGS)
  - Early-onset encephalopathy
  - Brain calcifications
  - CSF lymphocytosis

2

Systemic Autoinflammatory Disorders

- Familial Mediterranean Fever (FMF)
- Behçet's disease
- Neuro-Behçet's disease
- Cryopyrin-Associated Periodic Syndromes (CAPS)

38

Key Autoinflammatory Syndromes with Neurological Involvement

Syndrome	Genetic Defect	Key Neurological Features	Seizure Risk
CAPS	NLRP3 mutations	Aseptic meningitis, hydrocephalus, brain atrophy	Low
DADA2	CECR1 mutations	Ischemic/hemorrhagic strokes, peripheral neuropathy	Moderate
MKD	MVK mutations	Hypotonia, developmental delay, cerebellar atrophy	High in severe forms
AGS	TREX1, SAMHD1, etc.	Microcephaly, cerebral atrophy, calcifications	High

39

Diagnostic Approach to Autoinflammatory CNS Disorders

1

Clinical Suspicion

- Unexplained systemic inflammation
- Unexplained multisystem disease
- Improvement with corticosteroids

2

Neurological Clues

- Aseptic meningitis/meningo encephalitis
- Sensorineural hearing loss with multisystem disease
- Peripheral neuropathy with multisystem disease

3

Rule Out Other Causes

- Infection
- Malignancy
- Autoimmune diseases

4

Diagnostic Tests

- Blood cultures
- Viral/bacterial serology/PCR
- CSF analysis
- Autoimmune markers
- Imaging
- Genetic testing

40

General Diagnostic Work-up for Autoimmune Epilepsy

1 Clinical Suspicion

- Acute to subacute onset of focal epilepsy (especially temporal or perisylvian)
- Drug-resistant, frequent seizures (often daily)
- Specific semiologies like pilomotor or faciobrachial dystonic seizures
- Other neurological symptoms (cognitive impairment, encephalopathy)
- Systemic comorbidities (autoimmune conditions, cancer, hyponatremia)

2 Diagnostic Tools

- EEG (often abnormal, can reveal subclinical seizures)
- MRI (can be normal, or show mesial temporal/striatal hyperintensities)
- FDG-PET may show hypermetabolism
- Serologic testing for relevant antibodies
- CSF examination (can be unremarkable in up to 60% of cases)
- Brain biopsy in unclear, antibody-negative cases

41

General Therapeutic Approach for Autoimmune Epilepsy

1 Antiseizure Medications

First-line treatment for seizure control

2 First-line Immunotherapy

Corticosteroids (IV methylprednisolone) and IVIG

3 Plasmapheresis

For critically ill patients

4 Second-line Agents

Rituximab and cyclophosphamide for refractory cases

5 Maintenance Therapy

For patients who relapse

Patients with antibodies targeting cell surface antigens generally respond better to immunotherapy than those with antibodies to intracellular antigens

42

Future Research Directions

Early Diagnosis and Intervention

- Early diagnosis before structural epileptogenesis supersedes inflammation
- Timely and potentially more effective immunotherapeutic interventions

Improved Therapeutics

- Develop therapies targeting specific immunological mechanisms
- Tailored immunotherapeutic options for different pathways

Biomarkers

- Discover additional biomarkers of neuroinflammation and autoimmunity
- Precisely determine degree of active inflammation in chronic phase

Clinical Studies

- Empirically test operational definitions in prospective studies
- Establish registries for long-term outcome studies
- Conduct prospective controlled trials for therapeutic interventions

43

Key message 1: Comparison table of Autoimmune vs. Autoinflammatory Epilepsy

Feature	Autoimmune Epilepsy	Autoinflammatory Epilepsy
Immune System	Adaptive (T and B cells)	Innate (macrophages, neutrophils)
Pathogenic Markers	Autoantibodies, T cells	Cytokines, inflammasomes
Genetic Basis	HLA associations	Specific gene mutations
Onset Pattern	Often subacute	Often recurrent/episodic
Response to Treatment	Variable by antibody type	Often responsive to targeted therapy
First-line Treatment	***Immunotherapy + ASMs***	***Cytokine inhibitors + ASMs***

44

Key Messages 2

1

Distinct Mechanisms

Autoimmune and autoinflammatory epilepsies involve different immune pathways but both can lead to structural brain injury and chronic seizures

2

Early Recognition

Early diagnosis and treatment are critical to prevent progression from acute symptomatic seizures to chronic autoimmune epilepsy

3

Multimodal Approach

Management requires collaboration between epileptologists and neuroimmunologists, with both immunotherapy and antiseizure medications

4

Evolving Field

Research is needed to develop better biomarkers, targeted therapies, and evidence-based treatment protocols