Autoimmune encephalitis and Epilepsy

Hamid Nemati, MD/MPH
Pediatric Neurologist with Epilepsy & Video-EEG Training
Epilepsy Research Center, Shiraz University of Medical Sciences

Disclosure

- **Honoraria from Cobel Daruo**

Reference

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The beginning of the story

- The discovery of **IgG Ab against proteins on nerve cell surfaces** has been perceived as a major advance and even a breakthrough in neurology
- The first specific antibodies that have relevance and validity until to date are those **against the NMDA receptor**
- These were followed by those against **LGI1**, **CASPR2** and others

- The list of potentially relevant antibodies that is known today may not yet be complete, as **the field is still young** and there are still reports of **new associations from the neuro-pediatric age range**

TWELVE TYPES OF AUTOIMMUNE ABs IN THE SERUM AND/OR CSF OF PWE, AND OF OTHER PATIENTS WITH SEIZURES AND ENCEPAHLITIS

- **Type 1**: Autoimmune ABs to **Glutamate receptor AMPA type**, subunit GluR3, peptide B, called GluR3B peptide ABs, or GluR3B ABs
- **Type 2**: Autoimmune ABs to **Glutamate receptor NMDA type**, **NR1 subunit**, called NMDA-NR1 antibodies

Continued…

- **Type 3**: **Glutamate receptor NMDA type, subunit NR2**, called NMDA-NR2 ABs
- **Type 4**: **GABA-R** antibodies
- **Type 5**: Called **GAD-65** antibodies
- **Type 6**: Called **VGKC** antibodies
- **Type 7**: Called **LGI1** antibodies

- **Type 8**: Autoimmune ABs to Contactin-associated protein-like 2, called **CASPR2** antibodies
- **Type 9**: Autoimmune ABs to **Glycine receptor**
- **Type 10**: **Cardiolipin ABs**
- **Type 11**: **Beta2-glycoprotein-I antibodies**
- **Type 12**: **dsDNA antibodies**, and to other nuclear proteins

GRAUS CRITERIA

Existing diagnostic criteria for autoimmune encephalitis were **too reliant on antibody testing and response to immunotherapy**:

- Antibody testing is **not readily accessible** in many institutions

- The **absence** of autoantibodies **does not exclude** and a **positive test** does not always imply an **accurate diagnosis**

- **Use of the response to immunotherapy** is also **not practical** because this information is not available at the time of symptom onset or early clinical evaluation

- Some patients with autoimmune encephalitis might **not respond to immunotherapy**

- Conversely, patients with **other disorders might respond to immunotherapy (eg, primary CNS lymphoma)**

- Because **children do not develop many of the autoimmune encephalitis disorders that affect adults**, and the **syndrome presentation might be different or less clinically recognizable**, the **Graus criteria** should be applied **with caution** in children, particularly in children **younger than 5 years**

Initial clinical assessment: Patients suspicious for autoimmune encephalitis

Panel 1

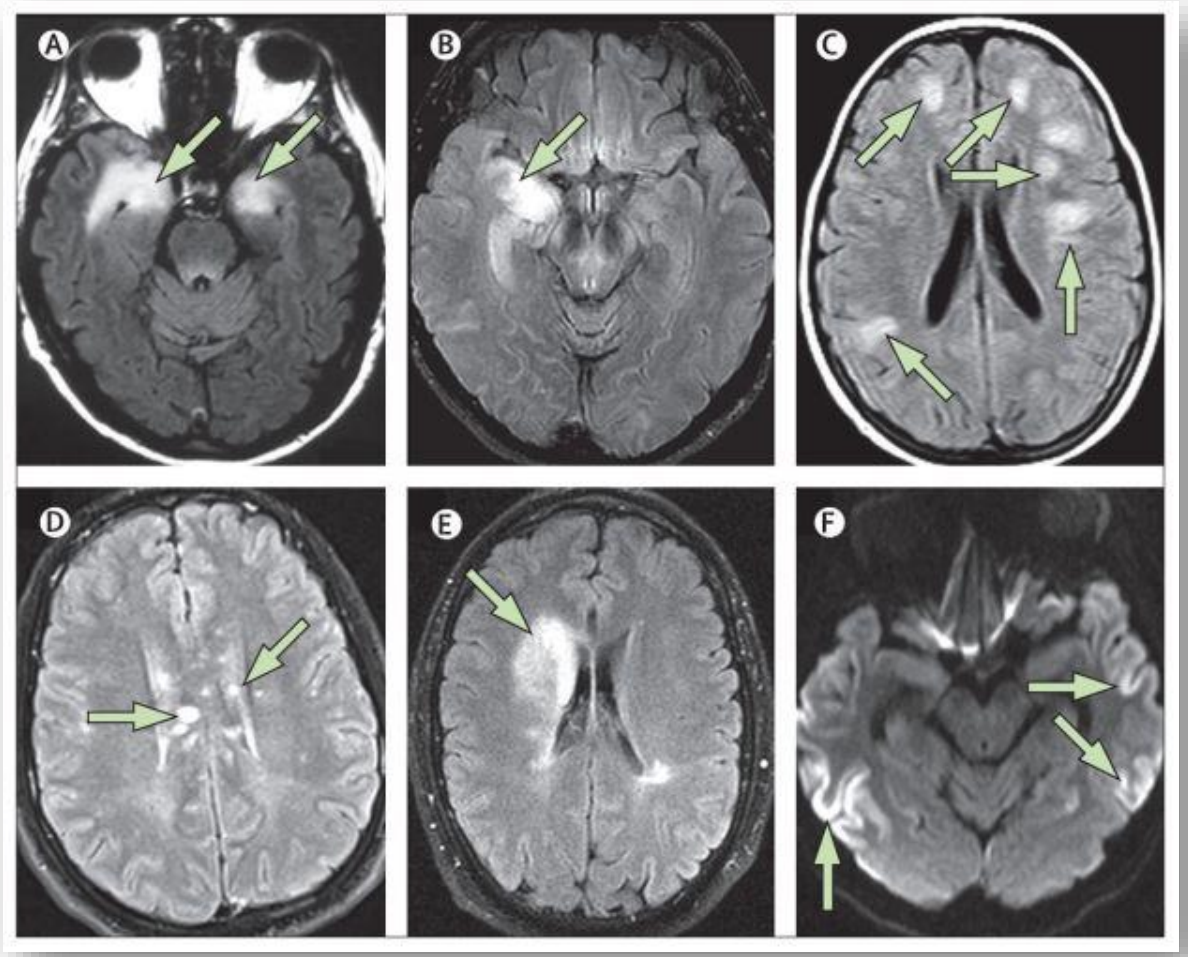
Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
2. At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - MRI features suggestive of encephalitis†
3. Reasonable exclusion of alternative causes (appendix)

- These criteria differ from those previously proposed for encephalitis in which **changes in the level of consciousness, fever, CSF pleocytosis, and EEG alterations** are more often needed
- So, AE could present **with memory or behavioral deficits, without fever** or **alteration in the LOC**, or **with normal brain MRI or CSF results**

- Consider other diseases that can **mimic AE**
- These diseases should be excluded before treatment **(detailed history, complete general and N/E, routine blood and CSF analysis, and MRI will suffice)** to accomplish this goal
- The **most frequent DDX are HSV encephalitis and other CNS infections**. Importantly, CSF-HSV PCR can be negative if done too early (eg, within 24 h), and this test should be **repeated** if the clinical suspicion remains high


A
B
C
D
E
F

patients with clinically recognizable syndromes

- **Autoimmune limbic encephalitis**
- **ADEM and other syndromes with MRI features of demyelination**
- **Anti-NMDA receptor encephalitis**
- **Bickerstaff's brainstem encephalitis**

Panel 2

Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

- The **onco-neuronal ABs** that more frequently occur with LE and underlying **cancer** are **Hu** and **Ma2**
- By contrast, the **neuronal cell-surface ABs** that are associated with LE are **LGI1, GABAB and AMPA receptor**
- ABs against the **intracellular antigen GAD** occur in a subgroup of patients mainly **young women** (median age 23 years) with predominant **seizures** and **no evidence of cancer**
- The **risk of cancer**, usually SCL carcinoma or thymoma, is higher with **older than 50 years** or have concomitant **GABAB receptor AB**

Panel 3

Diagnostic criteria for definite acute disseminated encephalomyelitis[32]

Diagnosis can be made when all five of the following criteria have been met:

1. A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause
2. Encephalopathy that cannot be explained by fever
3. Abnormal brain MRI:
   - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter
   - T1-hypointense lesions in the white matter in rare cases
   - Deep grey matter abnormalities (eg, thalamus or basal ganglia) can be present
4. No new clinical or MRI findings after 3 months of symptom onset
5. Reasonable exclusion of alternative causes

- The inclusion of **MOG antibodies** in the diagnostic criteria for ADEM is **not considered** for two reasons: 1)the ABs can be **present** in demyelinating disorders **without MRI features of ADEM**, or in patients **without encephalopathy**; 2)antibody testing remains **unavailable** at many centers

Panel 4

Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

- **Analysis of CSF for the presence of NMDA receptor ABs is mandatory** in patients with **relapsing symptoms after HSV encephalitis** (20% of patients), and manifests with new-onset **choreoathetosis** (predominantly in children) or **psychiatric symptoms** (mainly in adults and teenagers) **a few weeks** or, rarely, months after the viral infection

Panel 5

Diagnostic criteria for Bickerstaff's brainstem encephalitis

Probable Bickerstaff's brainstem encephalitis

Diagnosis can be made when both of the following criteria have been met:

1. Subacute onset (rapid progression of less than 4 weeks) of all the following symptoms:
   - Decreased level of consciousness
   - Bilateral external ophthalmoplegia
   - Ataxia
2. Reasonable exclusion of alternative causes

Definite Bickerstaff's brainstem encephalitis

Diagnosis can be made in the presence of positive IgG anti-GQ1b antibodies even if bilateral external ophthalmoplegia is not complete or ataxia cannot be assessed, or if recovery has occurred within 12 weeks after onset

- **DDx of Bickerstaff's brainstem encephalitis** include **Listeria rhombencephalitis**, **EV71 encephalitis in children**, **paraneoplastic and postinfectious brainstem encephalitis**, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (**CLIPPERS**), **neurosarcoidosis**, and **primary CNS lymphoma**

Approach to patients without recognizable syndromes or autoantibodies

- After **excluding all well characterized syndromes** of autoimmune encephalitis (with or without autoantibodies) and other syndromes accompanied by well defined auto-antibodies**, a group of patients who have possible autoimmune encephalitis will remain** (panel 1)

- Patients in this group can be regarded as having probable autoimmune encephalitis if they satisfy criteria for **Hashimoto's encephalopathy** or **autoantibody-negative but probable autoimmune encephalitisthe**

Panel 6

Diagnostic criteria for Hashimoto's encephalopathy

Diagnosis can be made when all six of the following criteria have been met:

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or with non-specific abnormalities
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies*
5. Absence of well characterised neuronal antibodies in serum and CSF
6. Reasonable exclusion of alternative causes

Panel 7

Criteria for autoantibody-negative but probable autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
   - MRI abnormalities suggestive of autoimmune encephalitis*
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)
4. Reasonable exclusion of alternative causes

Work-up of children and adolescents with suspected autoimmune encephalitis

- **Brain MRI, CSF analysis and EEG**
- **Both Serum and CSF autoantibodies**

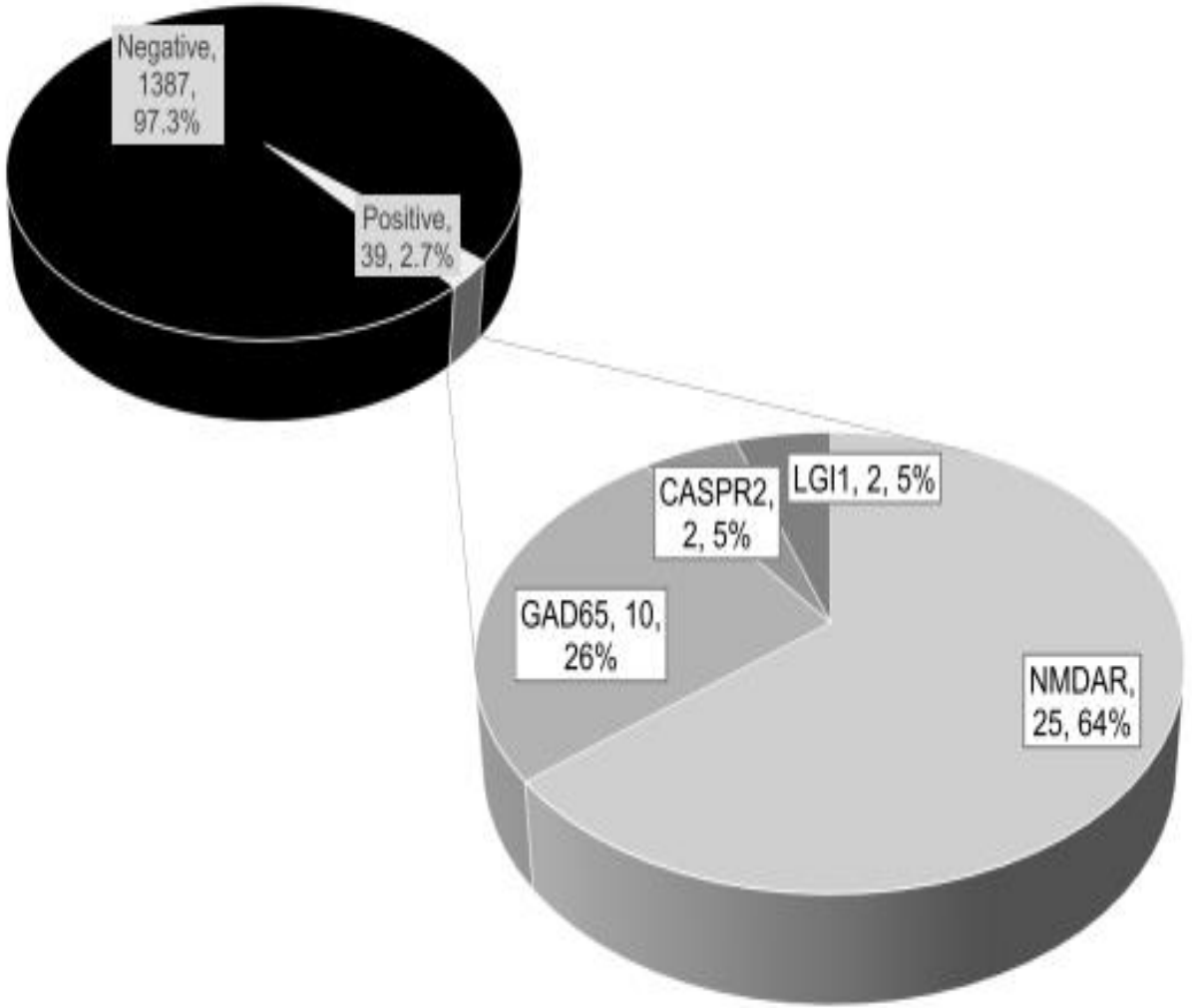


Fig. 1 Frequency of positive results from the testing of 1426 patients < 18 years in the years 2011–2015 in the antibody laboratory of the Epilepsy Center Bethel. For each patient, only the earliest sample(s) were included. Absolute numbers and percentages are indicated in the labels

First and Second Line Treatment in Pediatric AE

First line	
Corticosteroids	No details on doses or durations given
Plasma exchange	
Intravenous immunoglobulins	
Second line (if first line did not work within 10 days[a])	
Rituximab	4×375 mg/m^2 i.v., weekly administration
Cyclophosphamide[b]	750 mg/m^2 i.v. per month

[a]This has been said for anti-NMDAR encephalitis. In other, less severe forms of autoimmune encephalitis, one may wait longer before one moves on to second-line therapy. [b]In pediatric patients, cyclophosphamide is less frequently used compared to rituximab

AUTOIMMUNE EPILEPSY

- More than **50-70 million people** worldwide have **epilepsy**, and approximately **30-40%** of these patients **continue to experience seizures** despite management with ASMs
- The identification of neural ABs in patients with new-onset seizures of unknown etiology has led to the concept of **Acute symptomatic seizure secondary to autoimmune encephalitis (ASSAE)** and **Autoimmune-associated epilepsy (AAE)**

- The risk of AAE is generally **higher in patients with intracellular neuronal Abs** (suspected to be a **T cell-mediated process**) than in those with **cell surface** antibodies (often **directly** pathogenic)

Clinical Presentation

- AE related seizures present with **acute or sub-acute seizures**, often **frequent** from the onset. A history of **preceding viral prodrome** is common
- Frequent seizures can be the **first symptom** that raises **initial suspicion of ASSAE or AAE**, especially in patients who **do not have a history or risk factors**. Seizures are often **multifocal and refractory** to ASMs

- Patients may present with **new-onset refractory status epilepticus** (**NORSE**) or **febrile infection-related epilepsy syndrome** (**FIRES**)
- Autoimmune encephalitis is the **most common cause of NORSE (37%)**
- When the **etiology remains unknown** despite extensive work-up, it is labeled as **cryptogenic (cNORSE)**, which makes up around half of all NORSE cases

EEG Findings in ASSAE & AAE

- **variable findings**, including **normal, focal, or diffuse slowing; epileptiform discharges; or frank seizures**. The scalp EEG may also be normal (including **during faciobrachial dystonic seizures**) when the epileptic focus is **deep or involves too small area**

Imaging

- Brain MRI can be **normal (between 30% and 50%)**, especially at the **onset**, but abnormalities, including **bilateral and asymmetric mesial TL or limbic T2 hyper intensity, are commonly seen later**

Diagnostic Value of Structural and Functional Neuroimaging in Autoimmune Epilepsy

- According to previous content the current diagnosis of AE relies too much on antibody detection and immunotherapy response
- When the status of autoantibodies is not clear, **clinical syndrome and imaging** findings can determine the **diagnosis of probable or definite AE**

Types and imaging characteristics of antibodies related to AE

Antibody types	MRI		PET	SPECT
	Regular MRI	fMRI		
NMDAR antibody	T2/FLAIR hyperintensity in the cortex and subcortical white matter areas, including temporal lobe, cerebellum, thalamus, basal ganglia, etc.	Bilateral functional connectivity of hippocampus decreased. DTI revealed widespread changes in white matter. The decrease of NAA is related to clinical improvement	A high to low metabolic gradient from the frontal lobe to the occipital lobe	Hyperperfusion in basal ganglia and cortex, especially frontal cortex
Limbic encephalitis-related antibodies	T2/FLAIR hyperintensity in MTL. MTL and hippocampal volume from swelling to atrophy	Extensive damage to brain network connections. MRS showed that NAA decreased and lactate peak increased	MTL hypermetabolisma is the most common manifestation	Hypoperfusio-n in the frontal lobe, parietal lobe, thalamus, and cerebellum
GABAAR antibody	Multifocal cortical-subcortical T2/FLAIR abnormalities, predominantly involved temporal and frontal lobes but also basal ganglia and other regions	MRS showed elevated lactate signals and Lac/creatine ratio in the voxel of interest	—	—

Antibody types	MRI		PET	SPECT
	Regular MRI	fMRI		
CASPR2 antibody	T2/FLAIR hyperintensity in MTL and diffuse meningeal enhancement. Bilateral hippocampal and generalized cortical atrophy	—	Temporal hypermetabolism, temporomandibular, frontal and diffuse hypometabolism	—
GAD antibody	Acute/subacute lesions usually presented as temporal lobe encephalitis with high T2/FLAIR signal and swelling of unilateral or bilateral medial temporal structures. Hippocampal atrophy is associated with drug-resistant temporal lobe epilepsy	DTI showed wide range of effects in various regions of brain	Multiple hypermetabolism in brain tissue, mainly in the frontal or temporal lobes	—
Anti-Hu antibody	The most common abnormality on MRI was T2/FLAIR hyperintensity in the temporal lobe and showed multifocal subcortical/subcortical lesions in patients with SCLC	—	High metabolism in one or two temporal lobes, only a small number of brain MRI cases are related to PET	SPECT scan revealed asymmetric cortical activity, but distinct seizure focus could not be identified

Screening

- The **modified Antibody Prevalence in Epilepsy and Encephalopathy** (**APE2**) score, a **10-item, 16-point index, primarily based on clinical evaluation** has been developed to predict specific neuronal presence auto-Abs

Table 2 Antibody prevalence in epilepsy and encephalopathy (APE2 score)

Antibody prevalence in epilepsy and encephalopathy (APE2 score)	Value
New onset, rapidly progressive mental status changes that developed over 1–6 weeks or new onset seizure activity (within 1 year of evaluation)	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	(+1)
Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥20 mm Hg fall in systolic pressure or ≥ 10 mm Hg fall in diastolic pressure within 3 min of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility)	(+1)
Viral prodrome (rhinorrhoea, sore throat, low-grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic seizures	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two antiseizure medications	(+2)
CSF findings consistent with inflammation (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/μL, if the total number of CSF RBC is <1000 cells/μL)	(+2)
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter or both compatible with demyelination or inflammation)	(+2)
Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumour, cancer with brain metastasis)	(+2)
	Total (max: 18)

- **APE2 score** is useful to **pick up ASSAE** rather than AAE and may **not be sensitive** enough to diagnose patients with **chronic epilepsy** and underlying **intracellular ABs** such as GAD65 in which features of LE may be lacking

- The **Antibodies Causing Epilepsy Syndromes** (**ACES**) score, a **6-item** (cognitive symptoms, behavioral changes, autonomic symptoms, speech problems, autoimmune diseases, and temporal MRI hyper intensities) and a **6-point index**, *recently, have created by de Bruijn et al*

Table 3 Neuronal Autoantibody Confidence Scale*

Clinical/laboratory factor	Score
Ab against intracellular antigen (or high clinical relevance surface antibody)	1
Movement disorder and/or stiff person syndrome	1
Cancer and/or smoking history	1
Inflammatory CSF (either high cell count, IgG index and/or positive OCBs)	1
Serum hyponatraemia	1
Chronic course (>3 months)†	–1
Total	Maximum=5 Minimum=–1

- Although the items for ACES and APE2 scores partially **overlap**, the **ACES score is more sensitive for patients with focal epilepsy without overt encephalitis**
- Also, it is much **easier** to score than APE2 (a value-weighted score), thus **more likely to be used in clinical settings**

- In a broad spectrum, **autoimmune epilepsy** also includes **FIRES, NORSE**, **cerebral auto-inflammatory diseases**, and **epilepsy induced by systemic autoimmune disorders**

Autoimmune Encephalitis Associated Acute Symptomatic Seizures and Autoimmune-Associated Epilepsy

	Antibody-targeting antigen	Most common seizure type	Common nonseizure symptom	Acute symptomatic seizure prevalence	Risk of AAE	Prevalence of malignant neoplasm	Main type(s) of malignant neoplasm	Response to immunotherapy
Cell surface antigens	NMDAR[6,7]	• Tonic-clonic • Focal • EPC	• Behavioral and psychiatric changes • Dyskinesia	70%-80%	<5%	Varies with sex 30%-40%	Ovarian teratoma	Good
	AMPAR[12]	• Temporal lobe • Opsoclonus	• Cognitive dysfunction	30%-40%	<5%	50%-60%	• SCLC • Thymoma • Breast	Good
	GABAaR[8]	• Refractory status epilepticus • EPC	• Behavioral changes • Cognitive dysfunction	80%-90%	<5%	20%-30%	Thymoma	Good
	GABAbR[9]	• Focal onset impaired awareness • Focal to bilateral tonic-clonic seizures	• Behavioral changes • Cognitive dysfunction	90%-95%	20%-30%	50%-60%	SCLC	Good
	LGI1[4,5]	• Faciobrachial dystonic seizures • Focal aware • Focal to bilateral tonic-clonic seizures	• Hyponatremia • Cognitive dysfunction	80%	15%	<5%	Thymoma	Good
	CASPR2[5,13]	• Focal onset impaired awareness	• Morvan syndrome • Cognitive dysfunction	40%-50%	<10%	<20%	Thymoma	Good
	mGluR5[14]	• Myoclonic	• Psychiatric changes • Cognitive dysfunction	50%-60%	5%	50%-60%	Hodgkin lymphoma	Good

previous table continued

	Antibody-targeting antigen	Most common seizure type	Common nonseizure symptom	Acute symptomatic seizure prevalence	Risk of AAE	Prevalence of malignant neoplasm	Main type(s) of malignant neoplasm	Response to immunotherapy
	GlyR[15]	• Refractory SE • EPC • Myoclonus	• PERM • SPSD-plus phenotype	10%-40%	Unclear	10%-15%	• Thymoma • B-cell lymphoma • Hodgkin lymphoma • Breast • Melanoma	Good
Intracellular antigens	GAD65[10]	• TLE	• Stiff person SPSD • Cerebellar ataxia • Cognitive dysfunction	10%-50%	>80%	<10%	• Very rare, adenocarcinoma, thymoma	Poor
	Ma2[11]	• TLE	• Cognitive dysfunction hypersomnia • Ataxia	40%-50%	>60%	>90%	• Testicular germ cell • SCLC • Breast	Poor
	Hu/ANNA-1[16]	• TLE	• Dysphagia • Dysarthria • Hypoventilation • Ataxia	40%-50%	>60%	>95%	• SCLC	Poor

NORSE

- Can be the **most-severe form** of AE, and it is defined as a **clinical presentation**—**not a specific diagnosis**—in a patient with the new onset of RSE **without a clear acute or active structural, toxic, or metabolic cause**

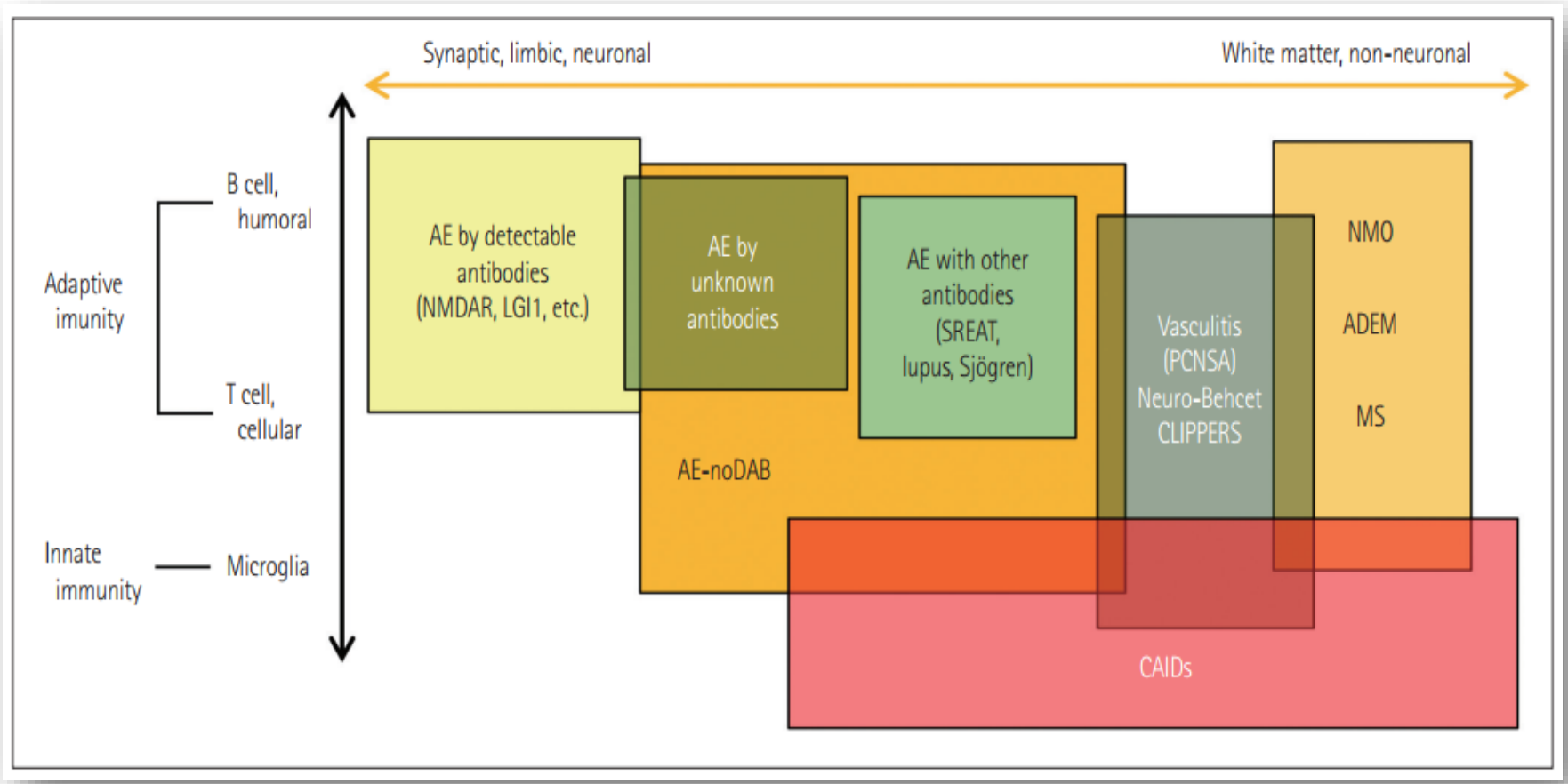
- A multicenter study found the **NORSE etiology in about half of the patients (47%),** with **autoimmune etiologies 37%, (**comprising 19% non-paraneoplastic and 18% paraneoplastic) being **more common than infection 8%**.
- These results indicate that an **autoimmune pathogenesis** is much more likely than a viral infection in NORSE

FIRES

- Is a **catastrophic** epileptic syndrome that strikes **previously healthy children** aged **3-15 years** and has an unknown pathogenesis and few treatments
- **Unknown** etiology, with a **biphasic presentation**, **acute phase beginning** as seizure activity lasting 1-12 weeks, then **chronic phase**, with refractory seizures that cluster every 2-4 weeks (multifocal and independent)

- **Treatment of FIRES is difficult, unresponsive to Anti-Seizure Medications**
- **Resolve temporarily** with **drug-induced burst suppression comas**. **kD have limited benefit**
- The outcome varies, usually **poor**, with up to **30%** of cases ending in **death** and **66-100%** of survivors having **intellectual disability**

Patho-mechanism of autoimmune epilepsy



Immunotherapy options for autoimmune epilepsy

Treatment	Mechanism	Side effect	Regimen
Corticosteroid[39,47,48]	Suppress lymphocyte activation and proinflammatory gene expression Expand the Th2 subgroup compared to the Th1 subgroup	Systemic infection Psychiatric symptoms (insomnia, depression, agitation, psychosis) Hyperglycemia Cushing syndrome Gastric ulcer Tremor Osteoporosis Avascular necrosis	Methylprednisolone via 1-g daily IV infusion for 3–5 days, followed by oral steroid if necessary
IVIg[49,50]	Block neonatal FcR, deplete FcR and $F(ab')_2$ receptor, inducing deactivation of both innate autoimmunity and adaptive autoimmunity	Elevated liver enzymes Allergy induction	400-mg/kg daily IV infusion for 5 days and monthly maintenance if necessary
Plasma exchange[51]	Clear autoantibodies and other pathologic substances from the plasma	Catheterization-related side effects (difficult to apply in patients showing irritability and autonomic symptoms)	1–1.5 plasma-volume exchange for five to seven sessions with a 48-hour interval
Rituximab[12,52,53]	Anti-CD20 of B cells	Systemic infection (viral) Chronic infection reactivation (HBV, HCV) Lymphopenia Infusion-related side effects (injection-site reaction, rash) Elevated liver enzymes	375-mg/m^2 weekly IV infusion for 4 weeks and monthly maintenance if necessary

Immunotherapy options for autoimmune epilepsy…*cont..*

Tocilizumab[24,54]	Block IL-6 receptor of lymphocytes	Systemic infection (bacterial) Neutropenia, thrombocytopenia Masked fever and C-reactive-protein elevation Hyperlipidemia Elevated liver enzyme	Initially 4 mg/kg, followed by an increase to 8 mg/kg monthly depending on the clinical response
Cyclophosphamide[55]	Alkylate DNA of actively proliferating lymphocytes	Bone-marrow suppression Infertility Hemorrhagic cystitis Alopecia Cancer risk Systemic infection Nausea, vomiting	750-mg/m^2 monthly IV infusion for 3–6 months (dose reduction if necessary)
Anakinra[23,30,56]	Block IL-1 receptor	Systemic infection Headache, nausea Injection-site reaction	100-mg daily SC injection
Bortezomib[25,57]	Inhibit proteasome, targeting Ig-producing plasma cells	Systemic infection Neutropenia Anemia Leukopenia Neuropathy	1.3 mg/m^2 bortezomib with 20-mg IV dexamethasone, twice-weekly SC injection for 2 weeks (days 1, 4, 8, and 11), followed by a 10-day rest
Azathioprine[51,58]	Inhibit purine synthesis, suppressing actively proliferating lymphocytes	Bone-marrow suppression Teratogenic Nausea, vomiting	Initially 1–1.5 mg/kg once daily or divided twice daily orally, target 2–3 mg/kg/day
Mycophenolate[51,59,60]	Inhibit purine synthesis, suppressing actively proliferating lymphocytes	Bone-marrow suppression Teratogenic Nausea, vomiting	Initially 500 mg twice daily orally, with a target of 1,000 mg twice daily

Comorbid symptoms of AE

- **NMDAR encephalitis**: **psychosis, dyskinesia, hypoventilation, and autonomic dysfunction**
- **LGI1-AB encephalitis: FBDS and hyponatremia**
- **GABA-A encephalitis: Refractory ES, EPC**
- **GAD encephalitis: seizures and memory decline[LE], cerebellitis, stiff-person syndrome, type I DM**

Tumor in Autoimmune Epilepsy

- **paraneoplastic syndromes** are more common in **Ovarian teratoma, thymoma, SCL cancer, and neuroendocrine tumors**
- **NMDAR encephalitis:** about 40% have **ovarian teratoma**
- **CASPR2** antibodies is associated with **thymoma** (50%)
- **GABA-B encephalitis** is associated with **SCLC** (70%)
- **AMPA encephalitis**: **SCLC and thymoma** (70%)
- **No tumor has been found to be associated with GAD**

ASMs in autoimmune epilepsy

- **Fewer side effects, no drug–drug interactions, and rapid loading of the drug**
- The candidate first-line treatments are next-generation ASMs such as **levetiracetam**, **lacosamide**, **carbamazepin**, **zonisamide**, with **levetiracetam being the most-used drug**

- In NMDAR encephalitis, **NMDAR antagonists** such as **ketamine should be avoided**
- The **duration** of ASM use also should be **personalized** in individual patients, and ASMs can be **tapered off** when the autoimmune encephalitis is in **full remission**

Best practice recommendations summary for long-term management of AE

- **1. Onco-neuronal antigens [intracellular] and typical clinical picture:** refer to oncology for treatment and surveillance of tumor **if one was found**. If **no tumor** was found, initiate **semiannual to annual cancer screening for at least 4 years**.
- **Treat neurological relapses** but **avoid** long-term immunosuppression

- **2. Positive antibody against neuronal surface antigen with high clinical relevance:** consider periodic **tumor screening**. Some with **higher rates** of screening as **in GABABR-Ab** and some with **less frequent screening as in LGI-1**
- Consider initiating **at least annual cancer screening** for an **average of 2–4 years** based on antibody type. **Consider long- term immunosuppression** preferably with **rituximab** after a **second attack or after the first attack** in patients with severe initial presentation or risk factors for relapse (eg, persistently positive oligoclonal bands)

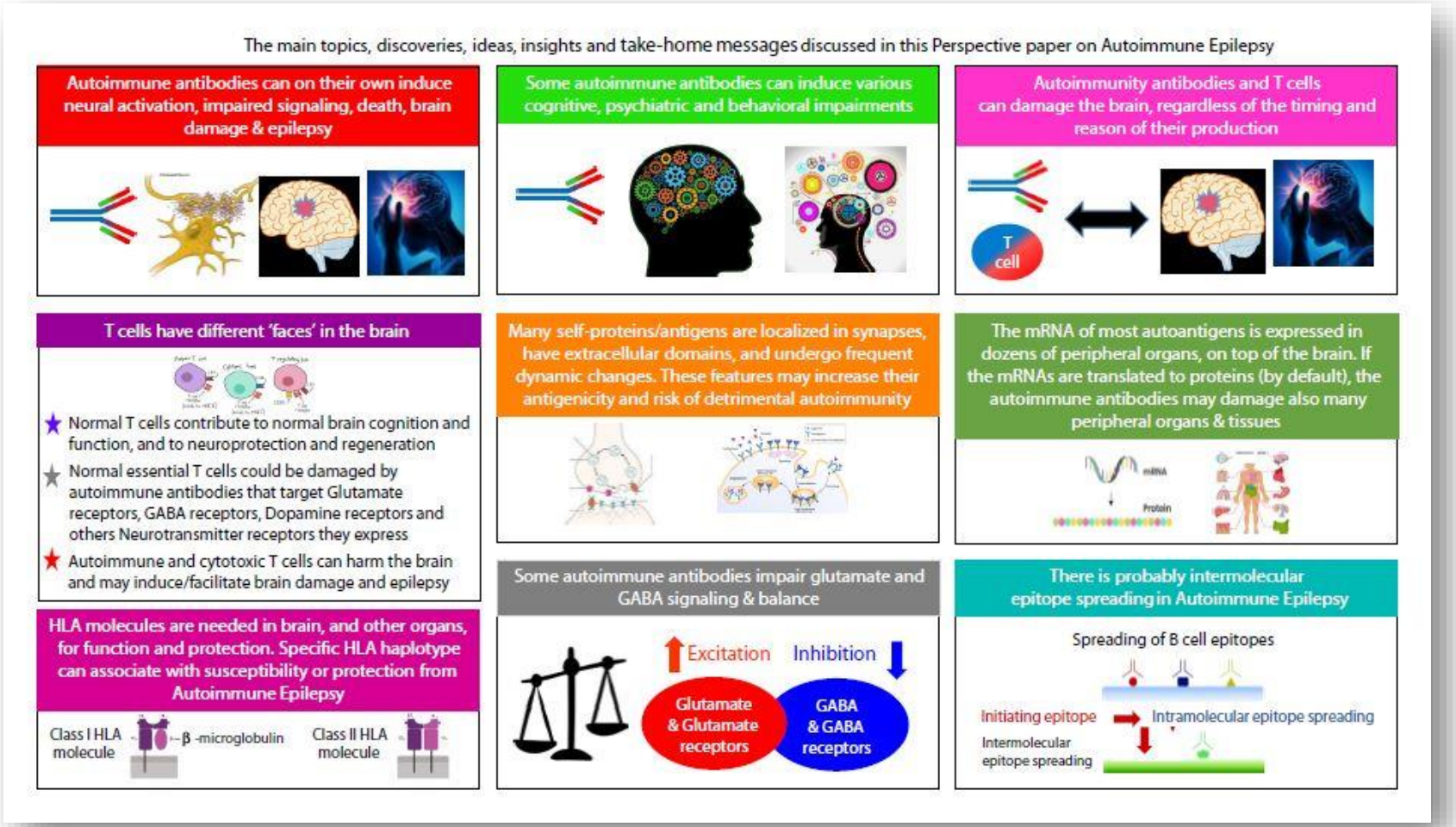
- **3. Positive antibody against neuronal surface antigen with low clinical relevance**: evaluate confidence in the clinical relevance of the positive antibody based on **clinical and ancillary data**. Evaluate for **alternative etiologies**. If the diagnosis of AE is felt to be **probable** and no other etiology found then **follow recommendation 2**

- **4. Seronegative AE**: **confirm** the diagnosis according to published **criteria and exclude alternative causes**
- **Annual cancer screening** for an average of **4 years for seronegative definite LE** and may consider 2 years for all other neuroanatomical variants.
- Start **long-term immunosuppression** with rituximab, mycophenolate or azathioprine after a second attack
- The **duration** of long-term immunosuppression are particularly anecdotal and **more research is needed** for this subtype of AE

- **5. For all AE subtypes:** treat **residual symptoms** including seizures, movement disorders, psychiatric symptoms, spasticity, sleep dysfunction and dysautonomia.
- Start **physical, occupational and speech therapy** depending on residual deficits

Table 1 Symptomatic management for autoimmune encephalitis

Symptom category	Therapeutic options	Precautions
Psychosis/agitation/mania	1. Acute immunotherapy with IVMP, IVIg and/or PLEX. 2. Benzodiazepines (eg, clonazepam, diazepam). 3. Antipsychotics (eg, quetiapine). 4. Mood stabilisers (eg, valproic acid). 5. Establish safety measures as necessary (eg, bed padding, soft restraints, room sitter).	1. Avoid over-sedation and unnecessary polypharmacy. 2. Avoid medications that lower seizure threshold in patients with high seizure risk (eg, clozapine, olanzapine). 3. Avoid medications that prolong QT interval in dysautonomic patients (eg, ziprasidone, haloperidol). 4. Watch out for worsening of involuntary movements or development of neuroleptic malignant syndrome.
Seizures	1. Acute immunotherapy with IVMP, IVIg and/or PLEX. 2. Antiseizure medications (sodium channel blockers like carbamazepine or lacosamide may be preferred in LGI1-antibody encephalitis). 3. Medically induced coma with midazolam, pentobarbital or propofol is required for NORSE.	1. Instate early immunotherapy for patients with seizures in the setting of suspected AE. Avoid use of anti-seizure medications alone. 2. May cautiously attempt weaning antiseizure medications in patients with early seizure freedom and normal brain MRI and EEG.
Movement disorders	1. Acute immunotherapy with IVMP, IVIg and/or PLEX. 2. Benzodiazepines (eg, clonazepam, diazepam) for myoclonus, SPS, PERM, catatonia, dystonia, stereotypies and hyperkinesia. 3. Anticholinergics (eg, trihexyphenidyl, benzatropine) for dystonia. 4. Muscle relaxants (eg, baclofen, tizanidine) for dystonia and spasticity. 5. Dopamine blockers (eg, risperidone) or depleters (tetrabenazine) for chorea, athetosis, ballism, tics and hyperkinesia. 6. Dopamine agonists (eg, pramipexole, ropinirole) or carbidopa/levodopa for acquired parkinsonism, rigidity and akinetic mutism.	1. Avoid over-sedation and unnecessary polypharmacy. 2. Watch for paradoxical worsening of involuntary movements or development of neuroleptic malignant syndrome. 3. Practice caution with anticholinergics in patients with dysautonomia. 4. Practice caution with anticholinergics and dopaminergic medications in patients with psychosis.
Dysautonomia	1. Acute immunotherapy with IVMP, IVIg and/or PLEX. 2. ICU monitoring for severe dysautonomia. 3. Beta-blockers (eg, propranolol), alpha-2 blockers (eg, clonidine), and/or acetylcholine esterase inhibitors (pyridostigmine) for increased sympathetic drive. 4. Midodrine, fludrocortisone or droxidopa for symptomatic postural hypotension. 5. Temporary pacing for heart block or severe arrhythmia. 6. Total parental nutrition for patients with severe gastrointestinal dysmotility. 7. Anti-muscarinics (eg, oxybutynin) for bladder incontinence.	1. Watch for exaggerated response to sympatholytic therapies. 2. Watch for supine hypertension when treating postural hypotension. 3. Watch for cognitive and cardiac side effects when using antimuscarinics.
Sleep disorders	1. Acute immunotherapy with IVMP, IVIg and/or PLEX. 2. Promote sleep hygiene and uninterrupted night-time sleep. 3. Melatonin to promote the sleep-wake cycle. 4. Sedating benzodiazepines (eg, temazepam), benzodiazepine receptor agonists (eg, zolpidem) and/or non-benzodiazepine hypnotics (eg, zopiclone) for insomnia. 5. Wake-promoting agents (eg, modafinil) and/or traditional stimulants (eg, methylphenidate) for excessive daytime sleepiness. 6. Evaluate residual sleep disorders with polysomnography and treat sleep disordered breathing if present.	1. Avoid over-sedation and unnecessary polypharmacy. 2. Practice caution when using stimulants in patients with seizures or hyperkinetic involuntary movements.


The main topics, discoveries, ideas, insights and take-home messages discussed in this Perspective paper on Autoimmune Epilepsy
Autoimmune antibodies can on their own induce neural activation, impaired signaling, death, brain damage & epilepsy
Some autoimmune antibodies can induce various cognitive, psychiatric and behavioral impairments
Autoimmunity antibodies and T cells can damage the brain, regardless of the timing and reason of their production
T cell
T cells have different 'faces' in the brain
Normal T cells contribute to normal brain cognition and function, and to neuroprotection and regeneration
Normal essential T cells could be damaged by autoimmune antibodies that target Glutamate receptors, GABA receptors, Dopamine receptors and others Neurotransmitter receptors they express
Autoimmune and cytotoxic T cells can harm the brain and may induce/facilitate brain damage and epilepsy
Many self-proteins/antigens are localized in synapses, have extracellular domains, and undergo frequent dynamic changes. These features may increase their antigenicity and risk of detrimental autoimmunity
The mRNA of most autoantigens is expressed in dozens of peripheral organs, on top of the brain. If the mRNAs are translated to proteins (by default), the autoimmune antibodies may damage also many peripheral organs & tissues
mRNA
Protein
HLA molecules are needed in brain, and other organs, for function and protection. Specific HLA haplotype can associate with susceptibility or protection from Autoimmune Epilepsy
Class I HLA molecule
β -microglobulin
Class II HLA molecule
Some autoimmune antibodies impair glutamate and GABA signaling & balance
Excitation
Inhibition
Glutamate & Glutamate receptors
GABA & GABA receptors
There is probably intermolecular epitope spreading in Autoimmune Epilepsy
Spreading of B cell epitopes
Initiating epitope
Intramolecular epitope spreading
Intermolecular epitope spreading

Thank you for your attention