# Autoimmune Movement Disorders


## Joseph Jankovic, MD

**Professor of Neurology, Distinguished Chair in Movement Disorders, Director, Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas**











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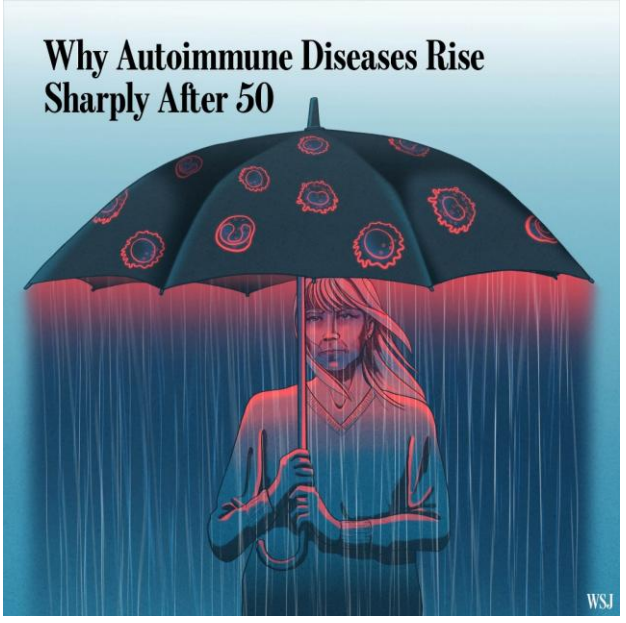
# Immune System

**Our bodies are confused by this 21st-century world.**

New York Times, June 3, 2016



**An estimated 1 in 13 Americans has one of these often debilitating, generally lifelong, conditions.**

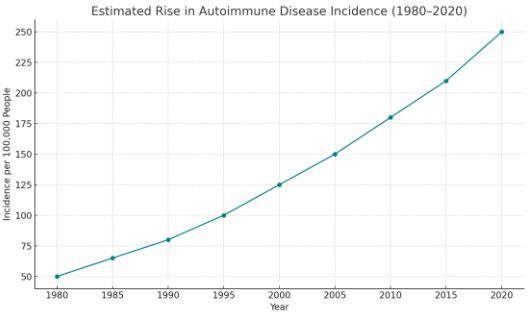



WSJ, November 23, 2025

**Scientists are developing faster, more accurate tools to diagnose autoimmune diseases.**

# The Autoimmune Surge: Unpacking the Causes

- 🌍 **Environmental toxins and pollution**
- 🍔 **Western diet and gut imbalance**
- 😴 **Stress, sleep loss, and lifestyle shifts**
- 🦠 **Viral triggers (e.g., COVID-19, EBV)**
- 🧬 **Genetic and hormonal factors**
- 🫃 **Hygiene hypothesis**
- 📈 **3–12% annual global increase in cases**




**Autoimmune diseases affect approximately 1/10 individuals, and their burden continues to increase over time at varying rates across individual diseases. The socioeconomic, seasonal, and regional disparities observed among several autoimmune disorders in our study suggest environmental factors in disease pathogenesis.**

Conrad et al. Lancet 2023;401:1878-90

**AI**

**"autoimmune" or "artificial intelligence"**

https://chatgpt.com/
https://www.openevidence.com/
Perplexity.ai
Beautiful.ai
Scite.ai

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Review Article

# Autoimmune and paraneoplastic movement disorders: An update

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*Keywords:*
Ataxia
Autoimmune disorders
Chorea
Movement disorders
Stiff-person syndrome

ABSTRACT

Movement disorders (MDs) are common in patients with autoimmune disorders affecting the central and peripheral nervous system. They may be observed in autoimmune disorders triggered by an infectious agent, such as streptococcus in Sydenham's chorea, or in basal ganglia encephalitis with antibodies against the dopamine-D2 receptors. In these patients chorea or dystonia are usually the most prominent hyperkinetic MDs. MDs are also observed in patients with diffuse or limbic encephalitis with antibodies directed against neuronal cell-surface antigens. Anti-NMDA receptor encephalitis is one of the most common and may present with a variety of MDs, including: chorea, stereotypies, dystonia and myorhythmia. The recognition of other abnormal motor phenomena such as "faciobrachial dystonic seizures" and neuromyotonia, observed in patients with LGI1 and Caspr-2 antibodies, is important because they may herald the onset of overt limbic encephalitis. Autoimmunity directed against the intracellular enzyme glutamic acid decarboxylase usually presents with MDs, most commonly stiff-person syndrome or cerebellar ataxia. Chorea may be observed in rheumatologic disorders such as systemic lupus erythematosus or antiphospholipid syndrome. Disorders with uncertain autoimmune mechanisms such as Hashimoto's encephalitis and idiopathic opsoclonus-myoclonus syndrome commonly present with tremor, myoclonus and ataxia. A rapid diagnosis of an autoimmune disorder, which typically presents with subacute onset, is critical as early therapeutic intervention improves long-term prognosis and may be life-saving. Treatment usually involves some form of immunotherapy and symptomatic therapy of the abnormal movements with dopamine depleters, dopamine receptor antagonists, or GABAergic drugs. Detection and removal of an underlying tumor is essential for optimal outcome.

Dalmau J, Graus F. N Engl J Med 2018;378:840-51
Dalmau J, Graus F. Lancet Neurol 2023;22:529-40

## Autoimmune conditions associated with movement disorders

| Disorder | Relevant antibodies | Movement disorders |
|---|---|---|
| Anti-NMDAR encephalitis | Anti-NMDAR | Stereotypies, dystonia, chorea, myorhythmia, other dyskinesias |
| Sydenham disease | ASO, Anti-DNAse B | Chorea, tics, OCD |
| SLE and APS | ANA, anti-dsDNA, aCL, LA, anti-B2 GP1 | Chorea |
| Sjögren's syndrome | Anti-Ro/SSA, anti La/SSB | Parkinsonism and chorea |
| Hashimoto's disease | Anti-TPO, anti-NAE | Tremor, chorea, myoclonus |
| Stiff person syndrome (SPS) | Anti-GAD65, anti-GAD67 Anti-amphiphysin, anti-gephryn, anti-Ri | Axial and limb stiffness, myoclonus, hyperekplexia |
| Progressive encephalomyelitis with rigidity and myoclonus (PERM) | Anti-GlyR | Rigidity, myoclonus, tremor, ataxia, hyperekplexia |
| Basal ganglia-Limbic encephalitis | Anti-IGLON5, anti-CRMP5, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPAR, anti-GABA, Anti-HU, anti-Ma2, anti-D2R | Chorea, parkinsonism, dystonia, facio-brachial dystonic seizures, neuromyotonia |
| Paraneoplastic cerebellar ataxias | Anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-mGluR1, anti-VGCC, anti-GAD65 | Progressive cerebellar syndrome |
| Celiac disease | AGA, anti-TG2, anti-TG6 | Ataxia |
| Cerebral folate deficiency syndrome | Anti-FR | Ataxia, choreoathetosis, dystonia |
| Opsoclonus-myoclonus syndrome | Anti-Ri | Opsoclonus, axial and limb myoclonus, ataxia, tremor |
| Neuromyotonia | Anti-VGKC complex (LGI1 and CASPR2) | Myoclonus, painful cramps, |

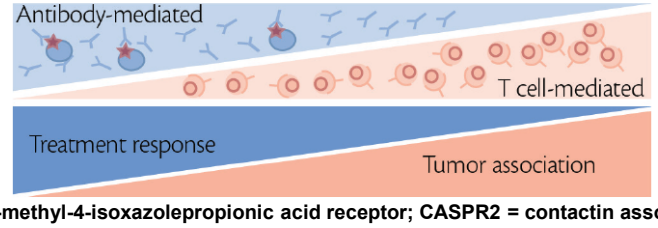
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# Three groups of neuronal antibodies and their pathogenic roles

| Cell-surface antigens | Intracellular synaptic antigens | Intracellular cytoplasmic/nuclear antigens |
|---|---|---|
| Pathogenic antigens are accessible in vivo; typically play important roles in synaptic transmission, plasticity, or excitability | Controversial role in pathogenesis antigen may be transiently accessible during synaptic vesicle fusion and uptake | Markers of paraneoplastic syndrome; poor prognosis poor treatment response, autoimmunity mainly via cytotoxic T-cells; antigens inaccessible in vivo |
| CASPR2, DPPX, D2R, $GABA_AR$, $GABA_BR$, GlyR, LGI1, NMDAR | GAD, amphiphysin | Hu, Ri, CRMP5/CV2, Ma2 |




**AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 = contactin associated protein like 2; D2R = dopamine 2 receptor; DPPX = dipeptidyl peptidase like protein 6; GABAAR and GABABR = gamma aminobutyric acid type A and type B receptors; GlyR = glycine receptor; LGI1 = leucine rich glioma inactivated protein 1; NMDAR = N-methyl-d-aspartate receptor.**

Balint et al. Brain 2018;141:13-36
Balint. Practical Neurology 2020 September:30-40

# Autoimmune Encephalitis

- Third most common cause of encephalitis, after infectious and post-infectious, acute disseminated encephalomyelitis (ADEM)
- Prevalence of 13.7 per 100,000; 20,000 cases in the US per year
- >$2 billion estimated inpatient costs alone
- Acute or subacute onset of flu-like symptoms, behavioral changes, psychosis, memory loss, dysautonomia, seizures, and a variety of hyperkinetic and hypokinetic movement disorders
- Up to 35% relapse
- 30-40% of patients have no identifiable CNS antibodies
- MRI and CSF are often abnormal, but not always
- Early diagnosis and treatment are critical:
  - Steroids, IVIG, plasma exchange, rituximab, anti-CD20 monoclonal antibodies and other emerging immunotherapies

# Autoimmune encephalitis: recovery, residual symptoms and predictors of long-term sequelae.

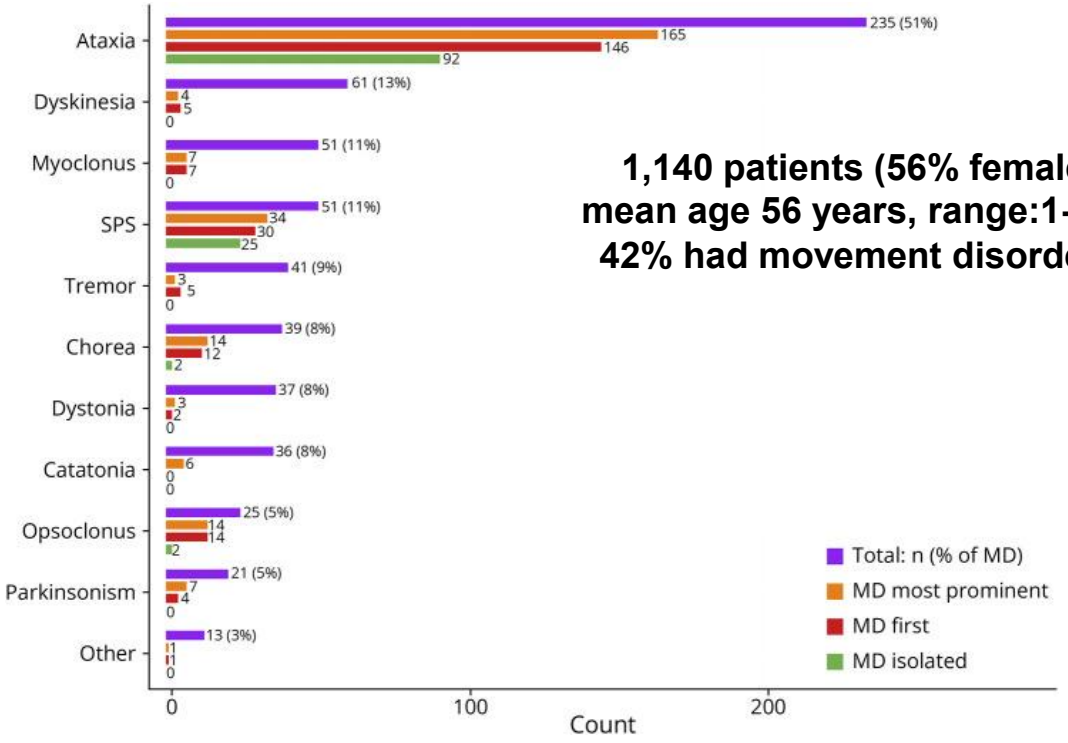
Thakolwiboon et al. J Neurol Neurosurg Psychiatry 2025;96:736-43

- **Of 172 patients, 80% achieved good recovery with a median recovery time of 4 months.**
- **CSF pleocytosis was associated with a lower likelihood of good recovery.**
- **Despite good recovery, several residual symptoms persisted ≥24 months, including cognitive deficits (53%), seizures (26%), sleep disorders (25%), depression (23%), brainstem/cerebellar symptoms (13%), movement disorders (14%) and autonomic symptoms (12%).**
- **11% died; the most common cause of death was progression of AE.**
- **Predictors of long-term sequelae included disabling cognitive deficit at onset and delayed immunotherapy.**
- **This study underscores the need for long-term follow-up of patients after the acute phase of autoimmune encephalitis, even those who make an initial good recovery.**

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# Movement Disorders in Antibody-Associated Neurologic Diseases

## Movement Disorder Frequencies




**1,140 patients (56% female; mean age 56 years, range:1-87); 42% had movement disorders**

Kerstens et al. Neurol Neuroimmunol Neuroinflamm 2026;13:e200516

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# Anti-NMDAR Encephalitis

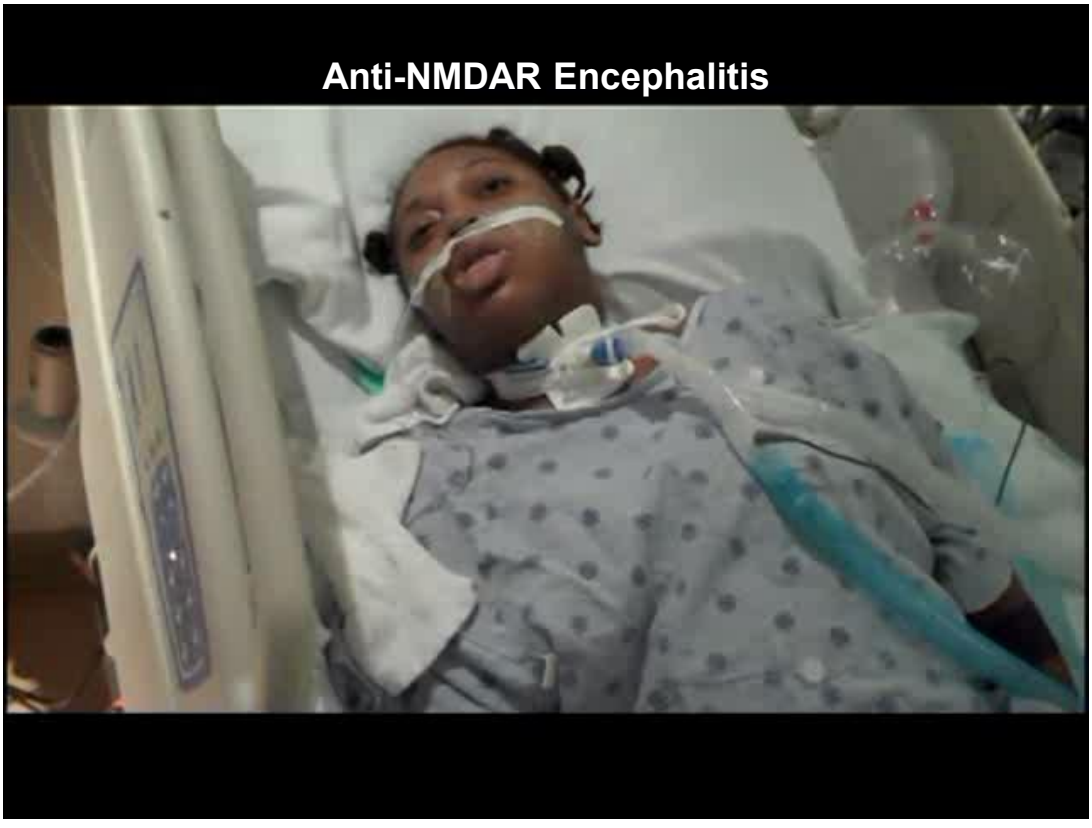
- Unrecognized until 2007 (Josep Dalmau), anti-NMDAR encephalitis is a potentially devastating neuronal autoimmune condition affecting children and adults, typically associated with ovarian teratoma with estimated prevalence of 0.6 per 100,000
- IgG antibodies against NR1 subunit of the NMDA receptor
  - The autoantibodies downregulate surface NMDARs, involved in signal transduction and control of ion channels via long-term potentiation of an action potential
- The classic clinical phenotype is subacute onset of:
  - Headache, fever
  - Seizures with abnormal EEG: slow and disorganized background with generalized rhythmic delta ("extreme delta brush")
  - Behavioral/neurocognitive changes, catatonia
  - Encephalopathy: insomnia → somnolence → wakeful unresponsiveness → coma
  - Dysautonomia
  - Abnormal movements: oromandibular-lingual stereotypies, myorhythmia, chorea, dystonia, tremor, opsoclonus-myoclonus, opisthotonic posturing; may be asymmetrical or bilateral

**3 y/o boy with subacute onset of myalgias, frontal headaches, malaise, and vomiting; followed by confusional state, insomnia, hallucinations, dysarthria and motor aphasia. Admitted with diagnosis of "viral encephalitis". During the hospitalization he developed generalized seizures, dysautonomia, repetitive orofacial stereotypies, dystonic contractions of the left side of his face, blepharospasm, dystonic flexion of the right hand and generalized chorea. Improved with tetrabenazine.**



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**13 y/o presented to the ER with recent onset ataxic gait, rapidly followed by altered mental status with perseverance, uncontrolled laughing, loud singing and delusional thoughts, generalized seizures, and facial and limb myorhythmia. She markedly improved after treatment with corticosteroids and IVIg, plasmapheresis and rituximab.**




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# The spectrum of movement disorders in children with anti-NMDA receptor encephalitis.

Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J.
Mov Disord 2013;28:543-7

| Case | Sex/age at onset | Myorhythmia (facial) | Myorhythmia (limb) | Chorea | Athetosis | Cranial dystonia | Opisthotonus | Limb dystonia | Stereotypic movements | Ataxia |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F/13 years old | + | + | | | +[b] | | | | + |
| 2 | M/8 years old | | | | | | | | + | |
| 3 | M/3 years old | | | + | | +[a] | + | + | + | |
| 4 | F/8 years old | | + | | | | | | | |
| 5 | M/3 years old | | | + | | | | | | + |
| 6 | M/11 years old | | | + | + | | | | | |
| 7 | F/5 years old | | | + | | | | | + | |
| 8 | F/14 years old | | | | | | | | + | |
| 9 | F/10 years old[c] | | | | | | | + | | + |

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# Myorhythmia: Phenomenology, Etiology, and Treatment

José Fidel Baizabal-Carvallo, MD, MSc,[1] Francisco Cardoso, MD, PhD,[2] and Joseph Jankovic, MD[1]*

[1]*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*
[2]*Movement Disorders Clinic, Neurology Service, Department of Internal Medicine, The Federal University of Minas Gerais, Belo Horizonte, MG, Brazil*

Mov Disord 2015;30:171-9

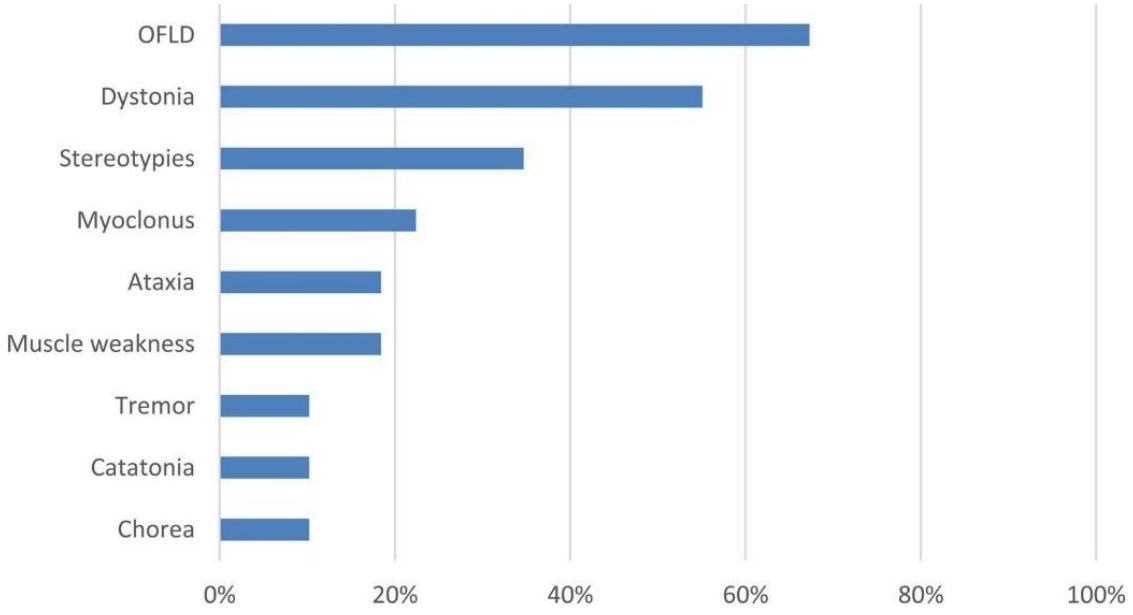



ABSTRACT: Myorhythmia is defined as repetitive, rhythmic, slow (1-4 Hz) movement affecting chiefly cranial and limb muscles. When occurring in the limbs it may be oscillatory and jerky, whereas oculo-masticatory myorhythmia, typically associated with Whipple's disease, is a slow, repetitive, often asymmetrical, facial and ocular movement. Thus, myorhythmia overlaps phenomenologically with tremor and segmental myoclonus. Although often present at rest, it must be differentiated from parkinsonian or dystonic tremor. Recognition of this movement disorder is important because it is usually associated with lesions involving the brainstem, thalamus, or other diencephalic structures with potentially treatable etiologies. In addition to Whipple's disease, myorhythmia has been described in patients with cerebrovascular disease, listeria encephalitis, anti-*N*-methyl-D-aspartate receptor encephalitis, steroid-responsive encephalopathy associated with autoimmune thyroiditis, multiple sclerosis, and other disorders. In addition to our own experience, we have systematically reviewed the medical literature, focusing on the phenomenology, pathophysiology, and etiology of this poorly recognized movement disorder. In this review, we aim to highlight the clinical features that differentiate myorhythmia from other movement disorders. Treatment should be directed against the underlying etiology. © 2014 International Parkinson and Movement Disorder Society

Key Words: myorhythmia; Whipple's disease; slow tremor; movement disorders; stroke

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# Movement disorders in anti-NMDAR encephalitis



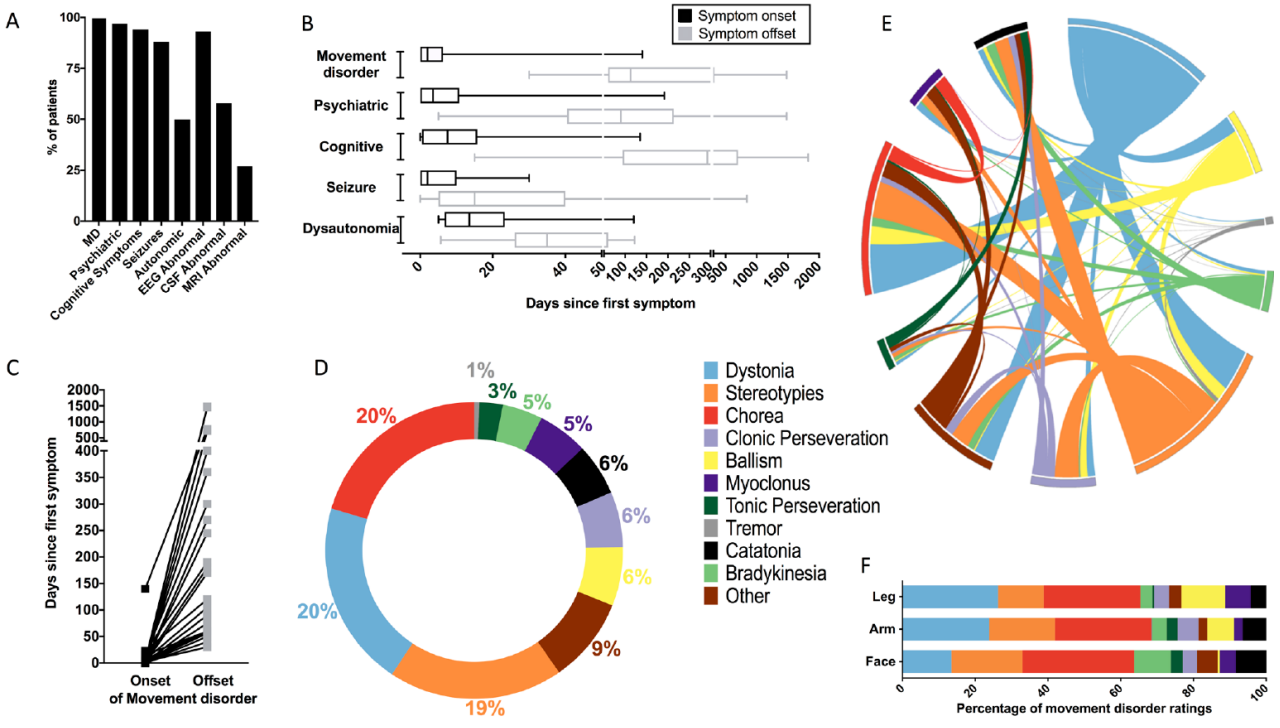

**49/64 (76.6%) presented with MDs; the median age at onset was 21 (15-35) years; 65.3% were female**

Li et al. Front Neurol 2024;15:1357697

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# The clinical features and movement disorder evaluations in patients with NMDAR encephalitis

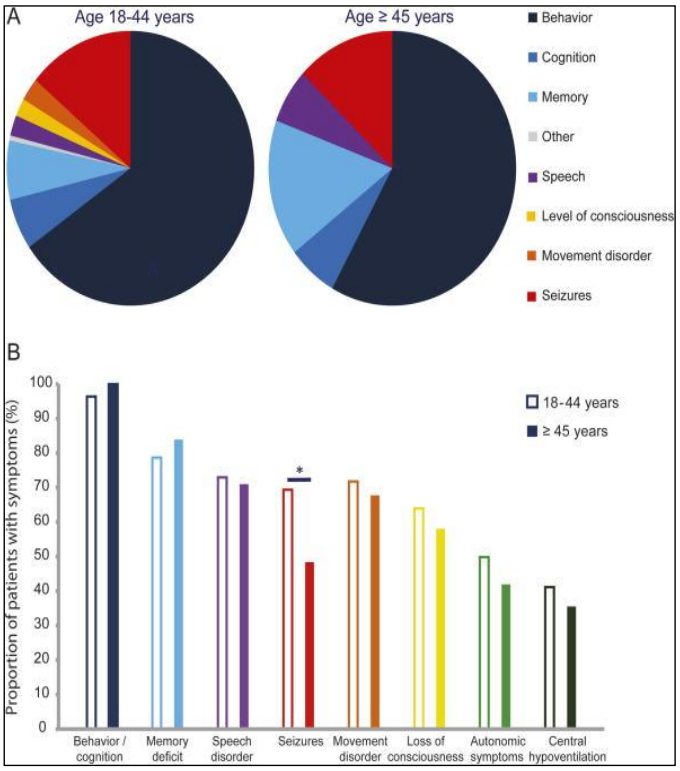
**34 patients, median age 7 years (range 0.2–32 years), 59% F**




Varley et al. JNNP 2019;90:724-6

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# Adult anti-NMDAR Encephalitis




- **31/661 (4.7%) patients with anti-NMDAR encephalitis ≥45 years**
- **Compared with younger adults (18-44 yrs), older patients were more often male, had lower frequency of tumors and seizures, and their outcome was poorer, partly because of delays in diagnosis and treatment**
- **Early and aggressive immunotherapy improves outcome**
- **60% of patients ≥ 45 years old had full or substantial recovery in 2 years**

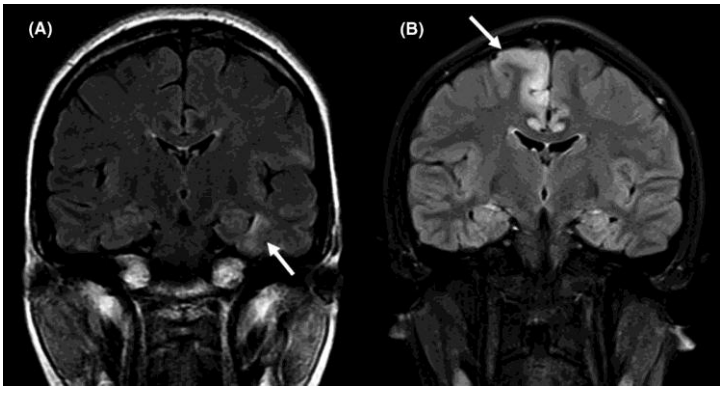
Titulaer et al. Neurology 2013;81:1058-63

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# Anti-NMDAR Encephalitis

- If NMDAR antibodies are not detected in serum (15%), test CSF
  - CSF lymphocytosis followed by oligoclonal bands
- MRI is normal in half of patients; the other half may show signal hyperintensity on T2-weighted FLAIR images involving the hippocampi, cerebral/cerebellar cortex, basal ganglia, brainstem, and spinal cord; leptomeningeal enhancement is a common early finding

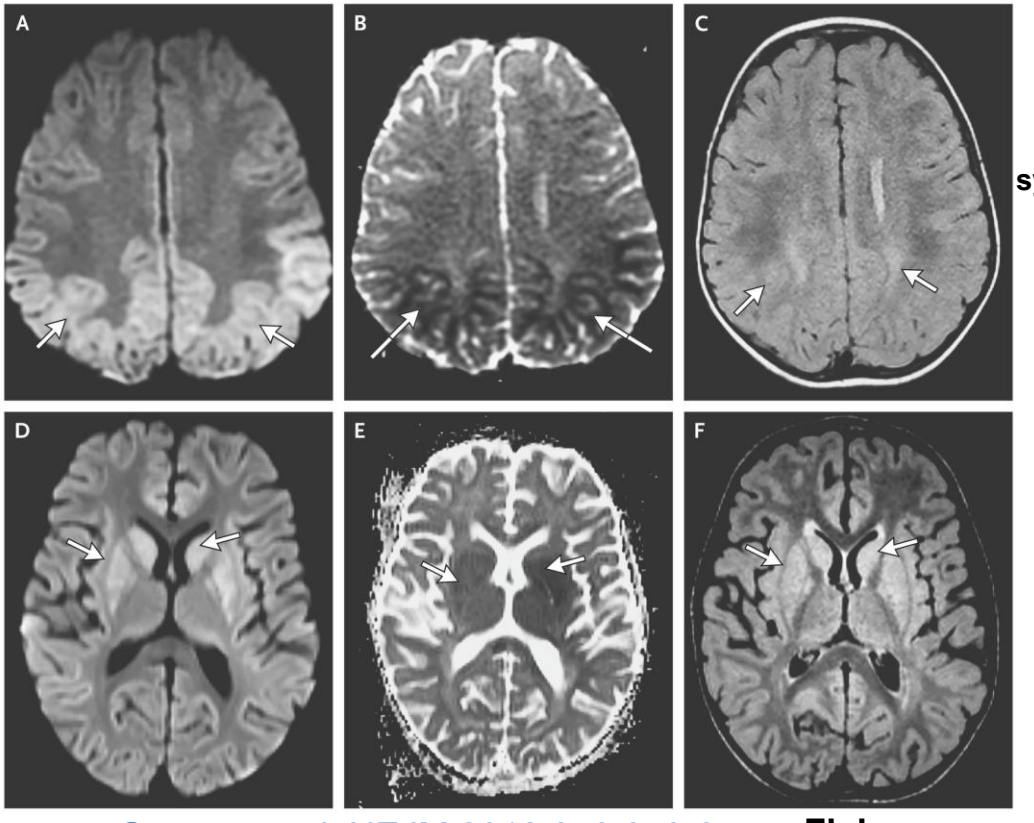



**Left temporal lobe, right superior frontal gyrus and bilateral cingulate gyrus**
Ni et al. Acta Neurol Scand 2020;142:460-5

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# NMDAR Encephalitis – MRI

**3 y/o boy presenting with seizures**




**symmetric restricted diffusion**

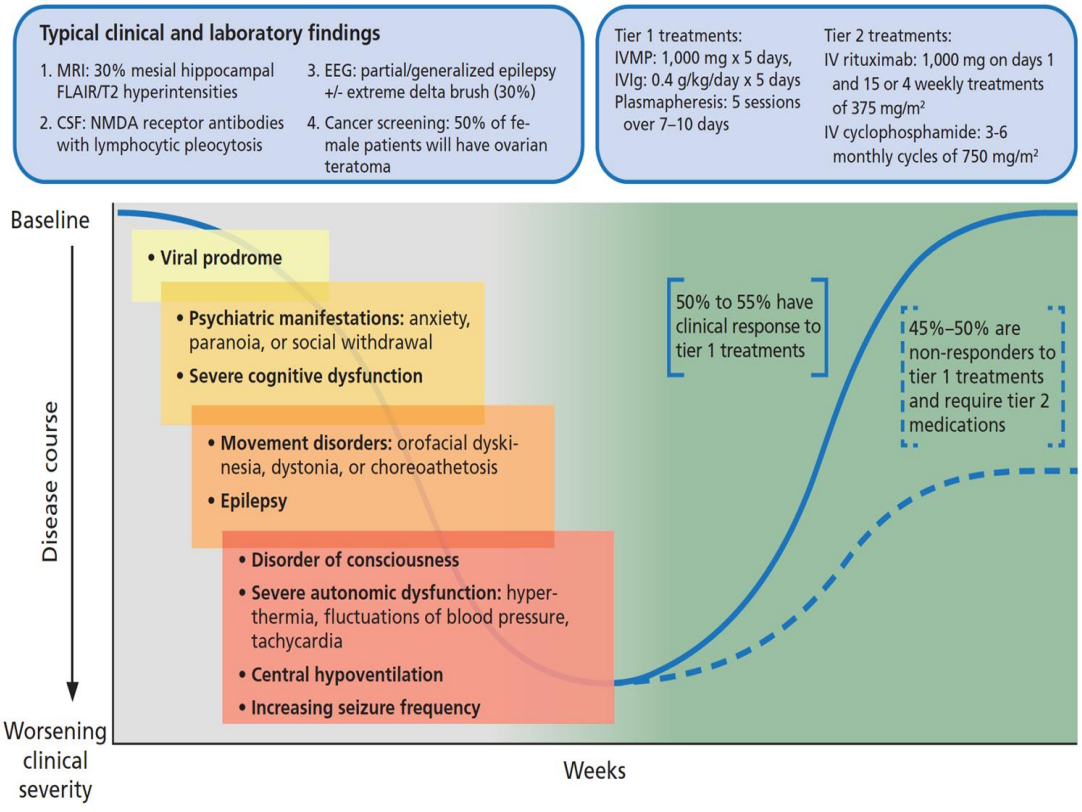
**hyperintensity in the basal ganglia**

Gorman et al. NEJM 2018;379:870-8

**Flair**

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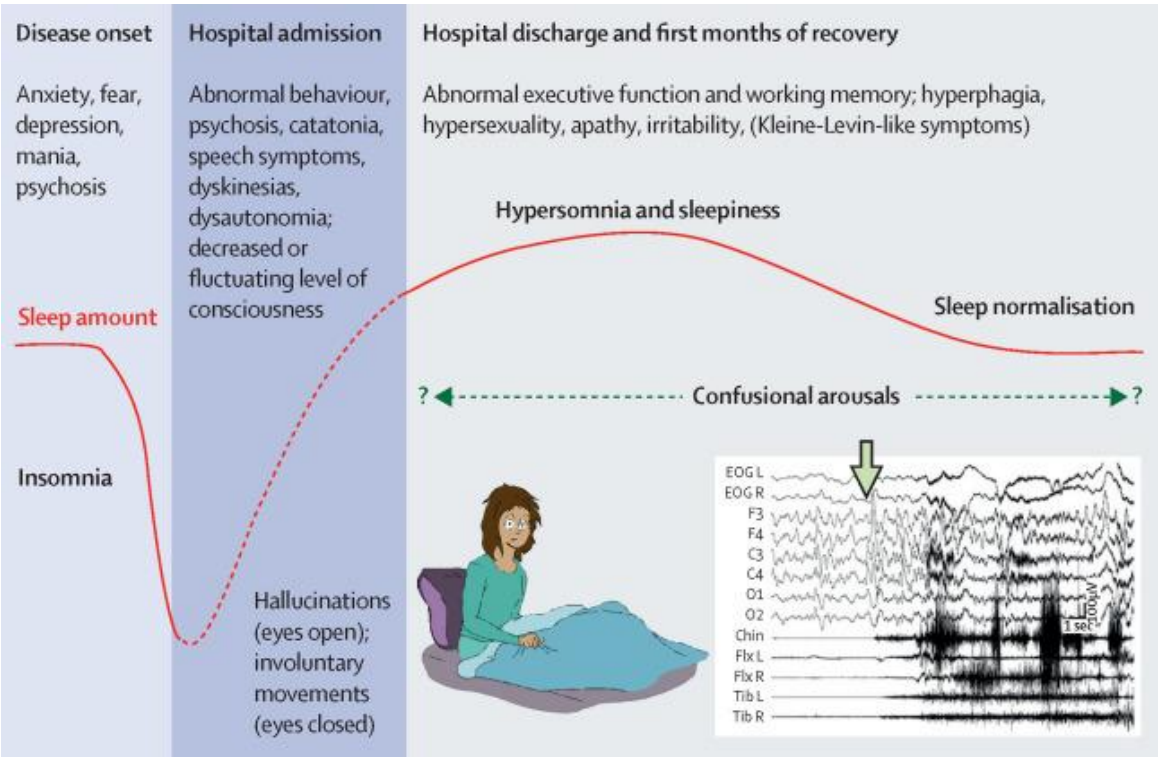
# Anti-NMDAR Encephalitis




Abbatemarco et al. Neurol Neuroimmunol Neuroinflamm 2021;8:e1033

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# Two-stage evolution of sleep disorders in patients with anti-NMDA receptor encephalitis




Muñoz-Lopetegi et al. Lancet Neurol 2020;19:1010-22

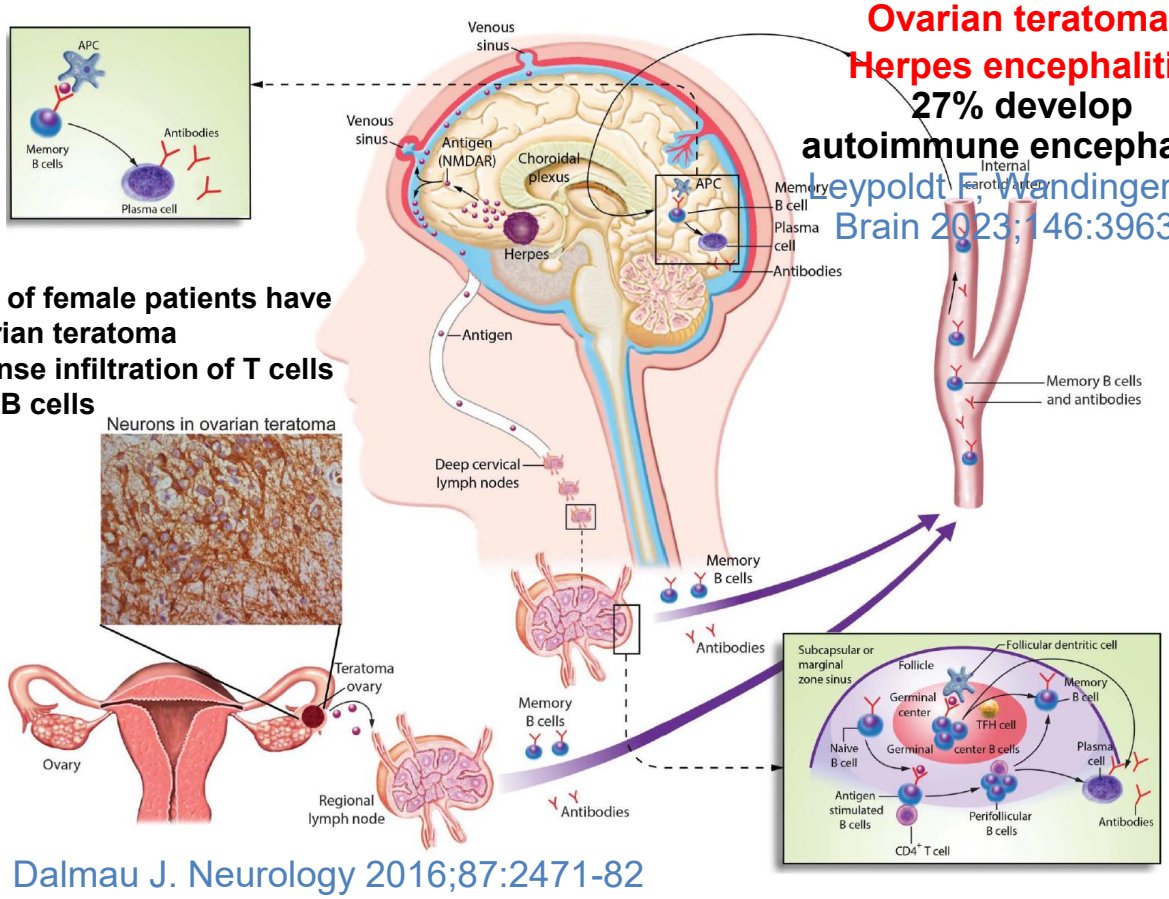
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# Immunologic triggers in anti–NMDAR encephalitis

**Ovarian teratoma**
**Herpes encephalitis**
**27% develop autoimmune encephalitis**

Leypoldt F, Wandinger KP. Brain 2023;146:3963-5

**50% of female patients have ovarian teratoma**
**- Dense infiltration of T cells and B cells**




Dalmau J. Neurology 2016;87:2471-82

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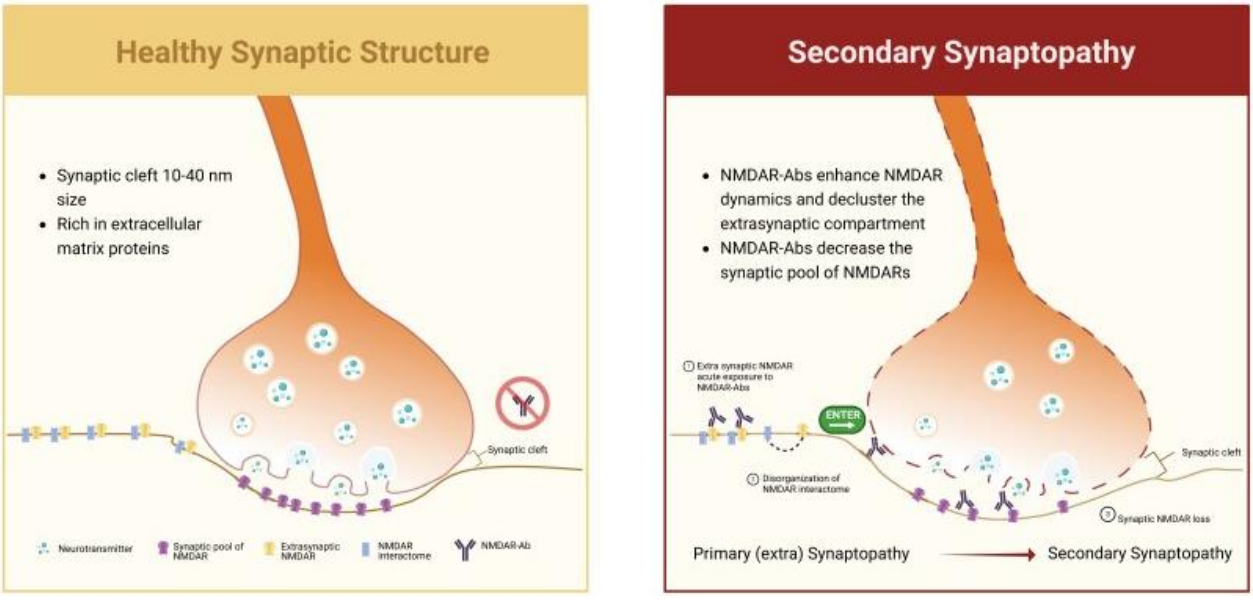
# Anti-NMDAR Encephalitis and Glia

- **4%-7.5% of patients with anti-NMDAR encephalitis have concurrent glial-Ab or neuronal surface-Ab. Some of these antibodies (MOG-Ab, AQP4-Ab, NS-Ab) confer additional clinical-radiologic features and may influence prognosis.**
  Martinez-Hernandez et al. Neurology 2020;94:e2302-e2310

- **Antibodies from patients with anti-NMDAR encephalitis specifically alter the function of NMDARs in oligodendrocytes, causing a decrease of expression of glucose transporter (GLUT1).**
  Matute et al. Ann Neurol 2020;87:670-6

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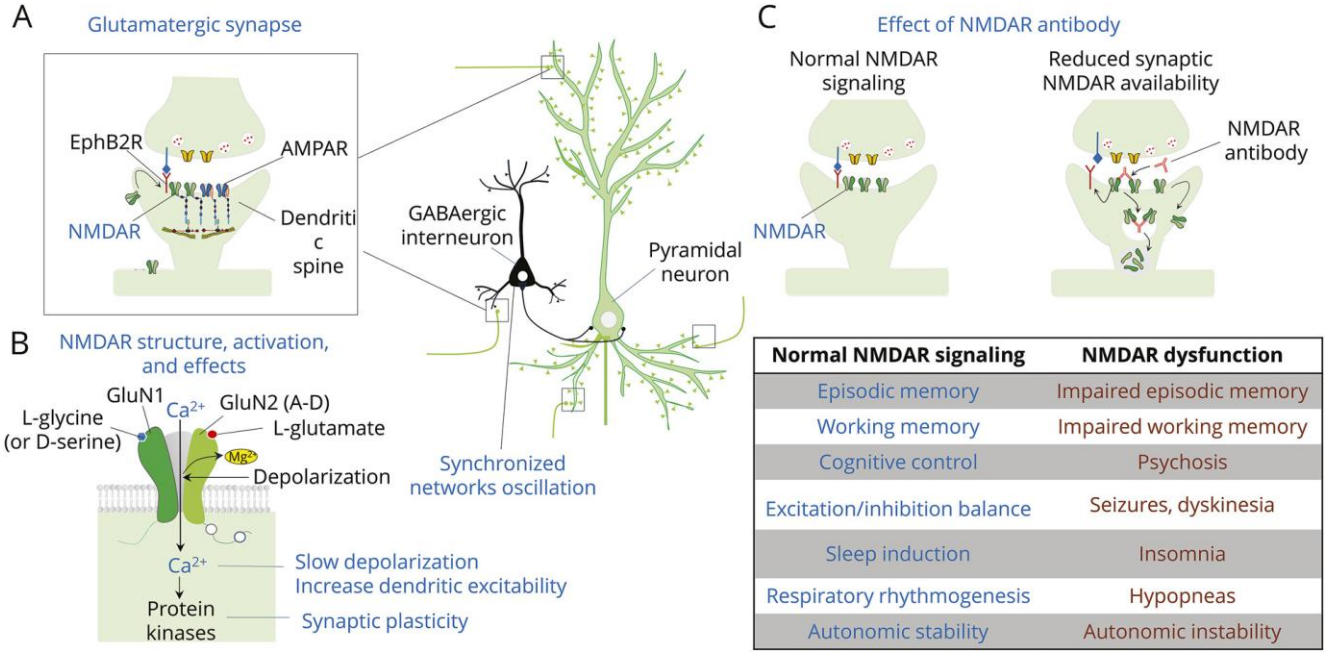
## Autoantibodies directed against N-methyl-D-aspartate receptor (NMDAR-Ab) initially impair extrasynaptic proteins, then the synaptic ones




Zhao et al. Brain 2024;147:2601-3
Jamet et al. Brain 2024;147:2745-60

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# NMDAR-Mediated Neurotransmission and Clinical Features of Anti-NMDAR Encephalitis




| Normal NMDAR signaling | NMDAR dysfunction |
|---|---|
| Episodic memory | Impaired episodic memory |
| Working memory | Impaired working memory |
| Cognitive control | Psychosis |
| Excitation/inhibition balance | Seizures, dyskinesia |
| Sleep induction | Insomnia |
| Respiratory rhythmogenesis | Hypopneas |
| Autonomic stability | Autonomic instability |

**Reduction in synaptic NMDAR availability, destabilization of receptor clustering, and impaired NMDAR-mediated signaling**

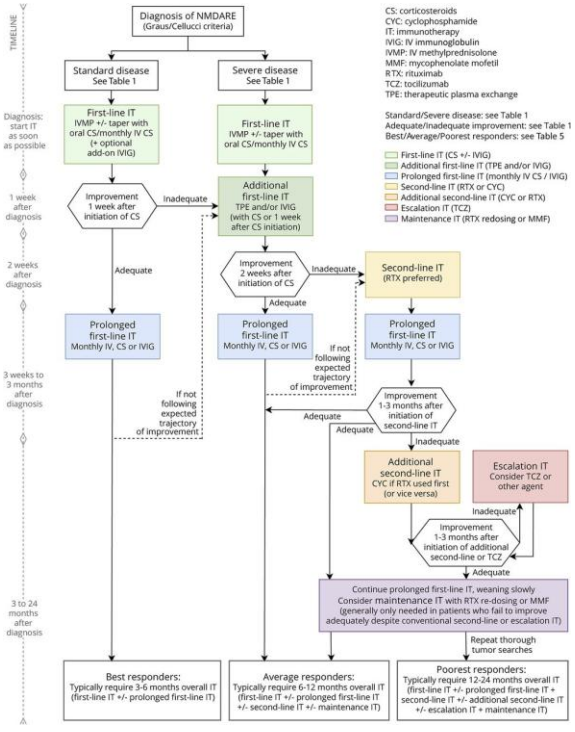
Vilaseca et al. Neurology 2025;105:e214232

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# Treatment of NMDAR Encephalitis

- **Removal of tumor (ovarian>>>testicular teratoma)**
  - **Oophorectomy recommended despite negative imaging**
- **IVIg 0.4 g/kg/d for 5 days and methylprednisolone 1 g/d for 5 days**
- **If above fails after 10-15 days start:**
  - **Rituximab (anti-CD20 monoclonal antibody that eliminates B-cell lineage and prevents formation of plasma cells)**
  - **A single course of rituximab reduces the risk of relapse of anti-NMDAR antibody-mediated encephalitis; administration at 6 months further delays relapses.**
    Seery et al. Neurol Neuroimmunol Neuroinflamm 2025;12:e200395
- **Or PEx (6 treatments over 10 days)**

# International Consensus Recommendations for the Treatment of First Event of Pediatric NMDAR Antibody Encephalitis

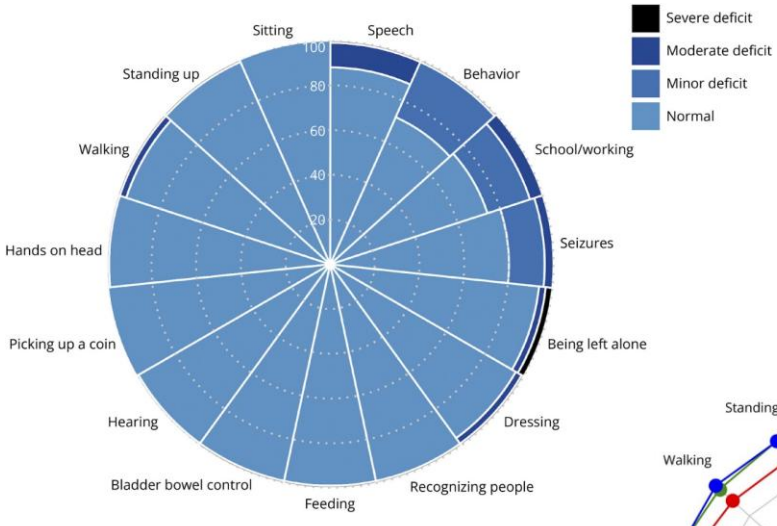



- **First-line treatments: Corticosteroids with additional IVIG or PEX in severe patients for up to 3-12 months (oral corticosteroids or monthly IV corticosteroids/immunoglobulin), dependent on disease severity.**
- **Second-line treatments are recommended for cases refractory to first-line therapies (rituximab preferred over cyclophosphamide) and should be considered about 2 weeks after first-line initiation.**

Nosadini et al. Neurol Neuroimmunol Neuroinflamm 2021;8:e1052

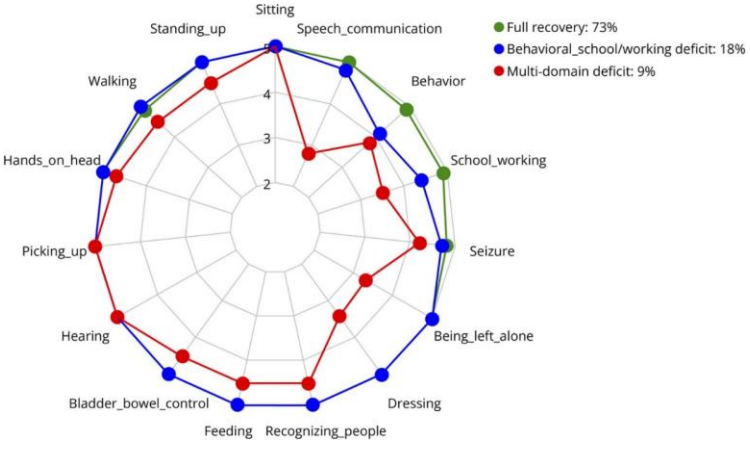
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# Very Long-Term Functional Outcomes in Children With Anti-NMDA Receptor Encephalitis




**11% of 76 patients died during a mean follow-up of 7.1 years**

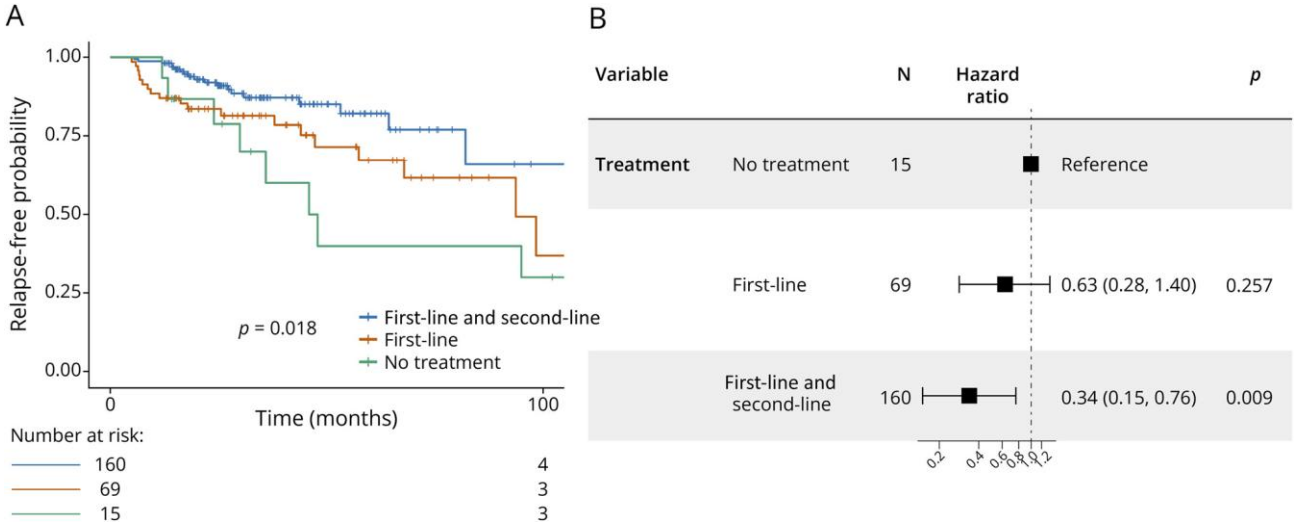
**1/5 remained with behavioral and school/working deficits**




Chen et al. Neurol Neuroimmunol Neuroinflamm 2024;11:e200235

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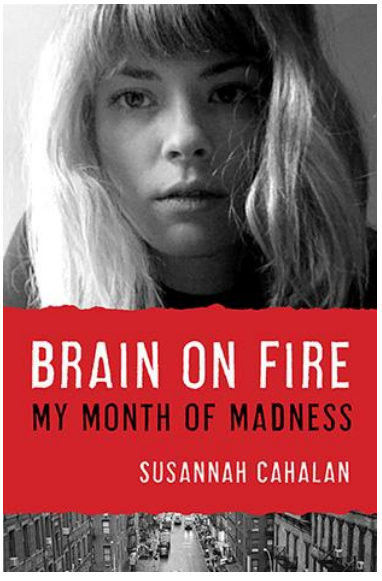
# Relapses in Anti-NMDAR Encephalitis



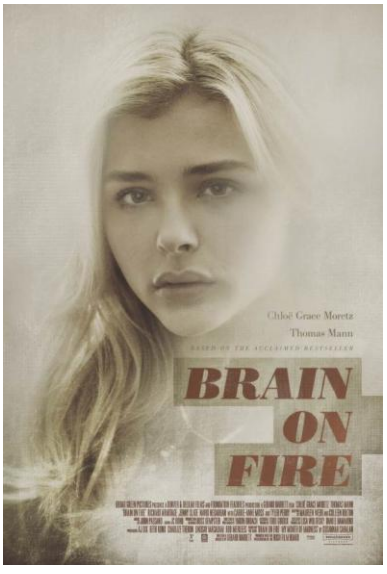

**Among 507 patients, 9% relapsed after a median time of 2 years. Early administration of first-line and second-line immunotherapies, particularly rituximab, could protect against further relapses.**
Ciano-Petersen et al. Neurol Neuroimmunol Neuroinflamm 2025;12:e200421

**Other studies indicate that relapses occur in 12%-16% of patients and can occur many years later.**

74






- **A reporter at The New York Post describes her horrifying story of anti-NMDAR encephalitis, manifested by progressive headaches, auditory and visual hallucinations and other behavioral and psychotic symptoms, seizures, (dystonia) and encephalopathy. Initially misdiagnosed as schizophrenia, bipolar disorder, and stress-related mental illness; finally correctly diagnosed as anti-NMDAR encephalitis.**
- **2016 Film adaptation staring Chloe Grace Moretz, co-produced by Charlize Theron.**

75

# Anti-immunoglobulin-like cell adhesion molecule 5 (Anti-IgLON5) disease

- Complex sleep disorder, rapid periodic leg movements, central hypoventilation, REM and non-REM parasomnias.
- May mimic PSP, CBS, MSA, DLB and ALS
- Bulbar/laryngeal symptoms (stridor), cognitive decline, chorea, myoclonus, dystonia, tics and other hyperkinesias; inspiratory stridor, gurgle or whistle; involuntary jaw, tongue, palatal movements.
- Insidious or subacute onset, protracted clinical course spanning months to years; may die of sudden death.
- Affects people between 45 and 75 years of age; 1 in 150,000 people.
- Only 10% of patients have a history of autoimmune disease, and malignancy is present in only 11% of individuals.
- Associated with antibodies against IgLON5, neuronal cell adhesion protein.
- HLA-DQ-mediated T-cell response to IgLON5 as a key step in the initiation of autoimmunity in this neurodegenerative disease.
- Autopsy: neuronal tauopathy involving predominantly the hypothalamus, hippocampus, and brainstem tegmentum.

Gaig et al. Neurology 2021;97:e1367-81
Yogeshwar et al. Brain 2024;147:2579-92

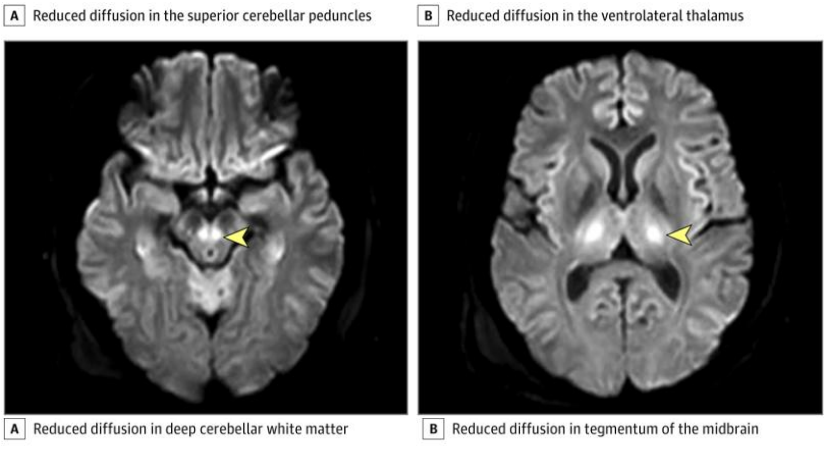
# Frequency and Characterization of Movement Disorders in Anti-IgLON5 Disease.

Gaig et al. Neurology 2021;97:e1367-81

- 72 patients; in 41 (57%) the main reason for initial consultation was difficulty walking along with one or several concurrent movement disorders: gait and balance disturbances (72%), chorea (33%), bradykinesia (28%), dystonia (26%), abnormal body postures or rigidity (25%), and tremor (21%); other hyperkinetic movements (myoclonus, akathisia, myorhythmia, myokymia, or abdominal dyskinesias) occurred in 26 (36%) patients.
- The craniofacial region was most frequently affected by multiple concurrent movement disorders including dystonia, myorhythmia, chorea or myokymia.
- 87% had sleep alterations, 74% bulbar dysfunction, and 53% cognitive impairment.
- 55 (76%) patients were treated with immunotherapy, resulting in important and sustained improvement of the movement disorders in only 7(13%) cases.
- Conclusions: Anti-IgLON5 disease should be considered in patients with multiple movement disorders, particularly if they occur in association with sleep alterations, bulbar dysfunction, or cognitive impairment.

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# MRI in IgLON5 is usually normal, but …




**Axial diffusion trace images show hyperintensity in the superior cerebellar peduncles and ventrolateral thalamus**

**Axial diffusion trace images show symmetrical areas of reduced diffusion involving bilateral medial cerebellar hemispheres and the tegmentum of the midbrain**

**Leptomeningeal enhancement**

Chen et al. JAMA Neurol 2020;77:125-6

94

**77 y/o man with tic-like movements and positive anti-IgLON5 antibody.**
Cao et al. Neurology 2022;99:26-30



**Tic-like movements improved with immunosuppression**
Kandadai et al. Mov Disord Clin Pract 2024;11:94-6

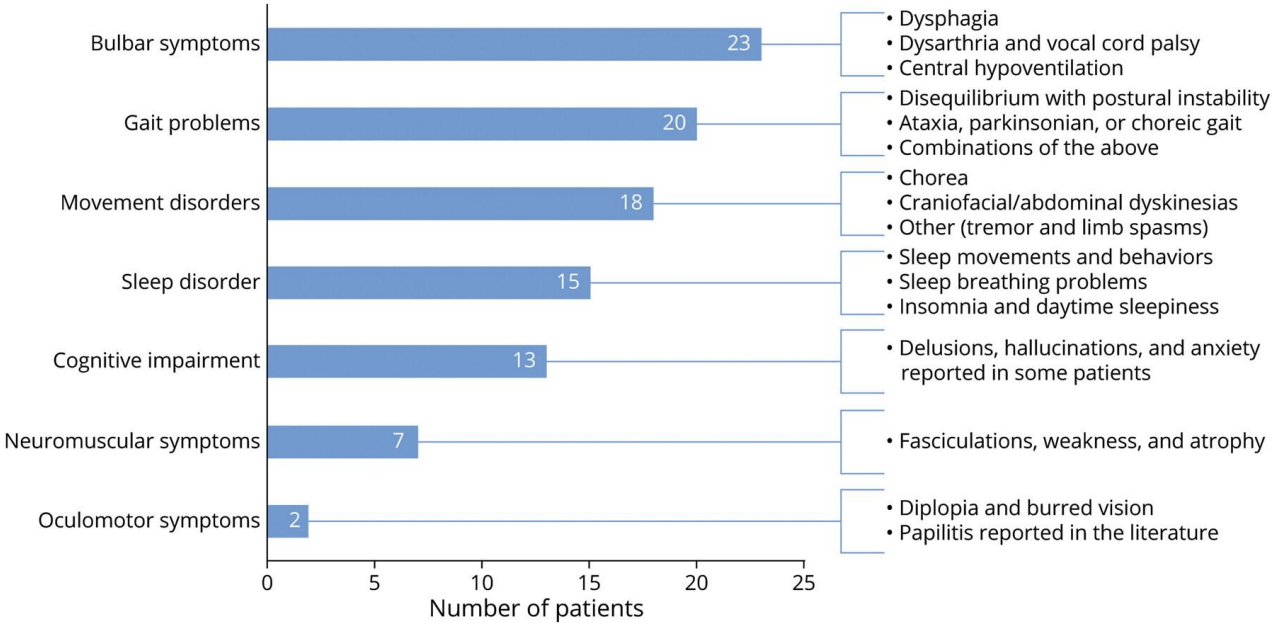


**“Head Drops”**
Bavdhankar et al. Mov Disord Clin Pract 2024;11:575-7



95

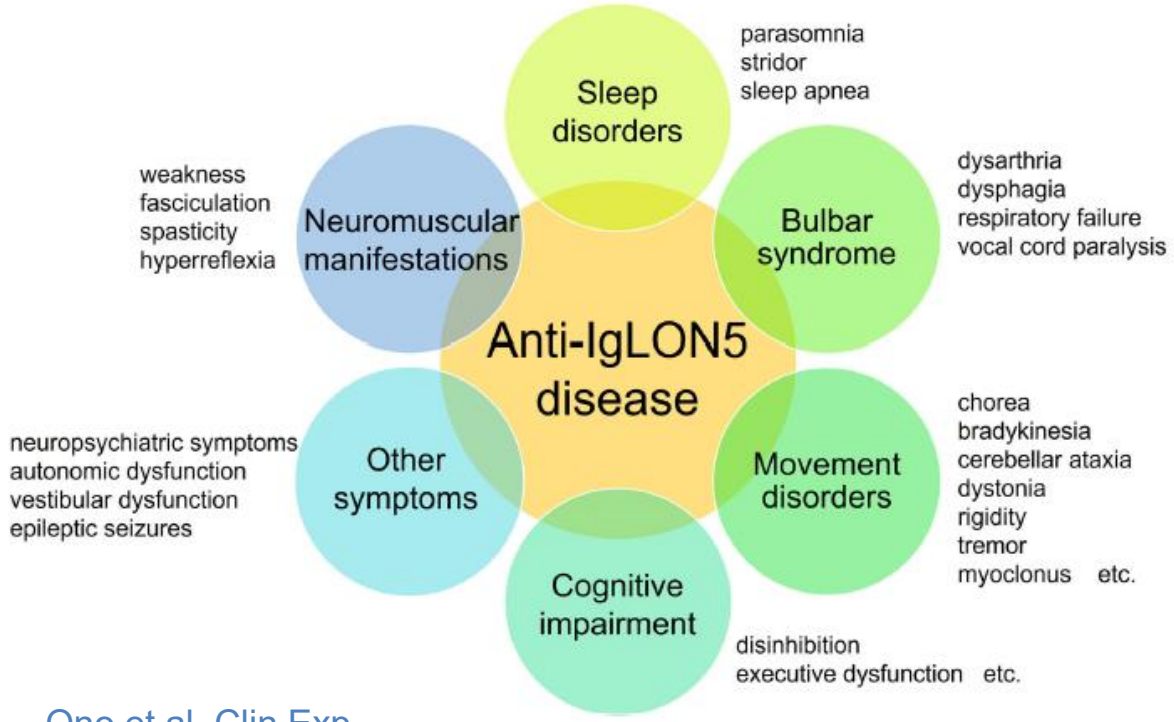
## Reasons for Consultation in 98 Patients With Anti-IgLON5 Disease




Graus et al. Neurol Neuroimmunol Neuroinflamm 2025;12:e200353

99

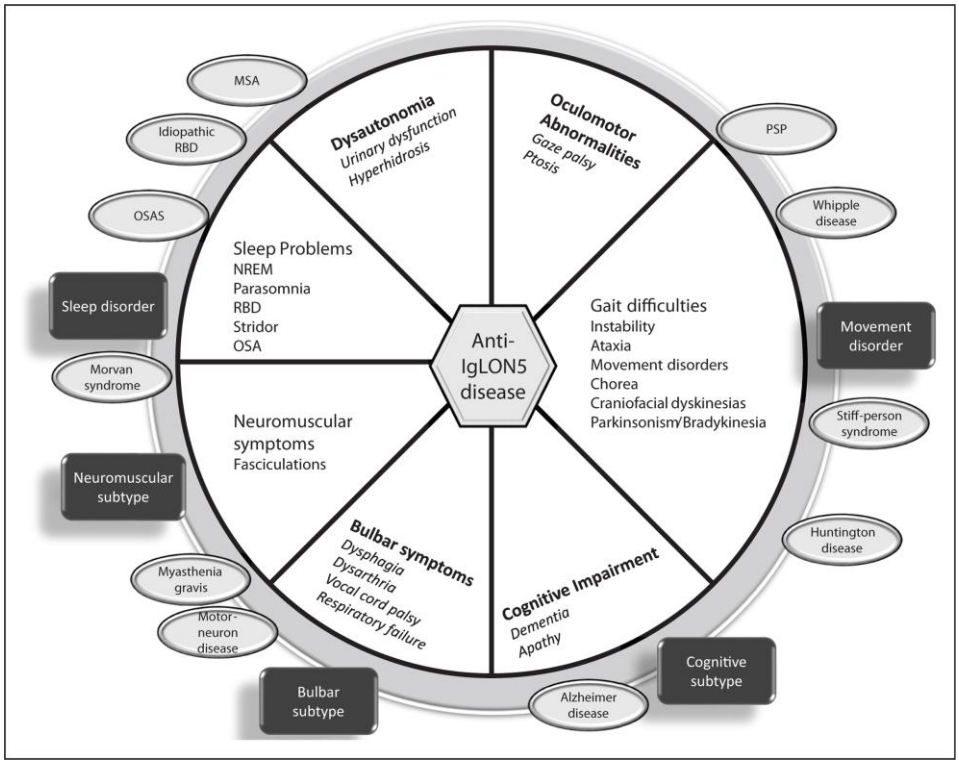
## The clinical phenotype and spectrum of anti-IgLON5 disease




Ono et al. Clin Exp Neuroimmunol 2023;14:167–74

100

# Clinical symptoms observed in anti-IgLON5 disease




Gaig C, Sabater L. Curr Opin Neurol 2024;37:316-21

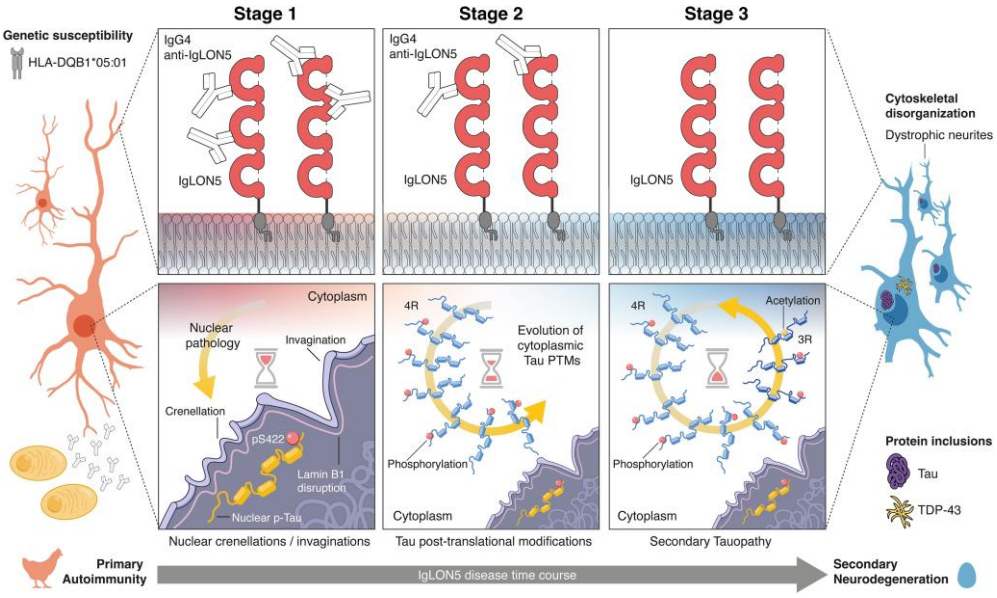
101

# Summary of What We Know and What We Do Not Know of Anti-IgLON5 Disease

| What we know | What we do not know |
|---|---|
| Disease onset after the fifth decade | Triggers and predisposing factors to develop anti-IgLON5 disease |
| Progressive course in >70% of patients | Prevalence/incidence of the disease |
| Most common presentation is a combination of gait impairment, bulbar symptoms, and a characteristic sleep disorder | Natural history/cause of death |
| Abnormal movements common—mainly chorea and facial dyskinesias | Profile of cognitive deficits |
| Characteristic sleep signature of polysomnographic studies | Frequency of motor neuron involvement |
| Absent signs of inflammation in MRI and CSF in >70% of patients | Variables associated with the presence of inflammation in brain MRI and CSF |
| Association with the HLA-DRB1*10:01- DQB1*05:01 haplotype | Significance of hippocampal tau deposits detected in some patients |
| Presence of a novel 3R and 4R neuronal brainstem tauopathy in most patients | Neuropathologic substrate of cognitive deficits and movement disorders such as chorea |
| IgLON5 antibodies induce irreversible reduction of membrane IgLON5 clusters and cytoskeletal changes in neurons in culture | The function of IgLON5 |
| Immunotherapy is indicated particularly in subacute deterioration at onset or relapses | The interactions between IgLON5 antibodies and the innate immune system |
| | Whether all patients must be treated with immunotherapy |
| | The best treatment |
| | The response of different symptoms to treatment |

Graus et al. Neurol Neuroimmunol Neuroinflamm 2025;12:e200353

# The evolution of anti-IgLON5 disease into tauopathy




**Proposed stages of IgLON5-antibody disease progress from prominent membrane associated IgG4 autoantibody binding and early nuclear pathology with tau phosphorylation at pS422, accumulation of 4R tau, through to 3R tau modifications, linking early immune-mediated injury to downstream neurodegenerative pathology (tauopathy).**

Di Liberto G, Irani SR. Brain 2026;149:1423-25

103

# IgLON5 autoimmune antibodies activate Tau via neuronal hyperactivity

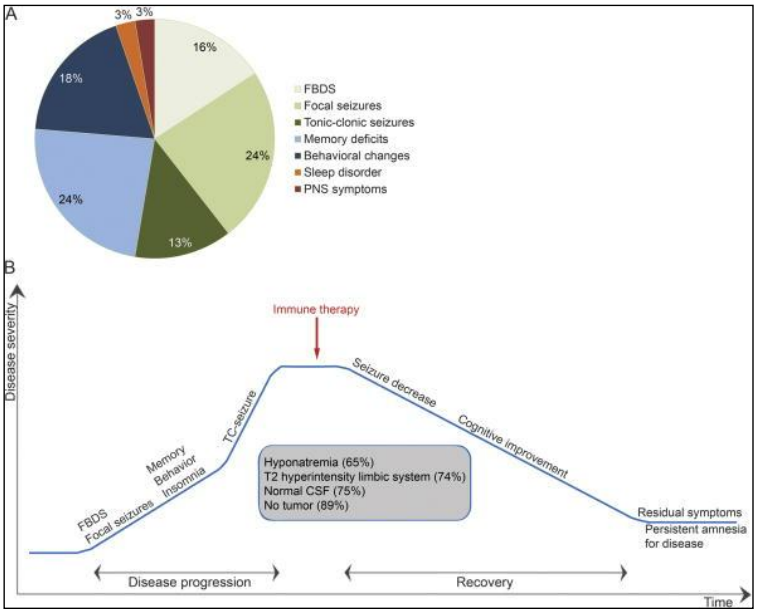
- **Patient-derived α-IgLON5 autoantibodies cluster IgLON5 proteins with other cell surface proteins, including the glutamate-sensing kainate receptor subunit GRIK3, leading to neuronal hyperactivity that triggers pathological Tau missorting and phosphorylation, typically observed early in Tau-related neurodegenerative diseases.**
- **The irreversible internalization and lysosomal degradation of IgLON5 antibody–protein complexes plays a role in this neurodegenerative disease.**
- **The findings establish a causal link between the α-IgLON5 autoantibodies and Tau pathology in anti-IgLON5 disease patients and highlight the role of neuronal hyperactivity as a disease-overarching driver of Tau pathology and provide a potential target for therapeutic intervention.**

Askin et al. Sci Adv 2026;12:eaec2042

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# Anti-LGI1 Encephalitis

van Sonderen et al. Neurology 2016;87:1449-56




**Presenting symptoms and disease course in 38 patients with anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis and disease course.**
**FBDS = faciobrachial dystonic seizures;**
**PNS = peripheral nervous system;**
**TC seizure = tonic-clonic seizure**

- **Faciobrachial dystonic seizures (47%) - involuntary contractions of 1–2 seconds, affecting the unilateral arm (or leg) and face, occurring up to 100 times a day**
- **Attacks may be preceded by sensory auras and automatisms**
- **EEG - epileptic discharges (31%) or focal slowing (25%) in half of the patients**
- **80%, improved with immunotherapy, but not with antiepileptics**
- **Two-year case fatality rate was 19%**
- **Residual cognitive deficit and relapses were common**

Campetella et al. Neurol Neuroimmunol Neuroinflamm 2024;11:e200228

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## Faciobrachial dystonic seizures with LGI1 limbic encephalitis



Courtesy Prof. Angela Vincent

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**18 y/o with new onset of altered mental status, psychiatric symptoms (initially misdiagnosed as "psychogenic"), less interactive, slurred speech; followed by abnormal movements in the right face and left faciobrachial dystonic seizures. EEG during the events – non-epileptiform. CSF was positive for LGI1-antibodies.**

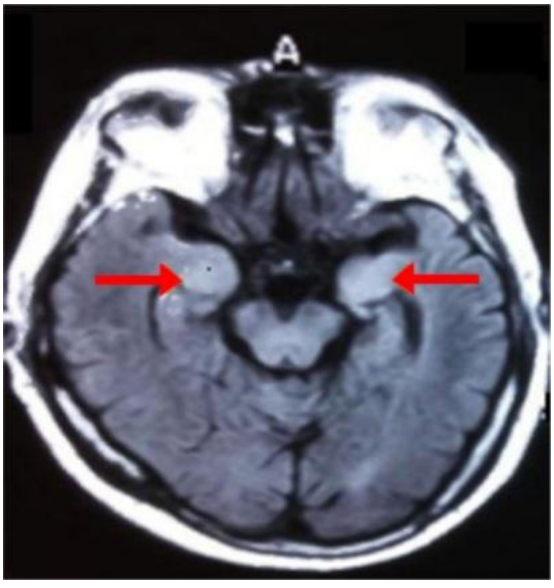


Courtesy M. Parnes, MD

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# Limbic encephalitis with LGI1 antibody

**Abnormalities in the mediotemporal lobe and the hippocampus**

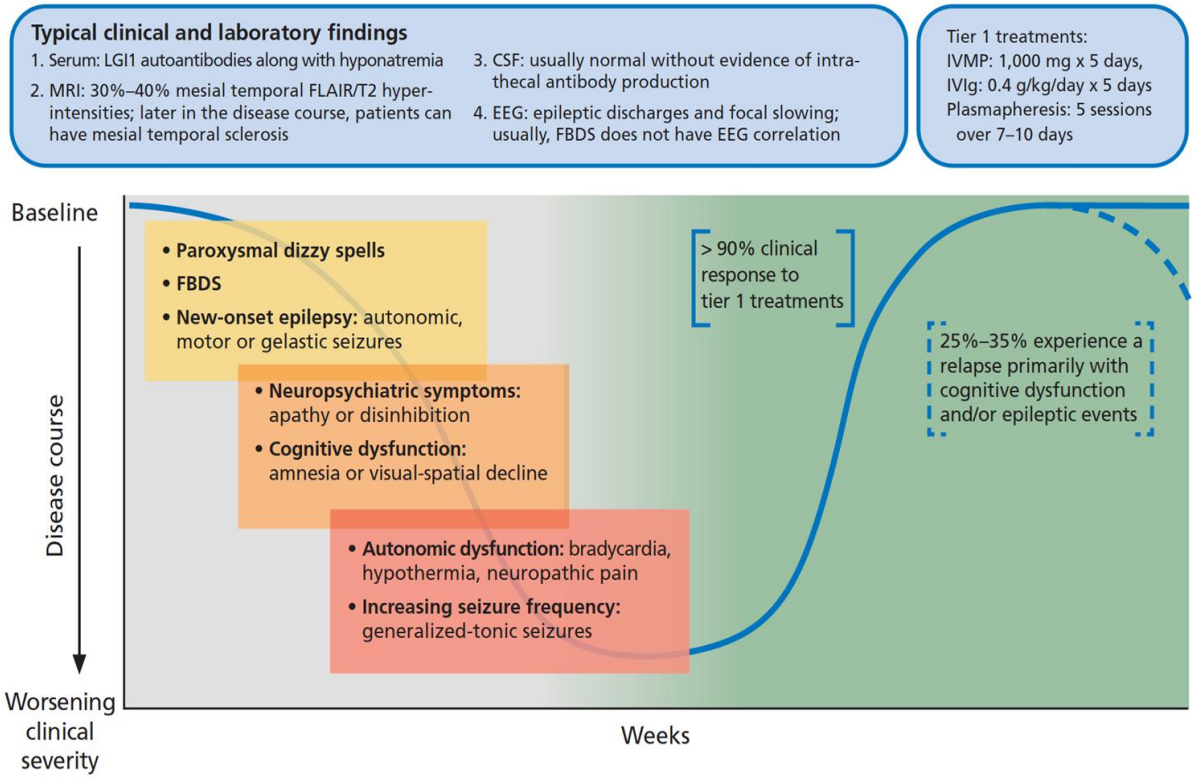



**74% hippocampal T2 hyperintensity**

Wang et al. Neuropsychiatr Dis Treat 2017;13:1589-96

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# Anti-LGI1 Encephalitis

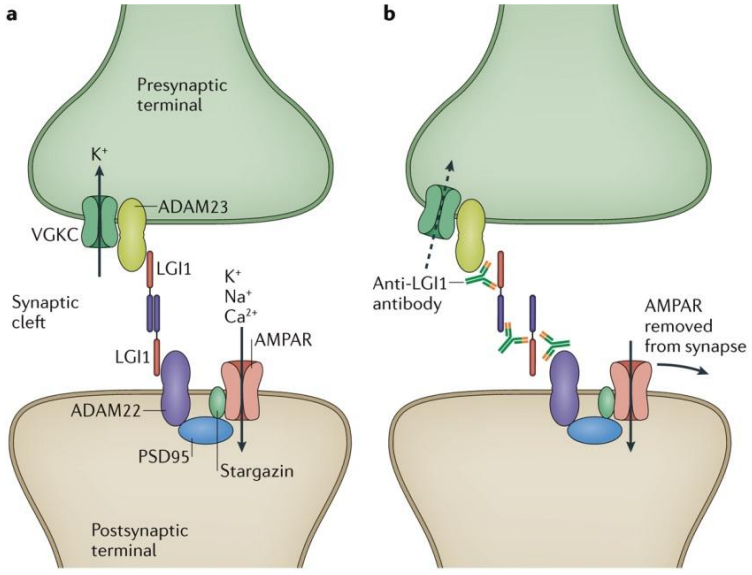



Abbatemarco et al. Cleve Clin J Med 2021;88:459-71

112

# Limbic encephalitis with LGI1 antibody

**LGI1 antibodies in the blood and/or CSF – not directed against K channels but probably act by interfering with protein–protein interactions between LGI1 and presynaptic protein (ADAM23)**




van Sonderen et al.
Nat Rev Neurol 2017;13:290-301

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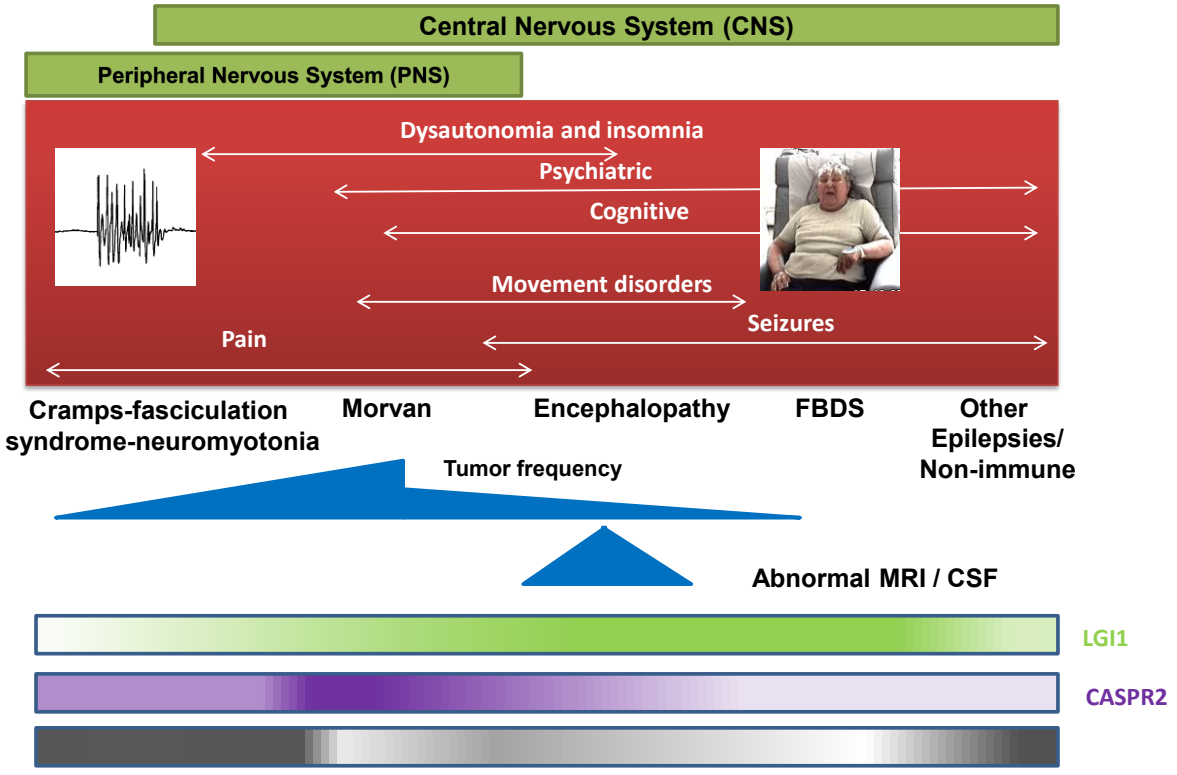
# Distinct movement disorders in contactin-associated-protein-like-2 (CASPR2) antibody-associated autoimmune encephalitis.

Gövert et al. Brain 2023;146:657-67

- **CASPR2 autoantibody-associated disorders are very diverse and include limbic encephalitis, Morvan's syndrome, peripheral nerve hyperexcitability syndrome, a variety of movement disorders, ataxia, pain and sleep disturbances.**
- **Of 164 patients with CASPR2 autoantibodies 149 (90.8%) had only CASPR2 and 15 (9.1%) had both CASPR2 and LGI1 autoantibodies.**
- **The small group of patients double-positive for LGI1/CASPR2 autoantibodies (15/164) significantly more frequently had myoclonus, tremor, 'mixed movement disorders', Morvan's syndrome and underlying tumors.**
- **Distinct movement disorders were observed in CASPR2 autoimmunity (14.6%): episodic ataxia (6.7%), paroxysmal orthostatic segmental myoclonus of the legs (3.7%) and continuous segmental spinal myoclonus (4.3%).**

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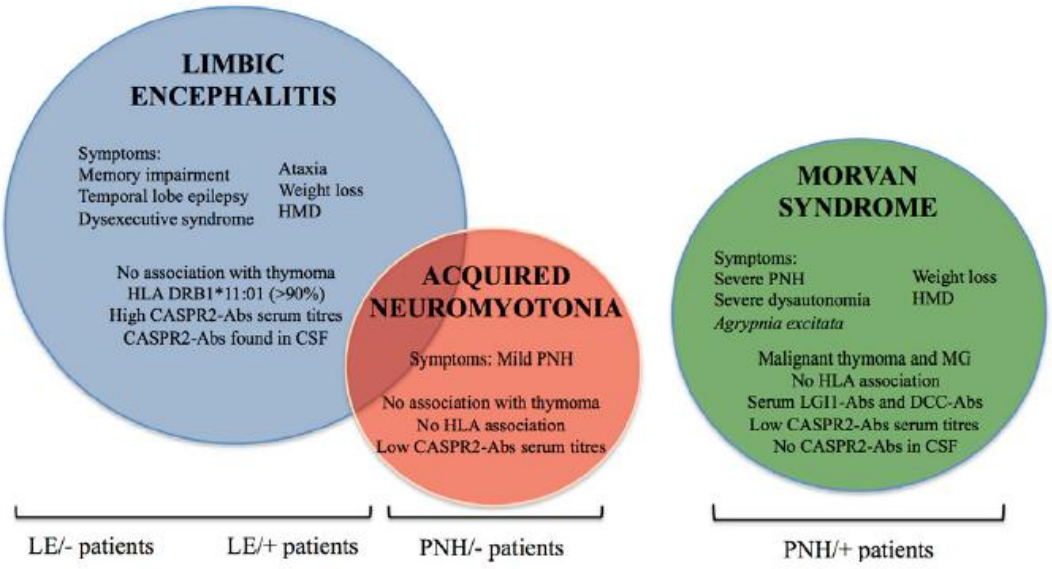
# Syndromes associated with VGKC antibodies LGI1/CASPR2




Irani SR, Vincent A. Handb Clin Neurol 2016;133:185-97

122

# Clinical and immunogenetic features of three major anti-CASPR2 antibodies diseases




LE = limbic encephalitis; NMT = neuromyotonia; DCC-Abs = netrin-1 receptor deleted in colorectal carcinoma; HLA = human leucocyte antigen; HMD = hyperkinetic movement disorders; PNH = peripheral nerve hyperexcitability

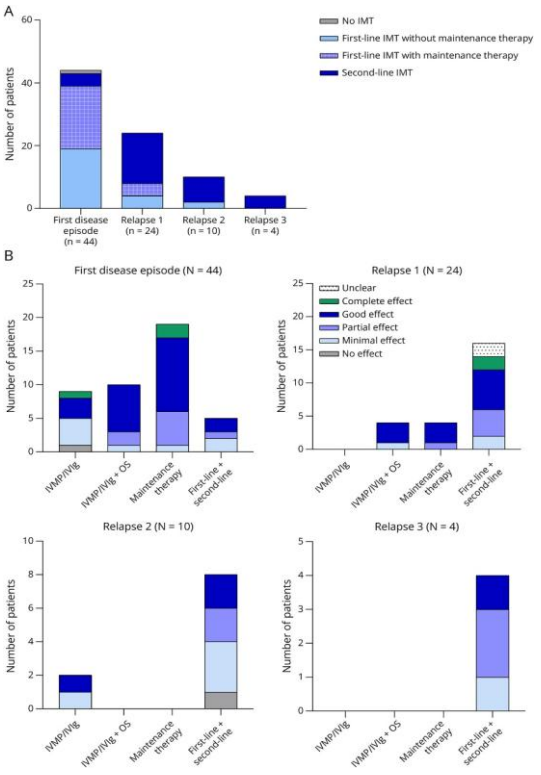
Muñiz-Castrillo et al. JNNP 2020;91:1076-84

123

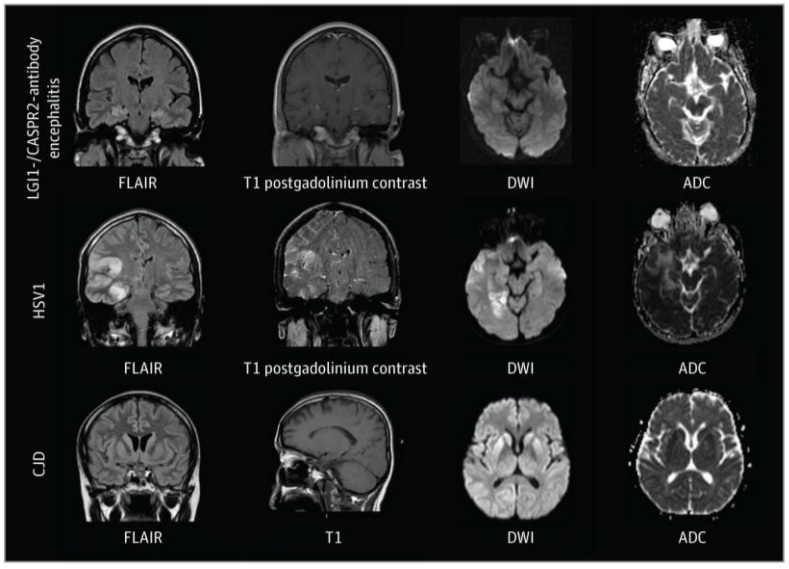
# High Relapse Rate in Anti-CASPR2 Disease: Implications for Prolonged Immunotherapy.

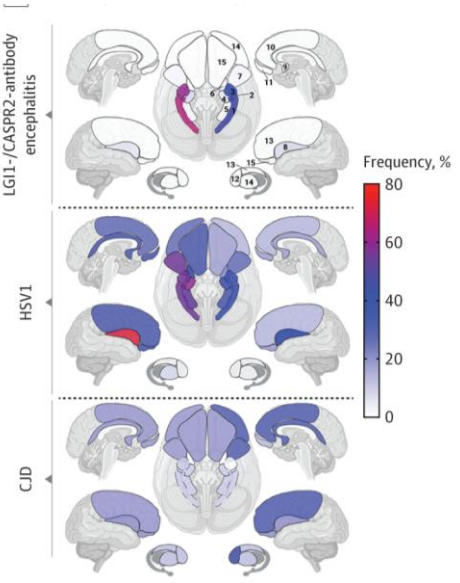
Brand et al. Neurol Neuroimmunol Neuroinflamm 2026;13:e200524

- **Prolonged immunotherapy beyond the acute stage is needed to prevent further relapses.**
- **Repeated courses of rituximab seem to be the treatment regimen of choice.**
- **If relapses occur, repeated tumor screening is warranted.**



# MRI Characteristics of LGI1-Antibody and CASPR2-Antibody Encephalitis



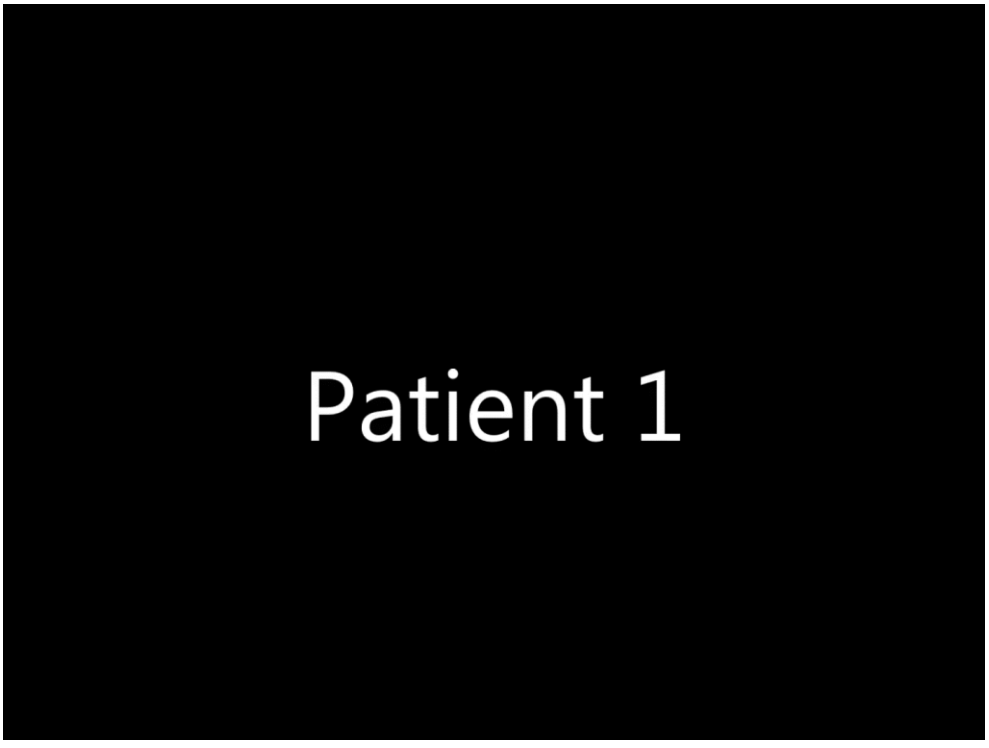

**T2 and/or FLAIR hyperintensities confined to the temporal lobes, without diffusion restriction or contrast enhancement, robustly distinguished LGI1/CASPR2-Ab encephalitis from other causes.**

Kelly et al. JAMA Neurol 2024;81:525-33

127

## Distinct movement disorders in contactin-associated-protein-like-2 (CASPR2) antibody-associated autoimmune encephalitis.

Gövert et al. Brain 2023;146:657-67




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# Morvan syndrome (Neuromyotonia)

- Morvan syndrome (fibrillary chorea or “la chorée fibrillaire”) – 1890 Isaacs Syndrome, Isaacs-Mertens Syndrome, Armadillo syndrome, Quantal squander syndrome, Pseudomyotonia
- M>F, median age 55 (12-85) years
- Gradual onset of muscle stiffness at rest, pain, sweating
- Continuous twitching (fasciculation) or rippling (myokymia)
- Cramps and delayed relaxation (pseudomyotonia)
- Some have mainly distal involvement (carpo-pedal spasms)
- Burning pain, pruritis, weakness, hyperhidrosis, weight loss hallucinations, encephalopathy, dysautonomia (cardiovascular instability, urinary incontinence, erectile dysfunction); may be associated with thymoma
- Insomnia with autonomic and motor hyperactivation, altered NREM sleep (agrypnia excitata)



Isaacs 1964

Vincent et al. JAMA Neurol 2018;75:1519-27

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# Morvan syndrome (Neuromyotonia)

- EMG: Continuous motor unit activity
  - Persists in sleep and after nerve block
  - Fasciculations
  - Grouped high frequency discharges
  - Neuromyotonic and/or myokymic discharges
  - After discharges
  - Denervation changes
  - Nerve conduction studies abnormal
- 1/3 have tumors (thymoma)
- Most cases are associated with voltage-gated potassium channel (VGKC)-complex antibodies
  CASPR2 > LGI1
  Caveolae-associated protein 4 autoantibodies
- Treatment: Carbamazepine, phenytoin, plasmapheresis or IVIG

Vincent et al. JAMA Neurol 2018;75:1519-27

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# Neuromyotonia



Courtesy of Prof. A. Vincent

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*Movement Disorders*
Vol. 6, No. 1, 1991, pp. 12–20
© 1991 Movement Disorder Society

# Stiff-Person Syndrome: An Autoimmune Disease

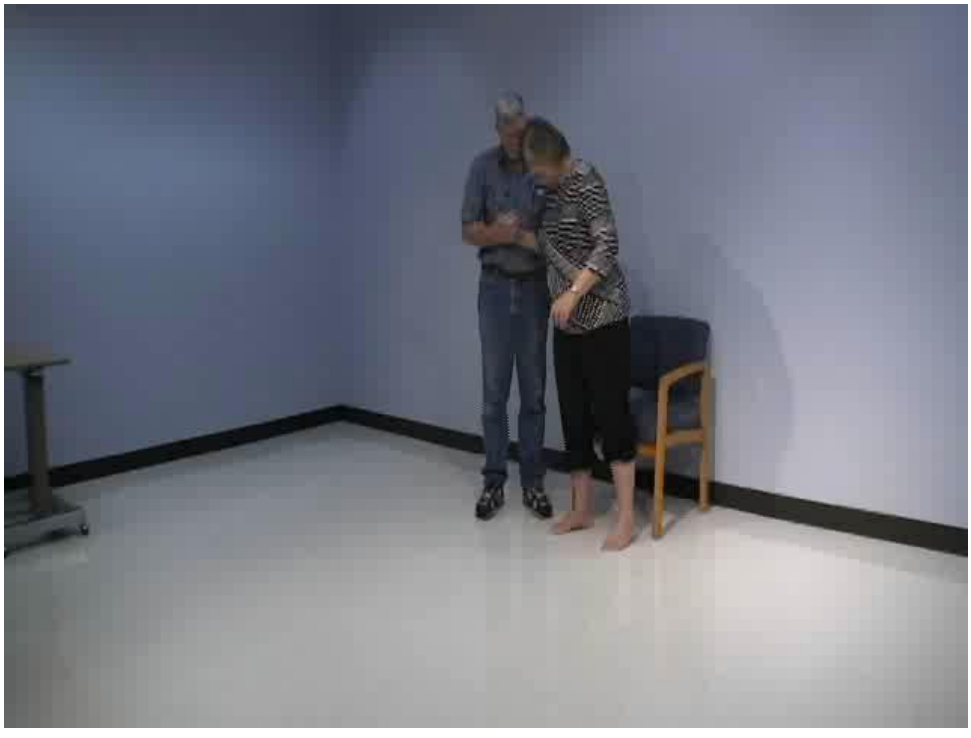
Philip Blum and Joseph Jankovic

*Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.*

**Summary:** Stiff-person syndrome (SPS) is characterized by progressive, usually symmetric rigidity of the axial muscles with superimposed painful spasms precipitated by tactile stimuli, passive stretch, volitional movement of affected or unaffected muscles, startling noises, and emotional stimuli. Electromyography demonstrates continuous normal motor unit potentials in the affected muscles. Both the rigidity and the spasms are relieved by sleep, general anesthesia, myoneural blockade, peripheral nerve blockade, and partially by diazepam. Evidence for an autoimmune etiology of SPS includes its association with other autoimmune diseases and autoantibodies and the presence of antibodies against glutamic acid decarboxylase (GAD) in the cerebrospinal fluid (CSF) of many affected patients. We describe two patients with this syndrome who had GAD antibodies in both CSF and serum. Partial relief of the symptoms in these patients by corticosteroid therapy provides additional evidence of an autoimmune etiology of SPS and of the role of immunotherapy in its treatment. **Key Words:** Stiff-person syndrome—Autoimmune diseases—Corticosteroid drugs.

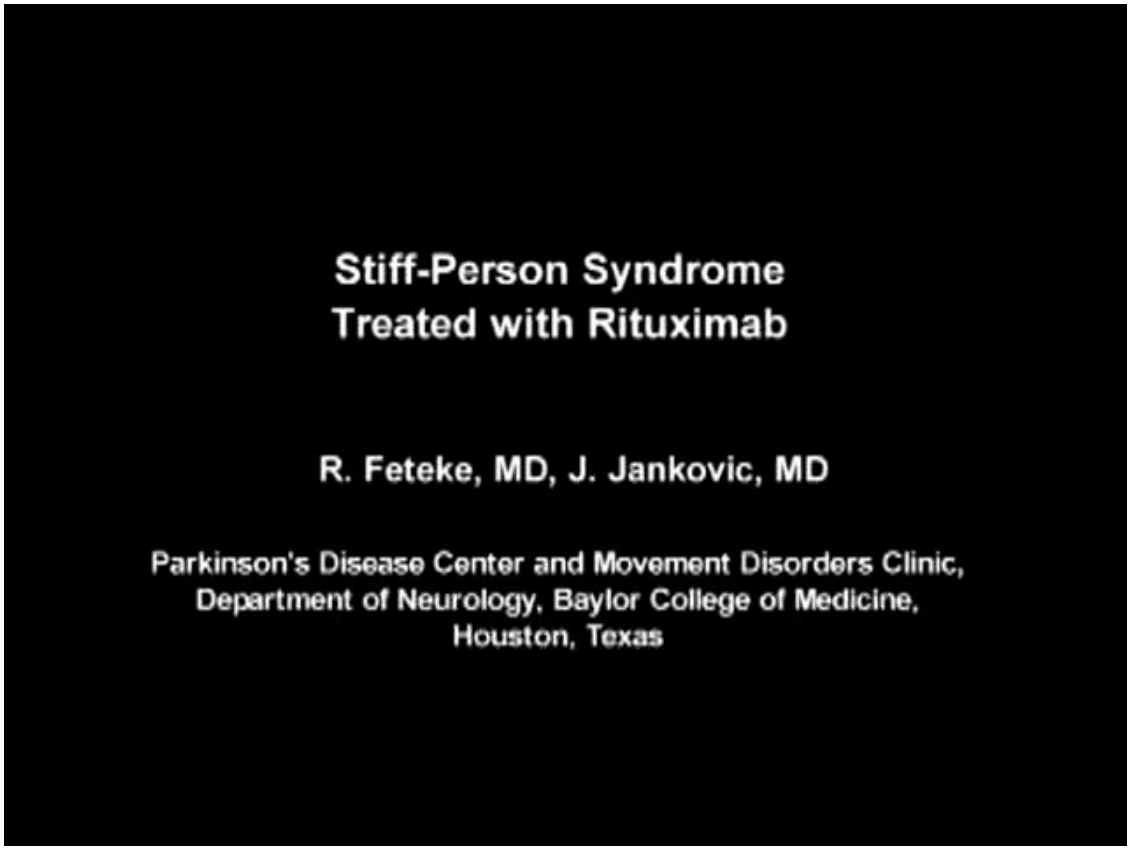
Stiff-man syndrome was first described by Moersch and Woltman (1) in a series of 14 cases in 1956. The world's literature was critically reviewed and diagnostic criteria were proposed by Gordon et al. (2) in 1967. Because the disease affects both men and women, we prefer the term "stiff-person" syndrome (SPS). Patients with SPS have progressive, usually symmetric rigidity of the axial muscles, and painful spasms that may fluctuate in intensity. Spasms may be precipitated by tactile stimuli, passive stretch, volitional movement of affected or unaffected muscles despite the patient's attempts to relax. Both the rigidity and the spasms are at least partially relieved by sleep, general anesthesia, myoneural blockade, peripheral nerve blockade, and usually, diazepam. The improvement in the cardinal symptoms is accompanied by cessation of the continuous motor unit potentials. Cranial nerve involvement, respiratory compromise, and deforming skeletal sequelae are common. Myoclonus, seizures, and psychiatric illnesses have also been reported in some patients.

**61 y/o woman with a long hx of insulin-dependent DM presented with a 6-month hx of progressive stiffness in both legs. On examination she had spasticity and peripheral neuropathy. Her anti-GAD65 antibody titer was >30U/cc (normal <1.2). She improved with diazepam and IVIG infusions with initial induction 2 g/kg over 4 days followed by 40 mg/kg q month.**



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Fekete R, Jankovic J. Case Rep Neurol 2012;4:92-6




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# Stiff-Person Syndrome.

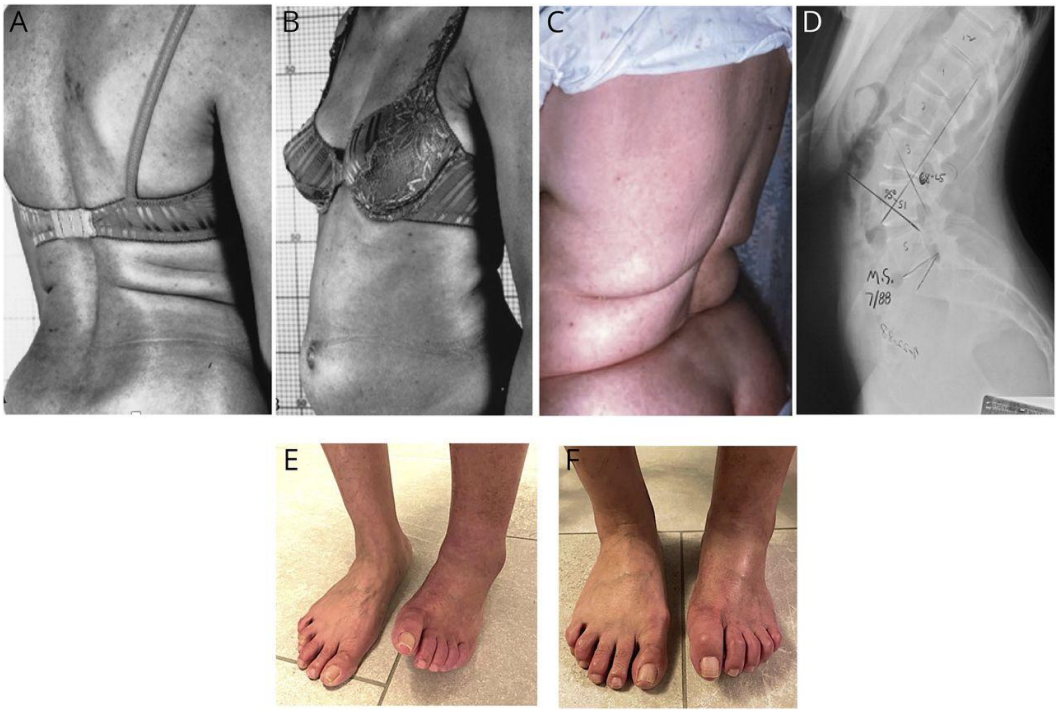
## New Insights into a Complex Autoimmune Disorder.

Baizabal-Carvallo JF, Jankovic J. JNNP 2015;86:840-8

- **Stiff-person syndrome (SPS) is characterized by progressive rigidity and muscle spasms affecting the axial and limb muscles**
- **SPS can be classified according to the clinical presentation into classic and SPS variants; jerking-SPS, and progressive encephalomyelitis with rigidity and myoclonus (PERM)**
- **Stiffness spreads from axial to proximal appendicular muscles**
- **Lumbar lordosis, kyphotic posture with shoulder elevation; limb rigidity associated, apraxia, freezing gait, falls**
- **Paroxysms of transient but intense muscle spasms, frequently triggered by emotional upset or external stimuli, diaphoresis, hypertension, tachycardia, and dysphoria**
- **Hyperreflexia, head retraction reflex, downbeat nystagmus, ophthalmoplegia**
- **EMG: continuous muscle activity in agonists and antagonists**

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**Figure 2 Characteristic Hyperlordosis, Thoracolumbar Stiffness With S-Shape Formation and Typical Spastic Foot in Patients With SPS**




Dalakas MC. Neurol Neuroimmunol Neuroinflamm 2023;10:e200109

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# Stiff-Person Syndrome

- **EMG: continuous muscle activity in agonists and antagonists**

- **>50% have a co-existent autoimmune disorder such as diabetes (29.0%, autoimmune thyroid disease (25.1%), hypothyroidism (12.0%), pernicious anemia (10.3%), myasthenia gravis (9.3%), Graves' disease (7.3%), vitiligo (5.8%), celiac disease (5.0%), Sjögren's syndrome (2.4%), systemic lupus erythematosus (2.1%), and rheumatoid arthritis (1.9%)**
  Hu et al. J Neurol 2026;273:442

- **Many patients with functional neurological disorder are misdiagnosed as SPS and vice versus**

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# Non-SPSD diagnoses

| Non-SPSD diagnosis | Number ($N$ = 125) |
|---|---|
| Non-neurologic or functional neurologic disease | 92 (73.6%) |
| Chronic pain syndrome and/or functional neurologic disease | 81 |
| Chronic pain alone | 44 |
| Functional neurologic disease alone | 25 |
| Both | 12 |
| Nonspecific somatic symptoms | 11 |
| Not immune-mediated neurologic disease | 29 (23.2%) |
| Motor neuron disease | 9 |
| Other myelopathies | 5 |
| Parkinsonian syndrome | 5 |
| Neuropathy | 4 |
| Other movement disorders (hyperekplexia, post-anoxic spasticity, dystonia) | 4 |
| Other ataxias | 1 |
| Developmental neurologic disorder | 1 |
| Immune-mediated neurologic disease | 4 (3.2%) |
| GAD65-IgG myelopathy and ataxia | 1 |
| GAD65-IgG ataxia | 1 |
| GlyR-IgG encephalomyelitis | 1 |
| Seronegative paraneoplastic encephalomyelitis | 1 |

Chia et al. Ann Clin Transl Neurol 2023;10:1083-94

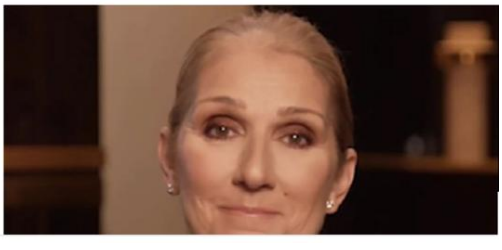
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# Céline Dion Reveals Diagnosis with Rare Neurological Disease Called Stiff Person Syndrome

In an emotional Instagram video shared on Thursday, Céline Dion opened up about her health, which she says will force her to cancel and postpone a series of upcoming concert dates

By **Marisa Sullivan**

Published on December 8, 2022 07:29 AM



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## "I am: Celine Dion"




Celine shared this footage to raise awareness about the disease.




9

https://x.com/dom_lucre/status/1810388580348666109

CNN Entertainment Subscribe

# Celine Dion announces her return to the stage

15 HR AGO

By Lisa Respers France




Celine Dion is seen at an "I Am: Celine Dion" ...

1

Celine Dion, who was previously sidelined from performing due to a rare neurological disorder, has announced a series of concerts that will bring her back to the stage.

CHICAGO — A single dose of an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy rapidly improved mobility and rigidity in patients with stiff person syndrome (SPS).

Early results of a phase 2 trial also showed the therapy — mivocabtagene autoleucel (miv-cel) — was well-tolerated and enabled patients to remain free of immunotherapies.



Amanda L. Piquet, MD

"In my expert opinion, as someone who sees so many patients with stiff person syndrome, the results of this trial are truly remarkable," lead trial investigator, Amanda L. Piquet, MD, director of the autoimmune neurology program at the University of Colorado Anschutz School of Medicine, and Celine Dion Foundation endowed chair, told *Medscape Medical News.*

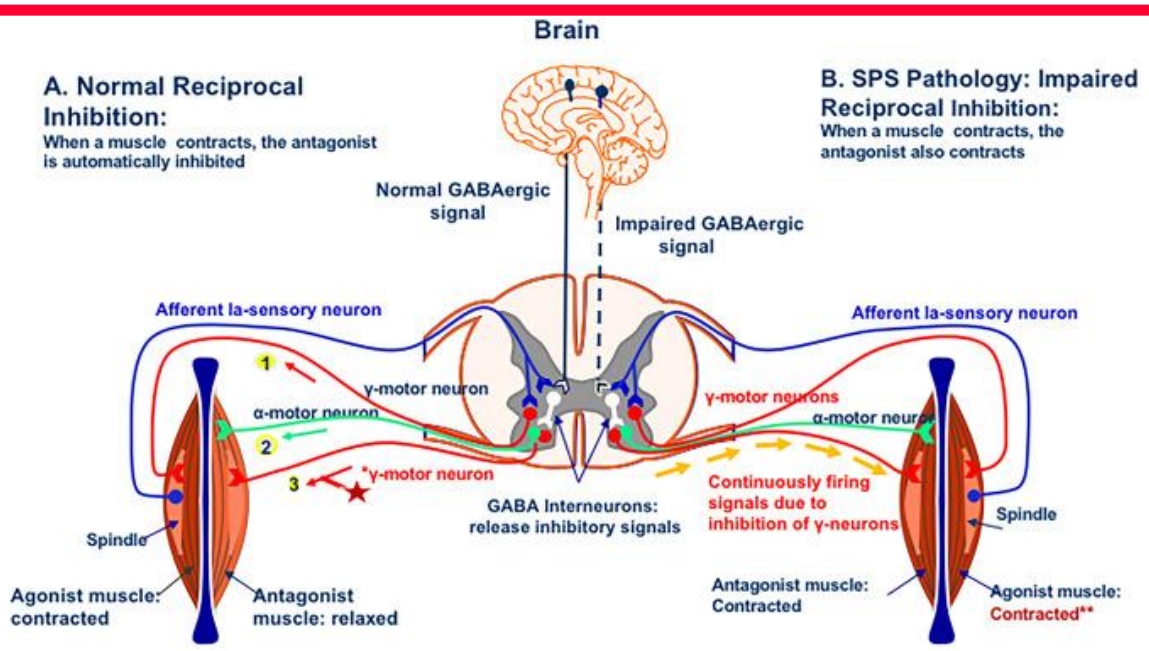
**'Transformative Outcomes'**

**"These transformative outcomes were possible through the ability of miv-cel to deliver this deep B cell depletion and broad immune reset," said Piquet. "From a clinical perspective, the magnitude and consistency of functional improvement observed is unprecedented."**

**Kyverna Therapeutics' mivocabtagene autoleucel (miv-cel; also known as KYV-101), an autologous anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy was presented at the 2026 AAN 4/21/26**

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# Pathophysiology of Stiff-person Syndrome



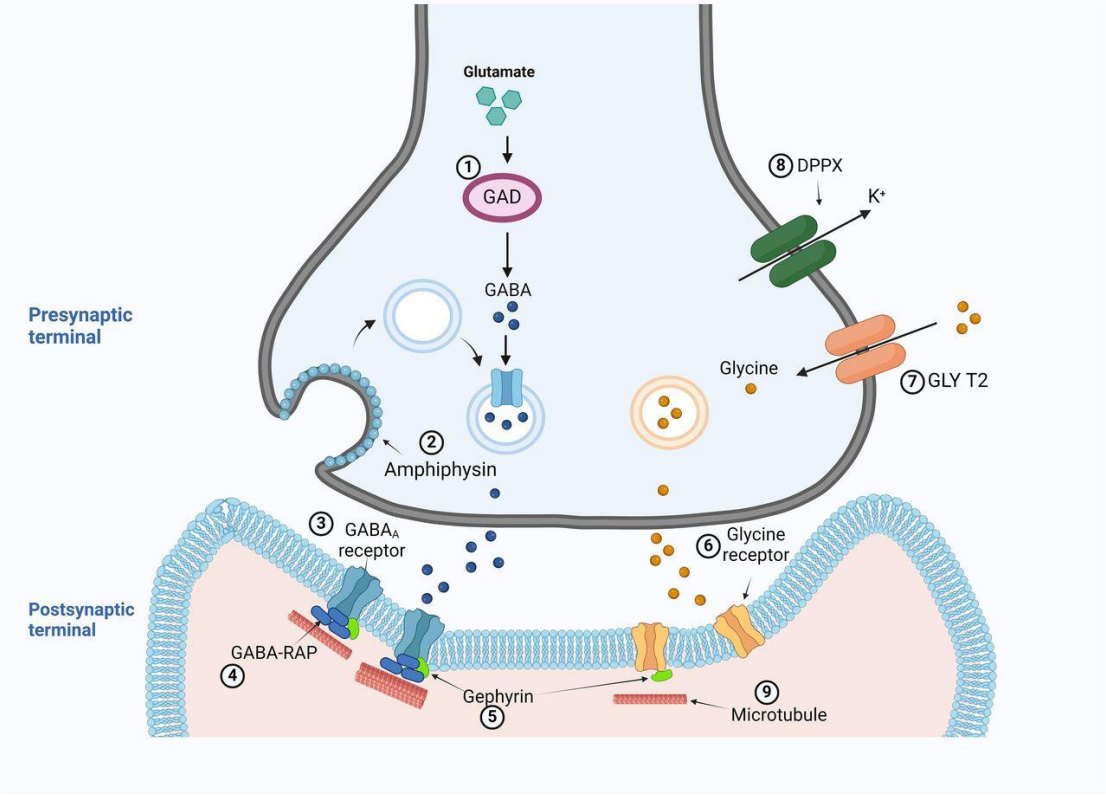

**Key mechanism in SPS: Impaired reciprocal GABAergic inhibition**

**The α-motor neuron is continuously firing and the muscle is continuously stimulated becoming hypertonic (spastic), without the ability to relax, due to simultaneous contraction of both, the agonist and the antagonist muscles**

Dalakas MC. Neurotherapeutics 2022;19:832-47
Dalakas MC. Nat Rev Neurol 2024;20:587-601

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# GABA pathway and antibody targets in SPS




Bose S, Jacob S. Pract Neurol 2025;25:6-17

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REVIEW OPEN ACCESS

# Therapies in Stiff-Person Syndrome

## Advances and Future Prospects Based on Disease Pathophysiology

Marinos C. Dalakas, MD, FAAN

*Neurol Neuroimmunol Neuroinflamm* 2023;10:e200109. doi:10.1212/NXI.0000000000200109

## Abstract

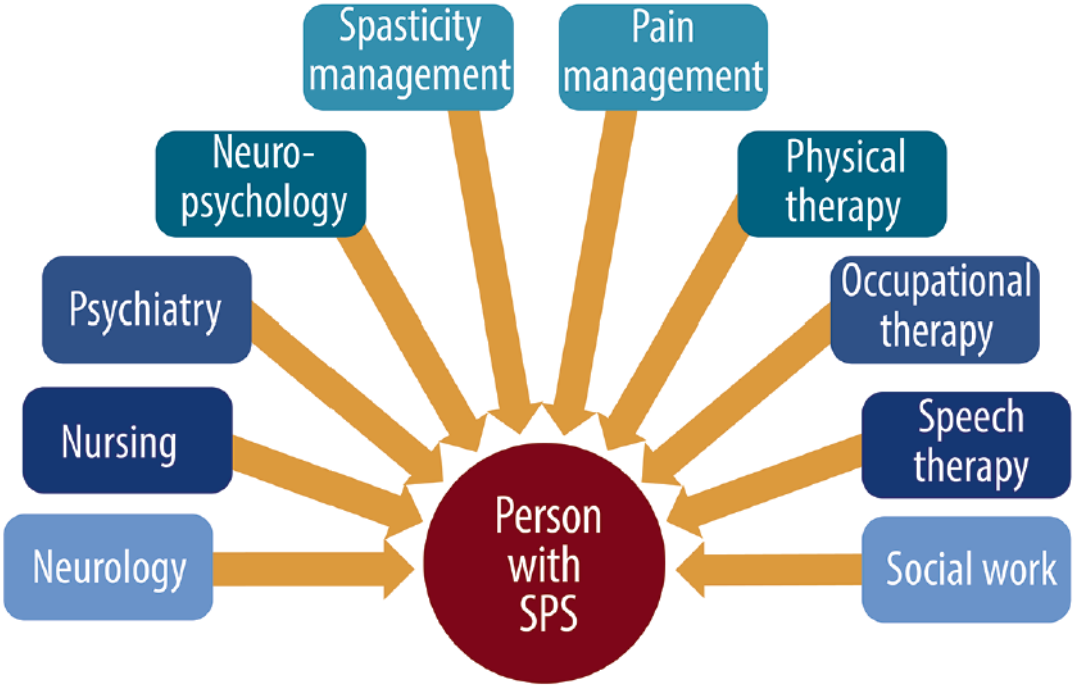
Among the glutamic acid decarboxylase (GAD)-antibody–spectrum disorders, the most common phenotypic subset is the stiff-person syndrome (SPS), caused by impaired GABAergic inhibitory neurotransmission and autoimmunity characterized by very high titers of GAD antibodies and increased GAD-IgG intrathecal synthesis. If not properly treated or untreated because of delayed diagnosis, SPS progresses leading to disability; it is therefore fundamental to apply the best therapeutic schemes from the outset. This article is focused on the rationale of specific therapeutic strategies based on the SPS pathophysiology targeting both the impaired reciprocal GABAergic inhibition to symptomatically improve the main clinical manifestations of stiffness in the truncal and proximal limb muscles, gait dysfunction, and episodic painful muscle spasms and the autoimmunity to enhance improvement and slow down disease progression. A practical, step-by-step therapeutic approach is provided, highlighting the importance of combination therapies with the preferred gamma-aminobutyric acid–enhancing antispasmodic drugs, such as baclofen, tizanidine, benzodiazepines, and gabapentin, that provide the first-line symptomatic therapy, while detailing the application of current immunotherapies with intravenous immunoglobulin (IVIg) plasmapheresis, and rituximab. The pitfalls and concerns of long-term therapies in different age groups, including children, women planning pregnancy, and especially the elderly considering their comorbidities are emphasized, also highlighting the challenges in distinguishing the conditioning effects or expectations of chronically applied therapies from objective meaningful clinical benefits. Finally, the need for future targeted immunotherapeutic options based on disease immunopathogenesis and the biologic basis of autoimmune hyperexcitability are discussed, pointing out the unique challenges in the design of future controlled clinical trials especially in quantifying the extend and severity of stiffness, episodic or startle-triggered muscle spasms, task-specific phobias, and excitability.

# Stiff-person syndrome:
## Treatment

- **Symptomatic**
  - **Diazepam, baclofen, tizanidine, gabapentin, botulinum toxin, physical therapy**
- **Etiologic**
- **Search for underlying autoimmune disease and cancer**
- **Steroids, plasmapheresis, IVIg (2g/kg over 4-5 days and then 1x/month); rituximab?**
  Dalakas. Neurol Neuroimmunol Neuroinflamm 2023;10:e200109
  - **In a placebo-controlled crossover study in 16 patients with SPS, IVIg significantly decreased stiffness scores and substantially increased walking and functions of daily activities**
    Dalakas et al. N Engl J Med 2001;345:1870-6
    Lünemann et al. Nat Rev Neurol 2015;11:80-9
  - **Of 58 patients, 78.3% reported improvement, 13% remained stable, and 4.3% either worsened or died**
    Sarva et al. Tremor Other Hyperkinet Mov 2016;6:340
  - **Monthly maintenance IVIg therapy provides long-term benefits in 67% of 36 patients for a median 3.3-year period.**
    Yi and Dalakas. Neurol Neuroimmunol Neuroinflam 2022;9:e200011

175

# Treatment of Stiff Person Syndrome




Nolan JD, Nicholas JA. Practical Neurology, September 2020

188

# Progressive Encephalomyelitis With Rigidity and Myoclonus With Glycine Receptor Antibodies

## Clinical Features and Outcomes.

Guasp et al. Neurol Neuroimmunol Neuroinflamm 2025;12:e200473

- **41 patients; median age 58 years (43–66), 88% male**
- **Predominant presentation rapid onset (2 weeks) dysphagia and trismus (56%), muscle stiffness and myoclonus (22%); dysesthesias or pruritus in (17%); and cacosmia with dysgeusia in 2 (5%); 12% never developed muscle stiffness.**
- **51% required admission to ICU, 27% died, 28% relapsed.**
- **62% had CSF pleocytosis, in 58% EMG showed continuous motor unit firing of agonist and antagonist muscles at rest or electrophysiologic features of myoclonus.**
- **All relapses responded to immunotherapy.**
- **GlyR antibody–mediated PERM is a rapidly progressive and severe disease that predominantly affects men and frequently presents with brainstem involvement. It should be considered separately from SPS, which typically follows a chronic course and is more commonly associated with anti-GAD antibodies (and rarely with other autoimmune diseases).**

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# PERM with anti-GlyR antibodies



Courtesy Prof. Angela Vincent

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# Anti-GAD65 antibody-associated hemiataxia.

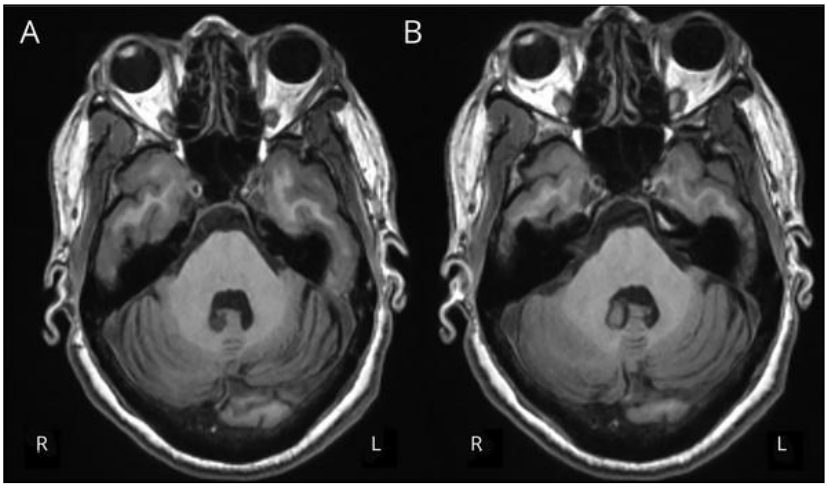
Hill EJ, Jankovic J. Mov Disord Clin Pract 2021;11:e564-e566

| Age/Sex | Hemiataxia duration and side | Comorbidities | Reported serum anti-GAD65 antibody | Treatment | Treatment response |
|---|---|---|---|---|---|
| 70/woman | 3 wks; right-sided | IDDM, thyroiditis, encephalopathy | >13,000 IU/mL | PLEX, rituximab | No improvement, lost to follow up |
| 68/woman | 2 mos; right- sided | DM | >677,000 IU/mL | methylprednisolone, IVIG, azathioprine | Marked response to corticosteroids |
| 44/man | 6 yrs; left-sided | IDDM, generalized epilepsy | "positive" | Mycophenolate mofetil | Symptoms stabilized |
| 75/woman (Case A) | 8 yrs; left-sided | Thyroiditis, stiff-person syndrome | >4800 IU/mL | IVIG | Initial improvement, some gradual progression |
| 62/woman (Case B) | 20 mos; left-sided | IDDM, thyroiditis | >250,000 IU/mL | IVIG | Initial improvement, persistent tremor |

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# Anti-GAD65 antibody-associated hemiataxia.

Hill EJ, Jankovic J. Mov Disord Clin Pract 2021;11:e564-e566




**MRI of the Brain From Case A**

**MRI of the brain from the patient taken 4 years after the onset of symptoms. Panels (A and B) show axial T2 fluid-attenuated inversion recovery sequence demonstrating moderate generalized atrophy of the cerebellum, which is more prominent in the left hemisphere, consistent with left-sided hemiataxia.**

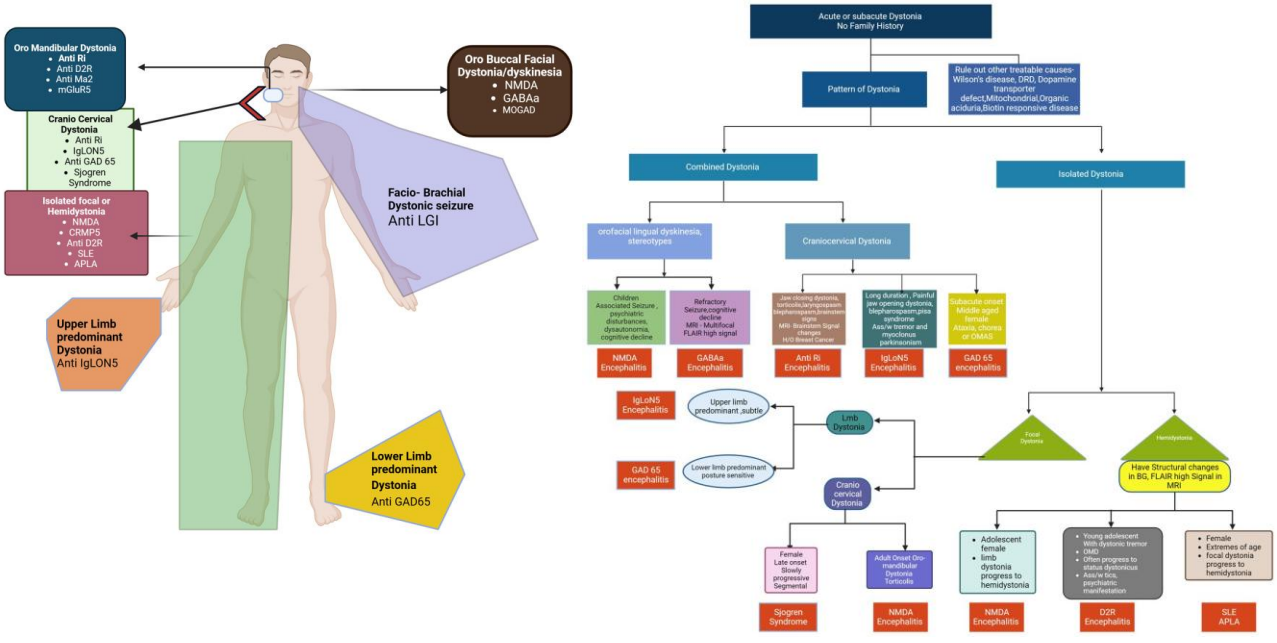
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# GAD Antibody-spectrum Disorders

- **GAD-SD includes**
  - **Stiff-person Syndrome (SPS)**
  - **Progressive Encephalomyelitis with Rigidity (PERM)**
  - **Cerebellar Ataxia**
  - **Autoimmune Epilepsy**
  - **Limbic Encephalitis**
  - **Eye movement disorder**
- **Very high serum anti-GAD antibody titers are commonly associated with the presence of GAD antibodies in the CSF, and reduced CSF GABA level**
- **The accumulation of GAD65-specific B cells and plasma cells in the CSF is an important feature of early disease**

Budhram et al. J Neurol Neurosurg Psychiatry 2021;92:645–54
Newsome SD, Johnson T. J Neuroimmunol 2022;369:577915
Dalakas MC. Neurotherapeutics 2022;19:832-47
Biljecki et al. Neurol Neuroimmunol Neuroinflamm 2023;10:e200090

# Autoimmune Dystonia

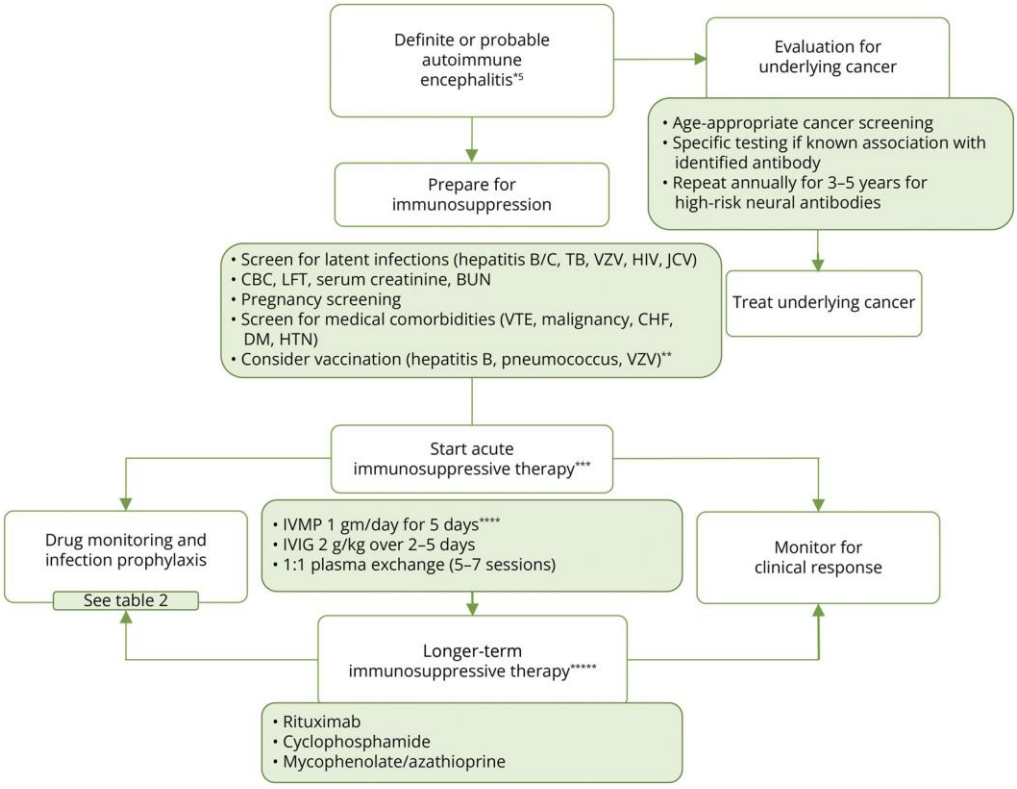



**Subacute, relapsing, progressive dystonia can be a unique feature in many autoimmune disorders**

Dutta D, Yadav R. Tremor Other Hyperkinet Mov 2024;14:60

**210**

# Approach to Treatment of Autoimmune Encephalitis




Mahadeen et al. Neurology: Clinical Practice 2024;14:e200306

225

# Systemic Autoimmune Disorders

**A broad spectrum of movement disorders pathophysiologically related to underlying autoimmune dysregulation**

- **Systemic Lupus Erythematosus (SLE)**
- **Antiphospholipid syndrome (APL)**
- **Hashimoto's Encephalopathy (HE)**
  - **Elevated titers of CSF anti-thyroxin peroxidase (TPO) anti-thyroglobulin (TG); may or may not respond to steroids**
- **Post-Streptococcal Infections**
  - **Sydenham's Chorea**
  - **Pediatric Autoimmune Neuropsychiatric Disorder Associated with a Streptococcal Infection (PANDAS)**
  - **Pediatric autoimmune neuropsychiatric symptoms (PANS)**
  - **Post-streptococcal Acute Disseminated Encephalomyelitis and Others**
- **Paraneoplastic Disorders**

Menozzi et al. Parkinsonism Relat Disord 2021;88:116-28

226

**19 y/o with history of “meningitis” at age 10 and subsequent arthralgias and myalgias; pericarditis at age 18 years. Presented with 10 day hx of involuntary movements and incoordination.**
**Improved with tetrabenazine.**



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# Movement disorders in systemic lupus erythematosus and the antiphospholipid syndrome.

Baizabal-Carvallo JF, Bonnet C, Jankovic J. J Neural Transm 2013;120:1579-89

- **Movement disorders, particularly chorea, may be the presenting neurological complication of systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS).**
- **Chorea occurs in 2% of patients with SLE; choreic movements precede the diagnosis of SLE in 22% of these cases; chorea gravidarum may be the first manifestation of SLE.**
- **Other movement disorders associated with SLE: tremor, dystonia blepharospasm, parkinsonism and SPS.**
- **Antigenic target within the CNS has not yet been identified.**
- **Laboratory: positive ANA, low complement C3 and C4, and the following antibodies: anti-Smith (Sm), anti-double stranded DNA (dsDNA), anti-RNP, anti-SS-A (also called Ro), and anti-SS-B (also La).**
- **aPL antibodies may contribute to BBB dysfunction leading to passage of other pathogenic antibodies into the CNS.**
- **dsDNA autoantibodies cross-react with the GluN2A and GluN2B subunits of the NMDA receptor.**
  Chen et al. Nat Commun 2020;11:1403

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# Hashimoto's Disease

- **First described in 1966** (Brain et al. Hashimoto's disease and encephalopathy. Lancet 1966;ii:512-4)
- **Initially named "Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)", but neither encephalopathy nor steroid responsiveness may be present**
- **Typical clinical presentation includes seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms, and movement disorders (myoclonus, dystonia, chorea, athetosis, tremor and ataxia)**
- **Thyroid function is usually normal (20% have hypothyroidism) but thyroiditis (by ultrasound or biopsy) is often present**
- **Elevated titers of CSF anti-thyroxin peroxidase (TPO) anti-thyroglobulin (TG), and alpha-enolase antibodies are more specific than serum antibodies but these findings do not help to predict whether patients will respond to steroids.**

Mattozzi et al. Neurology 2020;94:e217-e224

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# Systemic Autoimmune Disorders

A broad spectrum of movement disorders pathophysiologically related to underlying autoimmune dysregulation

- Systemic Lupus Erythematosus (SLE)
- Antiphospholipid syndrome (APL)
- Hashimoto's Encephalopathy (HE)
  - Elevated titers of CSF anti-thyroxin peroxidase (TPO) anti-thyroglobulin (TG); may or may not respond to steroids
- **Post-Streptococcal Infections**
  - **Sydenham's Chorea**
  - **Pediatric Autoimmune Neuropsychiatric Disorder Associated with a Streptococcal Infection (PANDAS)**
  - **Pediatric autoimmune neuropsychiatric symptoms (PANS)**
  - **Post-streptococcal Acute Disseminated Encephalomyelitis and Others**
- **Paraneoplastic Disorders**

Menozzi et al. Parkinsonism Relat Disord 2021;88:116-28

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# Neural autoantibodies in paraneoplastic movement disorders

| | Antibodies | | | |
|---|---|---|---|---|
| | Intracellular antigen | Cancer association | Cell-surface antigen | Cancer association |
| Ataxia | ANNA1 (Hu) | SCLC | CASPR2 | Thymoma |
| | ANNA3 (DACH1) | Lung, GI | *Lgi1* | Lymphoma |
| | AGNA1 (SOX1) | SCLC | DPPX | SCLC |
| | VGCC | SCLC | $GABA_B$-R | Hodgkin lymphoma |
| | CRMP5 (CV2) | SCLC | PCA-Tr (DNER) | Lymphoma |
| | ANNA2 (Ri) | SCLC, thymoma | *IgLON5* | Endometrial (1 patient) |
| | PCA1 (Yo) | Breast, gynecologic | mGLuR1 | Ovarian adenocarcinoma |
| | Ma2 | Testicular germ cell, other | *Septin5* | (1 patient) (Small cell |
| | KLHL11 | Seminoma | *AP3B2* | carcinoma, 1 patient) |
| | PCA2 (MAP1B) | SCLC | Neurochondrin | |
| | GAD65 | Diverse (rare) | SEZ6L2 | |
| | GFAP | Teratoma, other | mGluR2 | |
| | NIF | SCLC, Neuroendocrine | | |
| | RGS8 | Lymphoma | | |
| | Homer3 | SCLC | | |
| | TRIM9, 46, 67 | SCLC, neuroendocrine, other | | |
| | GRAF/ARHGAP26 | SqCC H+N, lung | | |
| | ITPR1 | Breast, endometrial | | |
| Stiff Person Syndrome | GAD-65 | Diverse, rare | GlyRα1 | Thymoma |
| | Amphiphysin | SCLC, breast | | |
| PERM | GAD65 | Diverse, rare | GlyRα1 | Thymoma |
| | Amphiphysin | SCLC, breast | DPPX | Lymphoma |
| Myoclonus | ANNA-1 (Hu) | SCLC | NMDA-R | Teratoma |
| | ANNA-2 (Ri) | Breast, SCLC | *LGI1* | Thymoma |
| | Ma2 | Testicular, other carcinoma | CASPR2 | |
| | | | *IgLON5* | |
| | | | *Neurexin3α* | |
| Chorea | CRMP5 (CV2) | SCLC | $GABA_B$-R | SCLC |
| | ANNA1(Hu) | SCLC | *LGI1* | Thymoma |
| | VGCC | SCLC | CASPR2 | Teratoma |
| | ANNA2 (Ri) | Breast, SCLC | NMDA-R | Adenocarcinoma |
| | GAD65 | Diverse, rare | *IgLON5* | |
| | | | PDE10A | |
| Dystonia | ANNA2 (Ri) | Breast, SCLC | AMPA-R | SCLC, thymoma, breast |
| | CRMP5 (CV2) | SCLC | *LGI1* | Teratoma |
| | GAD65 | Diverse, rare | *IgLON5* | |
| | Ma2 | Testicular, other carcinoma | NMDA-R | |
| | KLHL11 | Testicular | *Neurexin3α* | |
| Parkinsonism | Ma2 | Testicular, other carcinoma | *LGI1* | Thymoma |
| | GAD65 | Diverse, rare | CASPR2 | Lymphoma |
| | ANNA2 (Ri) | Breast | DPPX | |
| | CRMP5 (CV2) | SCLC, thymoma | IgLON5 | |
| | TRIM9, 46, 67 | SCLC, neuroendocrine, other | | |

McKeon A, Tracy J. Handb Clin Neurol 2024;200:211-7

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**60 y/o man with generalized seizure, followed by confusion, involuntary movements, and gait difficulties**



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# M.P.

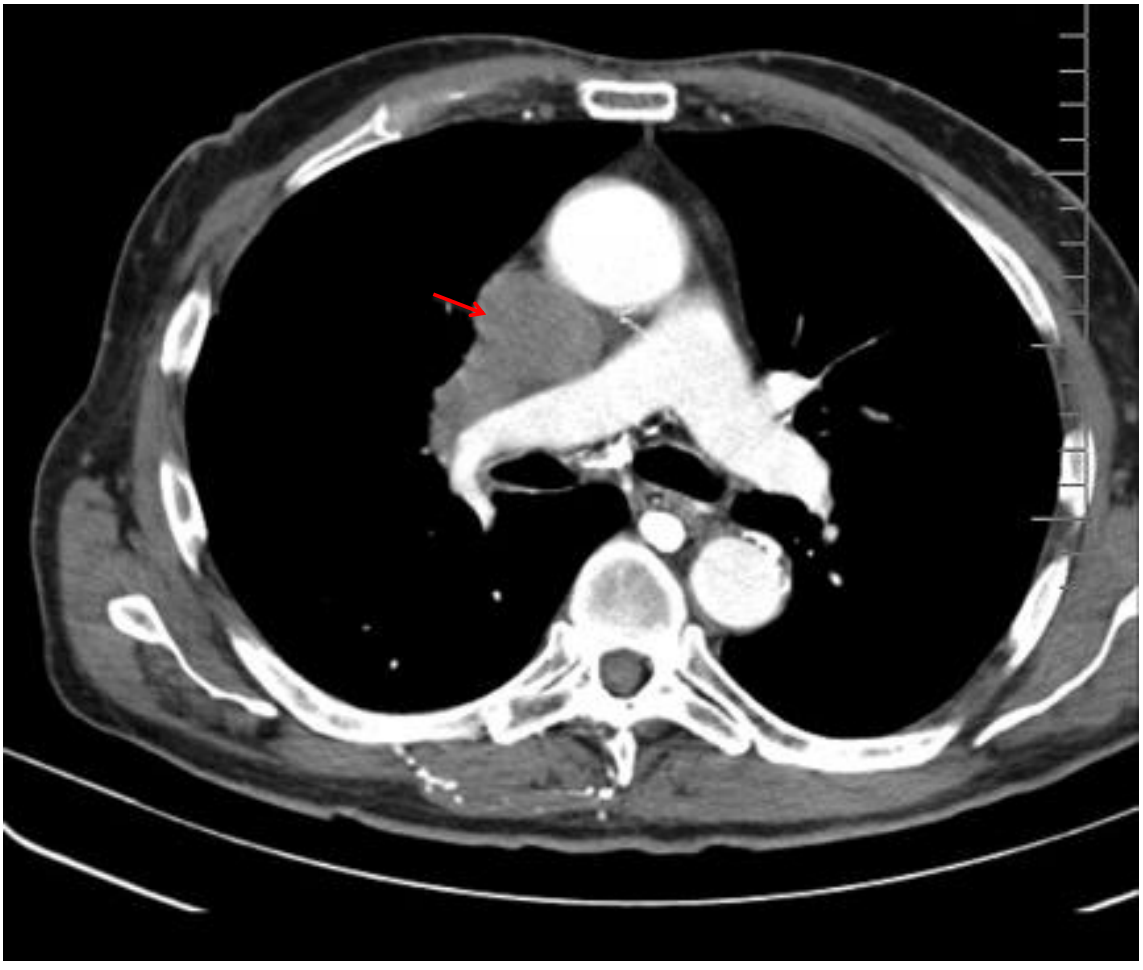
- 60 y/o man admitted to hospital with confusion
  - Hyponatremia 116 mmol/L – attributed to psychogenic polydipsia
  - Onset of involuntary shoulder movements
  - PET scan: no evidence of malignancy
- Progressive worsening of movements, involvement of limbs, face, and deterioration in gait
- MoCA score was 20/30
- MRI - hyperintensity in the striatum on T2-weighted images

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# M.P.

- 60 y/o man admitted to hospital with confusion
  - Hyponatremia 116 mmol/L – attributed to psychogenic polydipsia
  - Onset of involuntary shoulder movements
  - PET scan: no evidence of malignancy
- Progressive worsening of movements, involvement of limbs, face, and deterioration in gait
- MoCA score was 20/30
- MRI - hyperintensity in the striatum on T2-weighted images
- Positive titer of 1:245,760 of Collapsin Response-Mediator Protein-5 (CRMP-5) IgG (by immunofluorescence)
- Found to have lung cancer and died within three months after our evaluation

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# Other Autoimmune Movement Disorders

- **Behcet's syndrome – tremor, myoclonus, chorea**
- **Sjogren's syndrome – parkinsonism, dystonia, chorea**
- **Celiac disease – ataxia, cortical myoclonus (leg), cerebellum**
- **CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) – ataxia, dystonia, myoclonus**
- **Rasmussen's encephalitis – myoclonus, anti-AMPAR**
- **Neuropathic tremor – associated with IgM monoclonal gammopathy**
- **Paraneoplastic syndromes (chorea, ataxia, myoclonus) – anti-IgLON5, anti-CRMP5, anti-HU, anti-Ma2, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPAR, anti-GABA, etc**
- **Multiple sclerosis**

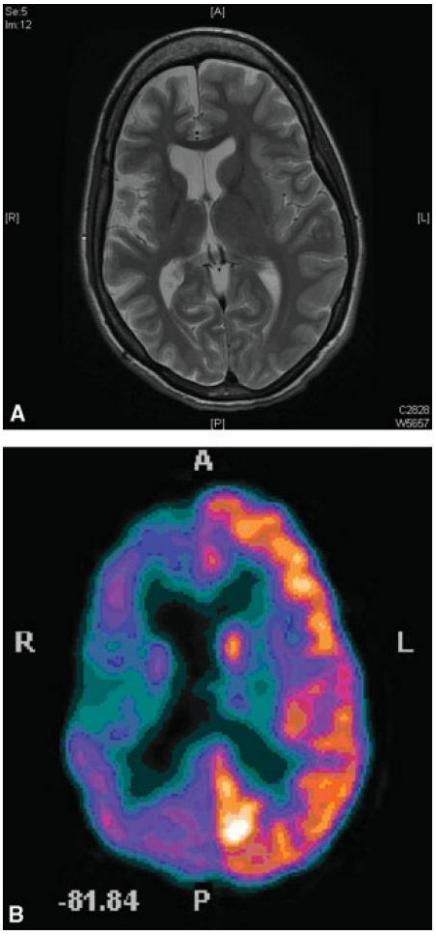
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# Botulinum Toxin Treatment of Facial Myoclonus in Suspected Rasmussen Encephalitis

Nina Browner, MD,[1] Shaheda N. Azher, MD,[2] and Joseph Jankovic, MD[2*]

*[1]Department of Neurology, Cleveland Clinic Foundation, Cleveland, Ohio, USA; [2]Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*

Video




***Abstract:*** **Patients with Rasmussen encephalitis (RE) may develop a variety of involuntary movements. We report a 26-year-old woman who presented with a 3-year history of progressive, continuous myoclonus of the left side of the face and left arm as well as left spastic hemiparesis. Magnetic resonance imaging of the brain showed right hemisphere and basal ganglia atrophy, and 24-hour electroencephalogram demonstrated diffuse slowing with random sharp waves in both hemispheres. An 18-fluoro-deoxy-glucose positron emission tomography scan indicated hypometabolism of the right cerebral hemisphere, including basal ganglia and thalamus. We successfully treated her myoclonus with injections of botulinum toxin A into the left zygomaticus muscle.** © 2006 Movement Disorder Society

# Movement disorders in multiple sclerosis and other demyelinating diseases.

Mehanna R, Jankovic J. J Neurol Sci 2013;328:1-8

Movement disorders in demyelinating diseases.

| Demyelinating disease | Movement disorder |
|---|---|
| Multiple sclerosis | – Tremor<br>– Paroxysmal dystonia<br>– Dystonia<br>– Ballism/Chorea<br>– Paroxysmal Kinesigenic Dyskinesia (PKD)<br>– Parkinsonism<br>– Myoclonus<br>– Hemifacial spasm and continuous facial myokymia<br>– Tics-tourettism<br>– Restless legs syndrome<br>– Complex hyperkinetic movement disorder |
| Neuromyelitis optica | – Paroxysmal dystonia after initiation of treatment and during the recovery phase. Good response to carbamazepine [128–130].<br>– Ataxia [131]. |
| Acute disseminated encephalomyelitis | – Acute ataxia (50%) [132].<br>– Acute choreoathetosis, hemidystonia, paroxysmal hemidystonia and hemichorea plus dystonia (12%) [132].<br>– Painless torticollis [134].<br>– Segmental myoclonus [135]. |
| Central pontine myelinolysis and extrapontine myelinolysis | – Parkinsonism, frequently responsive to levodopa [138,140,141].<br>– Dystonia. Multifocal, segmental or generalized. Responds well to trihexyphenidyl [138,143,144].<br>– Truncal ataxia [147].<br>– Paroxysmal dystonia [137].<br>– Chorea [138].<br>– Phenomenology can evolve from one movement to another over time [145].<br>– These movement disorders can be transient or permanent and can start as early as within a week of the brain insult, or be delayed by up to 5 months [138,139,143–145]. |
| Post bone marrow transplant demyelinating leukoencephalopathy. | – Parkinsonism responsive to intra venous methyl prednisolone [150]. |
| Hypomyelination with atrophy of the basal ganglia and cerebellum | – Dystonia, ataxia, rigidity, choreoathetosis and tremor [151]. |

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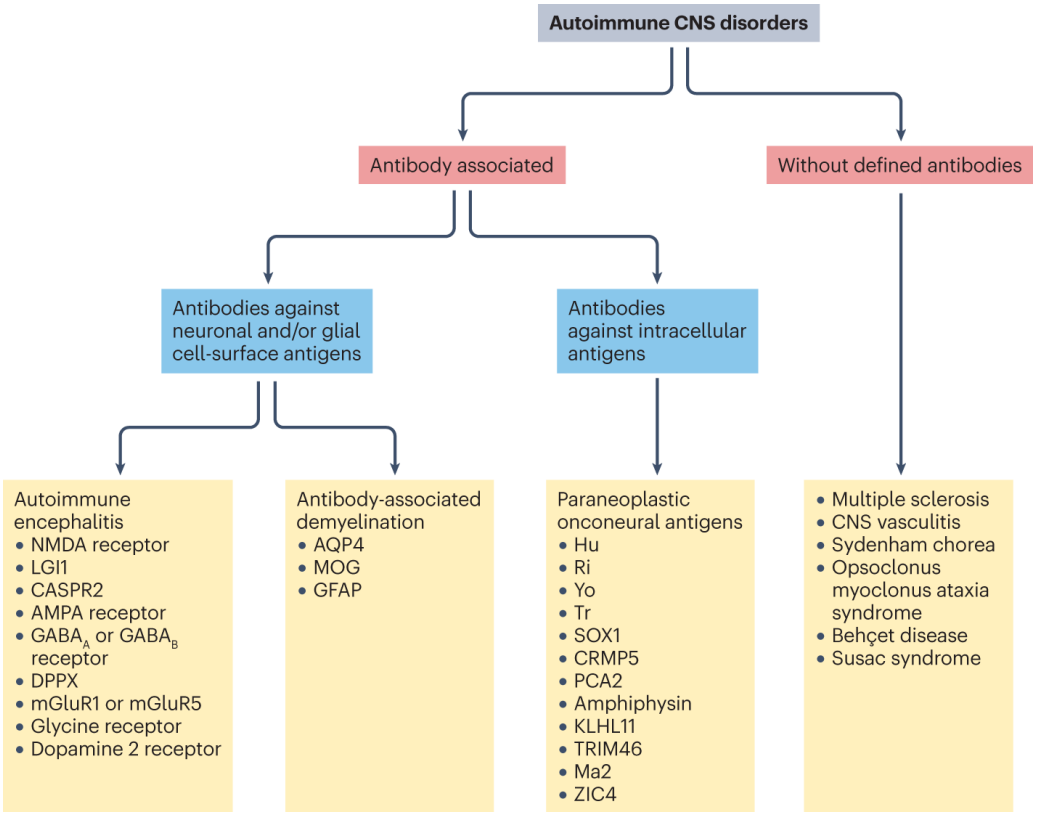
# Parkinson disease and the immune system — associations, mechanisms and therapeutics

*Eng-King Tan*[1,2,3]✉, *Yin-Xia Chao*[1,2,3], *Andrew West*[4], *Ling-Ling Chan*[3,5], *Werner Poewe*[6] *and Joseph Jankovic*[7]

Nat Rev Neurol 2020;16:303-18

Abstract | Multiple lines of evidence indicate that immune system dysfunction has a role in Parkinson disease (PD); this evidence includes clinical and genetic associations between autoimmune disease and PD, impaired cellular and humoral immune responses in PD, imaging evidence of inflammatory cell activation and evidence of immune dysregulation in experimental models of PD. However, the mechanisms that link the immune system with PD remain unclear, and the temporal relationships of innate and adaptive immune responses with neurodegeneration are unknown. Despite these challenges, our current knowledge provides opportunities to develop immune-targeted therapeutic strategies for testing in PD, and clinical studies of some approaches are under way. In this Review, we provide an overview of the clinical observations, preclinical experiments and clinical studies that provide evidence for involvement of the immune system in PD and that help to define the nature of this association. We consider autoimmune mechanisms, central and peripheral inflammatory mechanisms and immunogenetic factors. We also discuss the use of this knowledge to develop immune-based therapeutic approaches, including immunotherapy that targets α-synuclein and the targeting of immune mediators such as inflammasomes. We also consider future research and clinical trials necessary to maximize the potential of targeting the immune system.

# The spectrum of autoimmune CNS disorders




Ramanathan et al. Nat Rev Neurol 2023;19:172-90

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# Association of Stress-Related Disorders With Subsequent Autoimmune Disease

Huan Song, MD, PhD; Fang Fang, MD, PhD; Gunnar Tomasson, MD, PhD; Filip K. Arnberg, PhD; David Mataix-Cols, PhD; Lorena Fernández de la Cruz, PhD; Catarina Almqvist, MD, PhD; Katja Fall, MD, PhD; Unnur A. Valdimarsdóttir, PhD

**IMPORTANCE** Psychiatric reactions to life stressors are common in the general population and may result in immune dysfunction. Whether such reactions contribute to the risk of autoimmune disease remains unclear.

**OBJECTIVE** To determine whether there is an association between stress-related disorders and subsequent autoimmune disease.

**DESIGN, SETTING, AND PARTICIPANTS** Population- and sibling-matched retrospective cohort study conducted in Sweden from January 1, 1981, to December 31, 2013. The cohort included 106 464 exposed patients with stress-related disorders, with 1 064 640 matched unexposed persons and 126 652 full siblings of these patients.

**EXPOSURES** Diagnosis of stress-related disorders, ie, posttraumatic stress disorder, acute stress reaction, adjustment disorder, and other stress reactions.

**MAIN OUTCOMES AND MEASURES** Stress-related disorder and autoimmune diseases were identified through the National Patient Register. The Cox model was used to estimate hazard ratios (HRs) with 95% CIs of 41 autoimmune diseases beyond 1 year after the diagnosis of stress-related disorders, controlling for multiple risk factors.

**RESULTS** The median age at diagnosis of stress-related disorders was 41 years (interquartile range, 33-50 years) and 40% of the exposed patients were male. During a mean follow-up of 10 years, the incidence rate of autoimmune diseases was 9.1, 6.0, and 6.5 per 1000 person-years among the exposed, matched unexposed, and sibling cohorts, respectively (absolute rate difference, 3.12 [95% CI, 2.99-3.25] and 2.49 [95% CI, 2.23-2.76] per 1000 person-years compared with the population- and sibling-based reference groups, respectively). Compared with the unexposed population, patients with stress-related disorders were at increased risk of autoimmune disease (HR, 1.36 [95% CI, 1.33-1.40]). The HRs for patients with posttraumatic stress disorder were 1.46 (95% CI, 1.32-1.61) for any and 2.29 (95% CI, 1.72-3.04) for multiple (≥3) autoimmune diseases. These associations were consistent in the sibling-based comparison. Relative risk elevations were more pronounced among younger patients (HR, 1.48 [95% CI, 1.42-1.55]; 1.41 [95% CI, 1.33-1.48]; 1.31 [95% CI, 1.24-1.37]; and 1.23 [95% CI, 1.17-1.30] for age at ≤33, 34-41, 42-50, and ≥51 years, respectively; *P* for interaction < .001). Persistent use of selective serotonin reuptake inhibitors during the first year of posttraumatic stress disorder diagnosis was associated with attenuated relative risk of autoimmune disease (HR, 3.64 [95% CI, 2.00-6.62]; 2.65 [95% CI, 1.57-4.45]; and 1.82 [95% CI, 1.09-3.02] for duration ≤179, 180-319, and ≥320 days, respectively; *P* for trend = .03).

**CONCLUSIONS AND RELEVANCE** In this Swedish cohort, exposure to a stress-related disorder was significantly associated with increased risk of subsequent autoimmune disease, compared with matched unexposed individuals and with full siblings. Further studies are needed to better understand the underlying mechanisms.

*JAMA*. 2018;319(23):2388-2400. doi:10.1001/jama.2018.7028

Supplemental content













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# THANKS



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