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Autoimmune Epilepsy

Diagnostic Challenge and Treatment Strategy

Metha Apiwattanakul MD.
Neuroimmunology Unit
Department of Neurology
Neurological Institute of Thailand

กรมการแพทย์
DEPARTMENT OF MEDICAL SERVICES

สถาบันประสาทวิทยา
Neurological Institute of Thailand

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What this talk should change in practice

1 Recognize

Identify seizure phenotypes and accompanying features that should trigger an autoimmune encephalitis work-up.

2 Classify

Separate acute symptomatic seizures, inflammatory relapse, and autoimmune encephalitis-associated epilepsy (AEAE).

3 Treat the Etiology

Escalate immunotherapy when inflammation is active; pivot toward comprehensive epilepsy care when structural epileptogenesis dominates.

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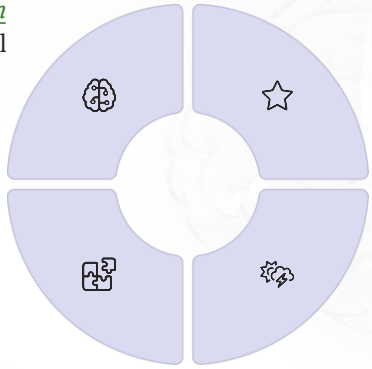
Term & Definition

Autoimmune epilepsy

Epilepsy caused by an *immune system attack on the brain*. Mostly from T cell mediated (intracellular Ag) such as paraneoplastic encephalitis from ANNA-1 or GAD-TLE

Autoimmune encephalitis associated with epilepsy (AEAE)

Epilepsy that *develops as a consequence or long-term complication* of autoimmune encephalitis (i.e. MTS after anti-LGI1)



Autoinflammation with seizure

Seizures as a *symptom of a broader autoinflammatory disorder*. Mostly from innate immunity disorder (i.e. cytokine storm)

Acute symptomatic seizure in autoimmune encephalitis

Seizures that occur *during the acute phase* of autoimmune encephalitis. Mostly from cell surface (pathogenic Ab) such as anti-NMDAR, Anti-LGI1, Anti-GABAb

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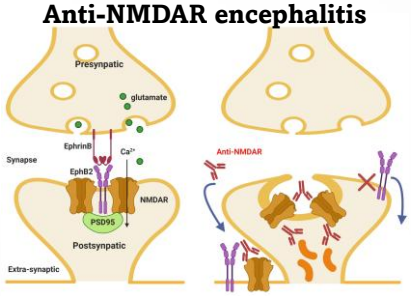
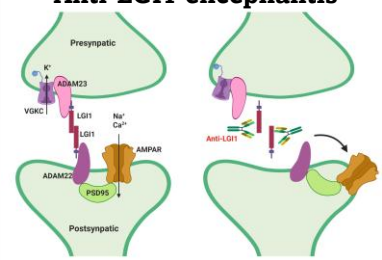
Pathogenesis of acute symptomatic seizure in AE

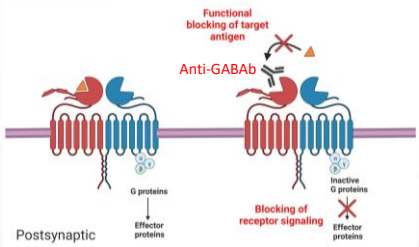
Anti-NMDAR encephalitis



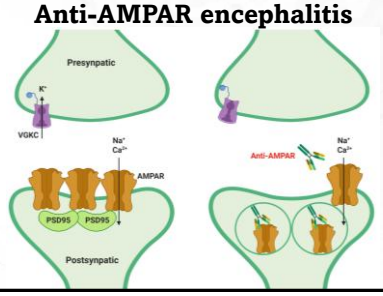
Anti-LGI1 encephalitis



Anti-GABAb encephalitis



Anti-AMPAR encephalitis



Pathogenic IgG
CSF-compartment immune response

↓

Target binding
NMDAR / LGI1 / GABAR/ AMPAR

↓

Receptor/channel change
Internalization or altered synaptic organization

↓

Network hyperexcitability
E/I imbalance and oscillatory disturbance

↓

Acute symptomatic Seizure

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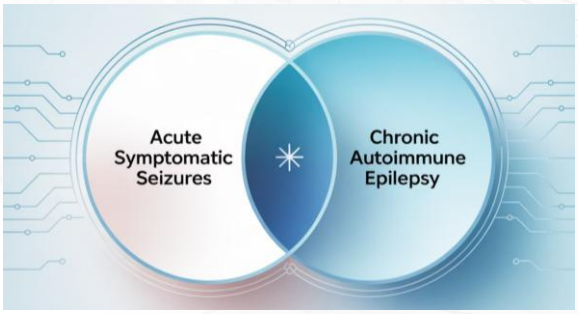
Core Concept: Autoimmune Encephalitis-Associated Epilepsy (AEAE)

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



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Distinguishing Autoimmune Encephalitis Associated Epilepsy from Acute Symptomatic Seizures

1

Acute Symptomatic Seizures (ASS)

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

2

Autoimmune Encephalitis Associated 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

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Central Hypothesis for AEAE Development

Initial Inflammation

Immune-mediated inflammation in the brain

Structural Injury

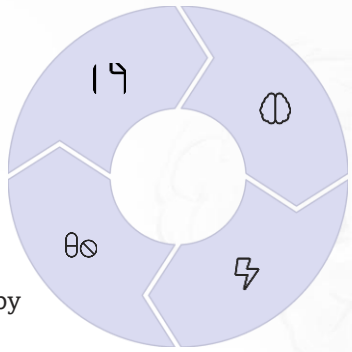
Focal neural loss and structural damage

Treatment Resistance

Reduced efficacy of immunotherapy

Epileptogenesis

Development of epileptic networks



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

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A practical definition of AEAE

All five criteria proposed for AEAE-surface-antibody AE

1. Previous AE: NMDAR, LGI1, CASPR2 or GABABR
2. Seizures persist ≥2 years after immunotherapy began
3. MRI: no active encephalitic signal; hippocampal sclerosis allowed
4. FDG-PET: no hypermetabolism
5. Normal CSF cell count + substantial antibody-titre decrease

Important caveat

Time alone is insufficient: seizures can occasionally take >1 year — even years — to resolve while inflammatory activity is still waning.

Rada A, Bien CG. Epilepsia. 2023;64:2249–2255. doi:10.1111/epi.17699.

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Autoimmune Epilepsy

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

Ma2 limbic and diencephalic encephalitis

Testicular germ-cell tumor in young men; residual mesial temporal injury with chronic seizures after the acute phase.

GAD65 Antibody-Associated Epilepsy

Temporal lobe epilepsy with high GAD65 antibody titers

Limbic encephalitis in T cell mediated paraneoplastic disease

ANNA-1, CRMPS LE → Related to tumors

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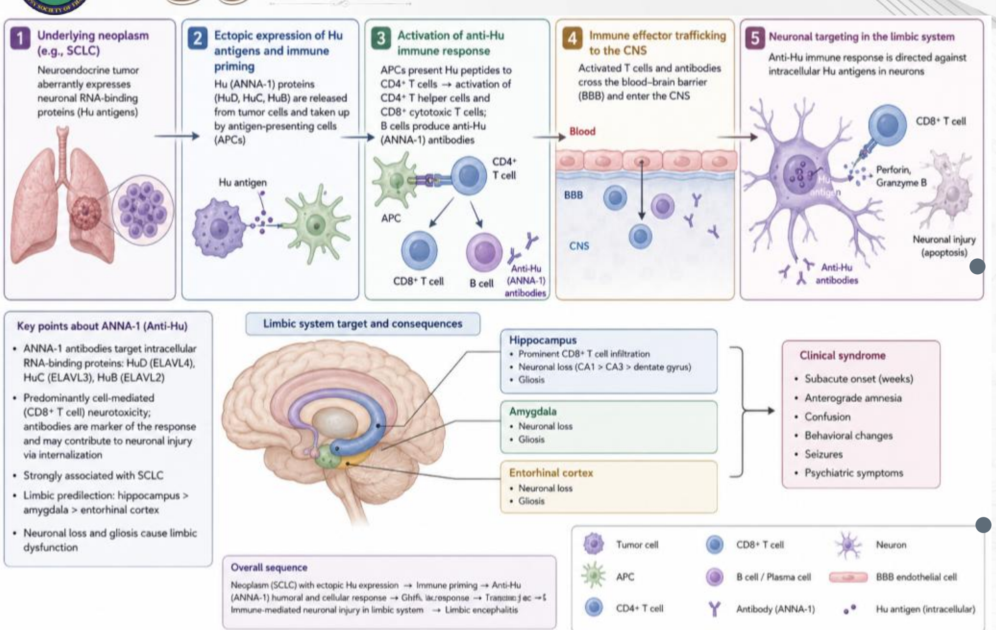
Pathogenesis of Paraneoplastic Encephalitis



1 Underlying neoplasm (e.g., SCLC)
Neuroendocrine tumor aberrantly expresses neuronal RNA-binding proteins (Hu antigens)
2 Ectopic expression of Hu antigens and immune priming
Hu (ANNA-1) proteins (HuD, HuC, HuB) are released from tumor cells and taken up by antigen-presenting cells (APCs)
Hu antigen
3 Activation of anti-Hu immune response
APCs present Hu peptides to CD4+ T cells → activation of CD4+ T helper cells and CD8+ cytotoxic T cells; B cells produce anti-Hu (ANNA-1) antibodies
CD4+ T cell
APC
CD8+ T cell
B cell
Anti-Hu (ANNA-1) antibodies
4 Immune effector trafficking to the CNS
Activated T cells and antibodies cross the blood–brain barrier (BBB) and enter the CNS
Blood
BBB
CNS
5 Neuronal targeting in the limbic system
Anti-Hu immune response is directed against intracellular Hu antigens in neurons
CD8+ T cell
Perforin, Granzyme B
Hu antigen
Neuronal injury (apoptosis)
Anti-Hu antibodies
Key points about ANNA-1 (Anti-Hu)
ANNA-1 antibodies target intracellular RNA-binding proteins: HuD (ELAVL4), HuC (ELAVL3), HuB (ELAVL2)
Predominantly cell-mediated (CD8+ T cell) neurotoxicity; antibodies are marker of the response and may contribute to neuronal injury via internalization
Strongly associated with SCLC
Limbic predilection: hippocampus > amygdala > entorhinal cortex
Neuronal loss and gliosis cause limbic dysfunction
Limbic system target and consequences
Hippocampus
Prominent CD8+ T cell infiltration
Neuronal loss (CA1 > CA3 > dentate gyrus)
Gliosis
Amygdala
Neuronal loss
Gliosis
Entorhinal cortex
Neuronal loss
Gliosis
Clinical syndrome
Subacute onset (weeks)
Anterograde amnesia
Confusion
Behavioral changes
Seizures
Psychiatric symptoms
Overall sequence
Neoplasm (SCLC) with ectopic Hu expression → Immune priming → Anti-Hu
(ANNA-1) humoral and cellular response →
Immune-mediated neuronal injury in limbic system → Limbic encephalitis
Tumor cell
CD8+ T cell
Neuron
APC
B cell / Plasma cell
BBB endothelial cell
CD4+ T cell
Antibody (ANNA-1)
Hu antigen (intracellular)

CD8+ T-cell recruitment

Clonal immune response enters brain parenchyma

Cytotoxic synapse

Granzyme-mediated neuronal injury; microglial activation

Focal neuronal loss

Gliosis / hippocampal sclerosis / durable epileptogenic network

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RECOGNITION

When should new-onset seizures trigger an immune work-up?

Tempo
Subacute progression over days–weeks

Rapidly increasing frequency / status

Syndrome
Memory, psychiatric, speech or movement change

Dysautonomia / sleep disturbance

Paraclinical
Inflammatory CSF or limbic/multifocal MRI

EEG encephalopathy or unusual patterns

Clinical Context
Cancer or systemic autoimmunity

No better structural/toxic/metabolic explanation

Absence of one red flag does not exclude AE

Graus et al. Lancet Neurol. 2016;15:391–404; Smith et al. 2024; Chang et al. Epilepsia. 2022;63:1658–1670.

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Seizure semiology can be the first biomarker

FBDS	Very brief unilateral face–arm dystonic events; often many/day; strongly suggests LGI1.
Autonomic / pilomotor	Piloerection, thermal sensation, tachycardia; consider limbic/insular autoimmunity. (LGI1, GAD65)
Multifocal / changing semiology	New seizure types over days to weeks suggest a dynamic inflammatory network. (GAD65, GABAa)
Seizures + movement disorder	Orofacial dyskinesia, stereotypy and autonomic instability point toward NMDAR AE.
New focal RSE / NORSE	Autoimmune, infectious and cryptogenic inflammatory causes must be pursued in parallel.

Smith et al. Epileptic Disord. 2024;26:415–434; Thompson et al. Brain. 2018;141:348–356.

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Diagnose possible AE clinically — do not wait for the antibody

Subacute onset (<3 months): working-memory deficit, altered mental status, or psychiatric symptoms

PLUS ≥1

- New focal CNS finding
- New unexplained seizures
- CSF pleocytosis
- MRI suggestive of encephalitis

Reasonable exclusion of alternative causes

Graus F, et al. Lancet Neurol. 2016;15:391–404.

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The first 24–48 hours: parallel, not sequential, testing & treatment

1	2	3	4	5
STABILIZE	**EXCLUDE**	**PHENOTYPE**	**SAMPLE**	**TREAT**
Treat seizures / status; continuous EEG when indicated	HSV/VZV and other infection; metabolic, toxic, vascular and structural mimics	Neurologic + psychiatric exam; seizure semiology; cancer/autoimmune context	MRI with contrast; CSF cells/protein/OCB/IgG index; paired serum + CSF antibodies	If AE is reasonably probable, initiate immunotherapy while results are pending

Do not allow a negative initial MRI, normal routine CSF, or pending antibody panel to delay immunotherapy.

Graus et al. 2016; Abboud et al. JNNP. 2021; Smith et al. 2024.

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Antibody testing: match specimen to target and syndrome

ACUTE ENCEPHALITIC PRESENTATION

- Paired CSF + serum comprehensive neural antibody evaluation
- CSF essential for NMDAR and improves specificity for several surface antibodies, including anti-GFAP
- Serum often more sensitive for LGI1/CASPR2 — interpret low levels clinically
- Always pair results with phenotype and assay method

ESTABLISHED FOCAL EPILEPSY / AEAE SUSPECTED

- Focused serum testing: GAD65, LGI1, CASPR2 and high-risk paraneoplastic antibodies
- NMDAR/GABABR testing has low yield in isolated chronic seizures without prior AE syndrome
- Document titer, confirmatory assay and intrathecal synthesis when attribution is uncertain
- Search for tumor based on antibody risk

Smith et al. Epileptic Disord. 2024;26:415–434; Graus et al. 2016; Steriade et al. 2025.

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A positive antibody is NOT automatically the cause

Low-pretest probability panels	Increase false positives and distract from a structural epilepsy diagnosis. (Anti-thyroglobulin and anti-microsomal in Dx of encephalopathy)
Serum-only low titers	May be nonspecific; e.g.GAD65 relevance depends on titer → high titer is compatible with neurological disease), MOG-IgG low titer should be interpreted with clinical phenotype. CSF evidence may be needed such as MOG-IgG or other synaptic Ab.
VGKC-complex without LGI1/CASPR2	Not a clinically meaningful neural-specific biomarker.
Titer = activity?	Serial titers correlate only loosely with clinical status; never use in isolation. Mostly the titer is not needed for follow-up. Anti-NMDA may be persisted many years even patient is fully recovery.
Response = proof?	Steroids can transiently affect seizures by non-immune mechanisms; placebo and ASM changes confound.

Steriade et al. JAMA Neurol. 2021;78:1383–1390;Smith et al. 2024;Rada & Bien 2023.

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Imaging in helping of define disease

ACTIVE AE

↑ FLAIR
↑ FDG

Mesial temporal swelling/FLAIR hyperintensity; basal ganglia change in FBDS; multifocal lesions in GABAAR AE

FDG-PET may show hypermetabolism or characteristic network disturbance

RECOVERY

SERIAL CHANGE

Signal and metabolism normalize; volume loss may begin

Compare serial scans — a single normal MRI is not exclusionary

AEAE

HS / ATROPHY

Hippocampal sclerosis, focal atrophy, gliosis; PET hypometabolism

Structural substrate dominates; occult neuronal loss may exceed routine MRI

Smith et al. 2024; Rada & Bien 2023; Steriade et al. Nat Rev Neurol. 2025.

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EEG supports the syndrome — but not specific

EEG can distinguish dyskinesia from seizures.

LGI1

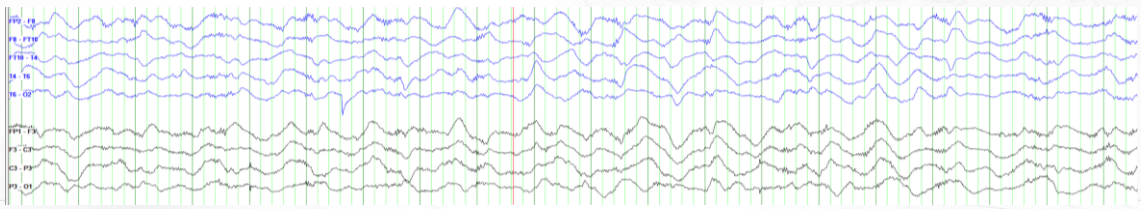
Temporal ictal/interictal abnormalities; FBDS may lack a clear scalp EEG correlate.

NMDAR

Diffuse slowing; ***extreme delta brush*** is characteristic but neither sensitive nor specific.

AEAE

Stable focal epileptiform activity supports a chronic network; EEG alone cannot prove inactive inflammation.



Smith et al. Epileptic Disord. 2024;26:415–434.

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Is inflammation still driving the seizures?

FAVOURS ACTIVE AE / RELAPSE

- New cognitive/psychiatric decline
- New seizure types or escalating frequency
- MRI/FDG-PET inflammatory activity
- CSF pleocytosis / intrathecal inflammation
- Meaningful antibody titre rebound
- Improves when immunotherapy is intensified

FAVOURS AEAE

- Stable stereotyped chronic seizures
- Fixed cognitive deficit
- Hippocampal sclerosis / focal atrophy
- Normal routine CSF
- Low or falling titre
- No durable response to adequate immune therapy

Rada & Bien 2023; Steriade et al. Nat Rev Neurol. 2025.

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Relapse is not the same as chronic AEAE

After a sustained seizure-free interval…

SEIZURE RECURRENCE

RELAPSE

Reemerged inflammation: same or *new* cognitive/behavioral syndrome, FLAIR or FDG-PET activation, CSF change or titer rise. Often responds again to immunotherapy.

AEAE

Ongoing or recurrent unprovoked seizures without renewed inflammatory evidence, on a background of fixed structural injury.

Rada & Bien. Epilepsia. 2023;64:2249–2255; Liu et al. Epilepsia. 2022;63:1812–1821.

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Treatment strategy: Immunotherapy + seizure management

1 ACTIVE AE

Immunotherapy + tumor treatment

Abort seizures / status epilepticus

Prevent irreversible injury

2 UNCERTAIN TRANSITION

Reassess clinical serially

Time-limited immune trial if justified

Optimize ASM in parallel

3 AEAE

Drug-resistant epilepsy strategy

ASM / surgery / neurostimulation

Rehabilitation + psychosocial care

Smith et al. 2024; Abboud et al. JNNP. 2021; Steriade et al. Nat Rev Neurol. 2025.

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Treatment strategy in Acute AE: Immunotherapy + Tumor treatment + Seizure controlled

FIRST LINE

IV methylprednisolone up to 1 g/day × 3–5 days

IVIg 2 g/kg over 2–5 days

Plasma exchange 5–7 exchanges over 10–14 days

Choose/combine according to severity, contraindications and likely antibody biology.

ESCALATE WHEN SEVERE OR NON-RESPONSIVE

Rituximab

Cyclophosphamide

Tumor-directed therapy

Cytokine-based Rx: Tocilizumab/Anakinra

Evidence is predominantly observational; early treatment is consistently associated with better outcomes.

Smith et al. Epileptic Disord. 2024;26:415–434; Abboud et al. JNNP. 2021.

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Antiseizure medication: necessary, phase-dependent

DURING ACTIVE AE

- Treat status and reduce seizure burden immediately
- Do not interpret ASM refractoriness as proof of non-epileptic events
- Immunotherapy often has the larger disease-modifying effect
- Watch levetiracetam behavioral toxicity and sodium-channel blocker rash/hyponatremia

IN AEAE

- Optimize as drug-resistant focal epilepsy
- Treat symptoms, not antibody
- Avoid using immunotherapy unless clear evidence of re-emerge or persistent inflammation
- Consider surgery or neuromodulation after careful localization and activity assessment

After resolved AE and sustained seizure freedom, selected patients may taper ASM after ~6–12 months — individualized.

Smith et al. 2024; Feyissa et al. Epilepsia Open. 2018;3:348–356; Steriade et al. 2025.

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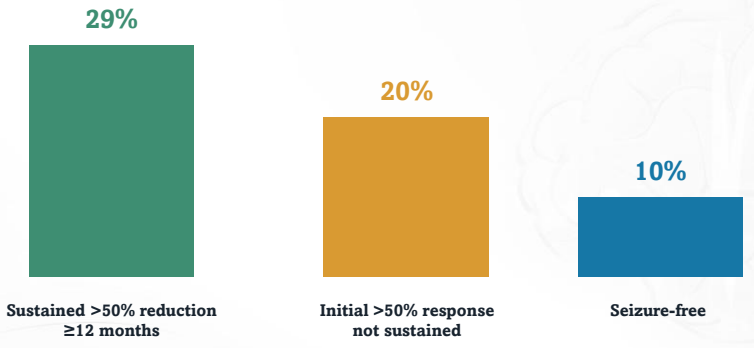
Empiric immunotherapy in chronic refractory epilepsy: Not proof

Single-center retrospective cohort | n=31 | median epilepsy duration 11.4 years | median 5 prior ASMs



Interpret cautiously

- No control group
- ASM changes confounded
- Only 4 antibody-positive; GAD65, Low titer VGKC
- No baseline feature predicted response
- Steroid / placebo / BBB effects possible

A time-limited trial may be reasonable in carefully selected patients — but response does not retrospectively validate AEAE.

Doran E, et al. Epilepsia. 2025;66:2743–2753. doi:10.1111/epi.18417.

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Special situation: NORSE/FIRES

DEFINE	New-onset refractory SE without clear acute structural, toxic or metabolic cause
SEARCH	Infection, neural antibodies, malignancy, metabolic/genetic causes; bank CSF/serum early
TREAT	Standard SE care + first-line immunotherapy when appropriate; ketogenic diet within the first week if ongoing
TARGET	If cryptogenic and refractory, consider *anakinra or tocilizumab* guided by consensus and inflammatory profile

Most evidence is consensus and observational; chronic epilepsy and cognitive impairment are common.

Wickström et al. Epilepsia. 2022;63:2827–2839 and 2840–2864;Smith et al. 2024.

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Take-home messages

1 Suspect

Subacute, rapidly escalating seizures plus cognitive, psychiatric, autonomic or movement features should trigger an urgent AE work-up.

2 Define Etiology

Triangulate serial clinical change, MRI/FDG-PET, CSF and EEG. Active relapse is not chronic AEAE.

Antibody positivity alone does not prove activity.

3 Match therapy

Active inflammation: immunotherapy + tumor treatment + ASM.

Fixed structural epilepsy: optimize ASM and evaluate surgery or neuromodulation.

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