Autoimmune Movement Disorders

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Immune System

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

New York Times, June 3, 2016

In the last half-century, the prevalence of autoimmune disease has increased sharply in the developed world. An estimated 1 in 13 Americans has one of these often debilitating, generally lifelong conditions.

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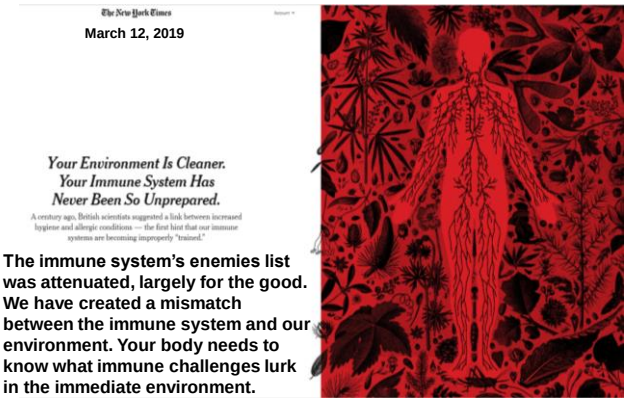

The immune system's enemies list was attenuated, largely for the good. We have created a mismatch between the immune system and our environment. Your body needs to know what immune challenges lurk in the immediate environment.

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Movement Disorders in Autoimmune Diseases

Baizabal-Carvallo JF, Jankovic J. Mov Disord 2012;27:935-46 - Updated

	Main antigen	Tumors
Intracellular antigens	Hu (ANNA1)	SCLC, other
(Commonly paraneoplastic)	Ma2	Testis (germ-cell); SCLC, breast
Cytotoxic – neuronal damage	CV2/CRMP5	SCLC, thymoma, non-Hodgkin's lymphoma
	Amphiphysin	Breast, SCLC
	Yo	Ovary, breast
	Ri (ANNA2)	Breast, SCLC
	Tr	Hodgkin's lymphoma
Surface (membrane) antigens	LGI1	SCLC, thymoma
(Less commonly paraneoplastic)	CASPR2	SCLC, thymoma
	NMDAR	Ovarian teratoma
Inflammatory infiltrates – reversible	AMPAR (GluR1 and GluR2)	SCLC, thymoma, breast
	GABA	SCLC
	mGluR1	Hodgkin disease
	VGCC	SCLC
Synaptic antigens	Glycine R(α1 subunit)	Lung
(Rarely paraneoplastic)	AMPAR (GluR3)	Rarely paraneoplastic
	GAD65	Thymoma
	GABA	
	Homer-3	
	Anti-Neurexin-3α	

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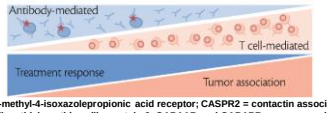
Three groups of neuronal antibodies and their pathogenic roles

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 B. Practical Neurology 2020 September:30-40

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Review Article

Autoimmune and paraneoplastic movement disorders: An update

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ARTICLE INFO

Keywords:
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Chorea
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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
Damato et al. Mov Disord 2018;33:1376-89
Balint et al. Brain 2018;141:13-36

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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
Limbic encephalitis	Anti-HU, anti-Ma2, anti-CRMP5, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPAR, anti-GABA, anti-IGLON5	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, myokymia, and neuromyotonia

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Autoimmune encephalitis

Lee et al. Neurology 2016;86:1683-91
Vollmer TL, McCarthy M. Neurology 2016;86:1655-6

- 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, rigidity and a variety of movement disorders
- 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, SCIG, plasma exchange, rituximab, anti-CD20 monoclonal antibodies and other emerging immunotherapies

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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
- 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 → coma
  - Dysautonomia
  - Abnormal movements: oromandibular-lingual stereotypies, myorhythmia, chorea, dystonia, tremor, opisthotonic posturing; may be asymmetrical or bilateral

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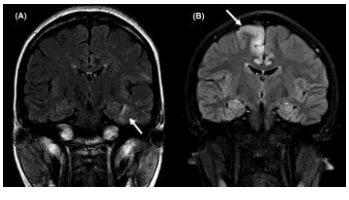
Anti-NMDAR Encephalitis

- 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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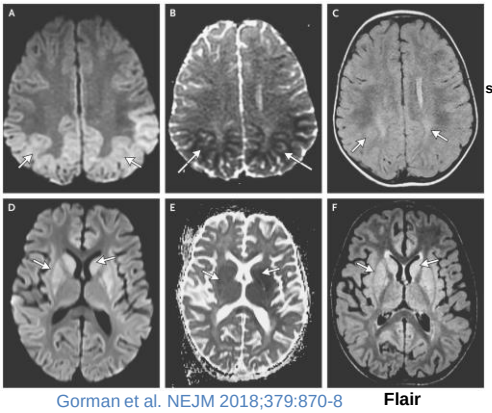
NMDAR Encephalitis – MRI

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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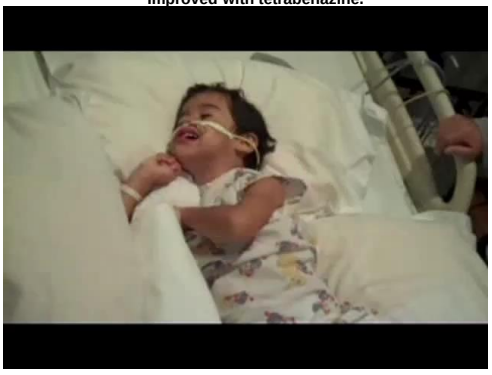
3 y/o boy with subacute onset of myalgias, frontal headaches, malaise, and vomiting; followed by confusional state, insomnia, hallucinations, dysarthria and motor aphasia. Admitted with diagnosis of "viral encephalitis". During the hospitalization he developed generalized seizures, dysautonomia, repetitive 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

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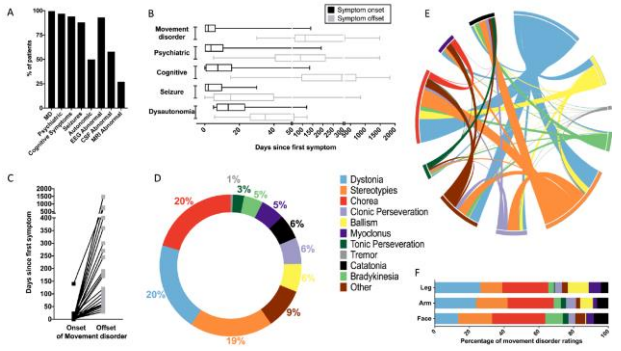
The clinical features and movement disorder evaluations in patients with NMDAR encephalitis

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



Varley et al. JNNP 2019;90:724-26

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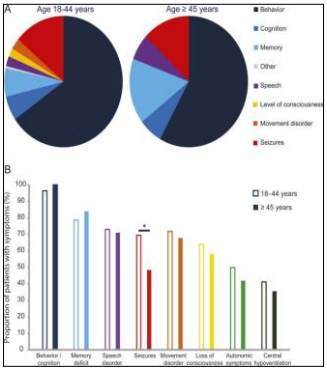
Adult anti-NMDAR Encephalitis



- **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 improve the 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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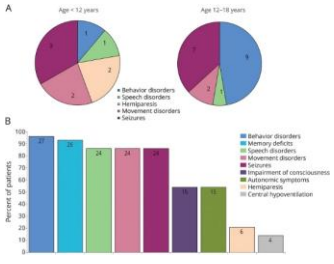
Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis.

de Bruijn et al. Neurology 2018;90:e1997-e2005

- **22/28 patients were included in the cross-sectional part of the long-term follow-up study**
- **Median follow-up 31(5-91) months**
- **Impaired cognition and attention**
- **Fatigue was strongly correlated with QoL**



Cumulative symptoms during disease course

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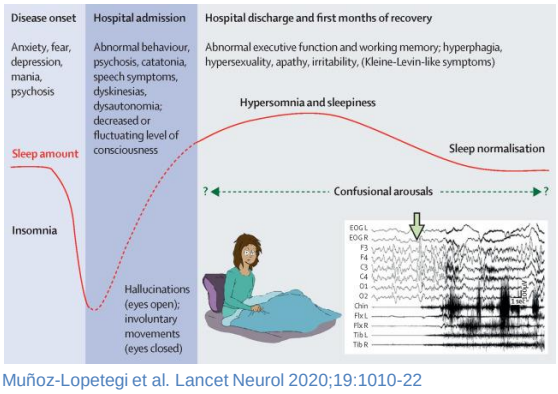
Two-stage evolution of sleep disorders in patients with anti-NMDA receptor encephalitis



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

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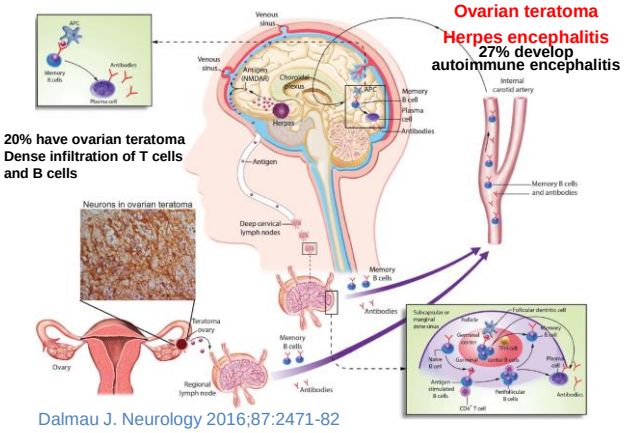
Immunologic triggers in anti–NMDAR encephalitis



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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Treatment of NMDAR Encephalitis

- **Removal of tumor (ovarian>>>testicular teratoma)**
  - **Oophorectomy 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 (eliminates B-cell lineage and prevents formation of plasma cells) at 375 mg/sq.m every week for 4 weeks ± cyclophosphamide 750 mg/sq.m for 4-6 months (interferes with DNA replication and eliminates T regulatory cells)**
  - **Rituximab is approved for the treatment of adults with previously untreated and relapsed or refractory follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia**
  - **June 2017- FDA approved subcutaneous rituximab to be marketed as Rituxan Hycela: subcutaneous injection in 5-7 mins instead of a 90 min IV infusion**
- **Or early Rituximab, IVIg, PEx (6 treatments over 10 days)**

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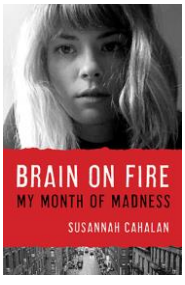

- **A reporter at The New York Post describes her horrifying story of anti-NMDAR encephalitis, manifested by progressive headaches, auditory and visual hallucinations and other behavioral and psychotic symptoms, seizures, (dystonia) and encephalopathy. Initially misdiagnosed as schizophrenia, bipolar 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.**

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Anti-Dopamine Receptor 2 Antibody-Positive Encephalitis

- D2 receptors are found mainly in the striatum, the nucleus accumbens, and the olfactory tubercle.
- D2 receptor extracellular N-terminus regulates receptor surface availability and is the target of human pathogenic antibodies.
- Serum and CSF anti-D2RAb detected by ELISA (normal: 5–36 U/L).
- Usually affects children and adolescents.
- The symptoms at onset are variable, but usually include dystonia, tremor, oculogyric crises, parkinsonism, and chorea.
- Other features: psychiatric symptoms, sleep disturbance, seizures.
- MRI is abnormal in 50% of the cases, lesions are typically localized to the basal ganglia.
- Treatment includes IVIG, methyl-prednisolone, plasma exchange, rituximab, cyclophosphamide IT methotrexate, tocilizumab, etc.

Dai et al. Front Neurol 2020;11:471

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Autoimmune chorea in adults

O'Toole et al. Neurology 2013;80:1133-44

- 36 adults with autoimmune chorea were identified at Mayo Clinic (Rochester, MN) from 1997 to 2012
- 58% women, median age at sx onset: 67 (18-87) years
- Onset was subacute in all
- 22/36 (61%) – idiopathic; 19/22 (86%) patients had a coexisting autoimmune disorder (SLE, APL)
- 14/36 (39%) - paraneoplastic
- Two had synaptic IgG antibodies novel to the context of chorea (GAD65, 1; CASPR2, 1)
- 6 patients had a cancer-predictive paraneoplastic autoantibody, CRMP-5-IgG and ANNA-1 most common
- The paraneoplastic group was older ($p = 0.001$), more frequently male ($p = 0.006$), had more frequent weight loss ($p = 0.02$), and frequently had peripheral neuropathy ($p = 0.008$)

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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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- 60 y/o man admitted to hospital with confusion
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- 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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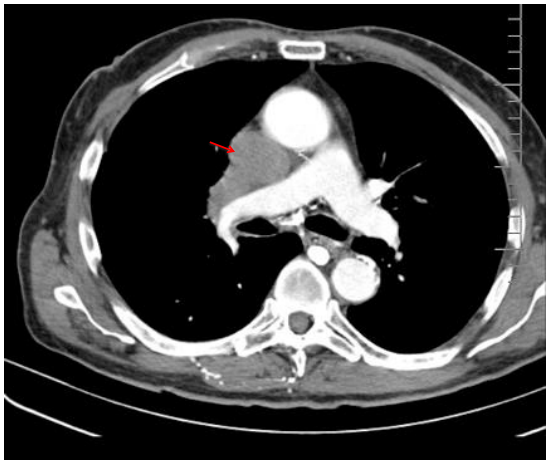

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Clinical manifestations of the anti-IgLON5 disease.

Gaig et al. Neurology 2017;88:1736-43

- 22 patients, median age at onset of 64 years, F=M
- Brainstem, hypothalamic manifestations associated with antibodies against the neuronal cell adhesion protein IgLON5
- Complex sleep disorder, rapid periodic leg movements during wakefulness that may briefly continue following sleep onset
- Cognitive decline, severe gait instability, chorea predominantly affecting the limbs (also orofacial dyskinesia), oculomotor dysfunction (PSP-like), bulbar/laryngeal symptoms (ALS-like) with stridor, dysphagia, central hypoventialtion
- Aggregates of tau in the brainstem, hypothalamus, hippocampus
- Variable response to immunosuppressive therapy; may die of sudden death during sleep or wakefulness

Graus F, Santamaría J. Neurol Neuroimmunol Neuroinflamm 2017;4:e393
Cagnin et al. J Alzheimers Dis 2017;59:13-20
Muñoz-Lopetegi et al. Lancet Neurol 2020;19:1010-22

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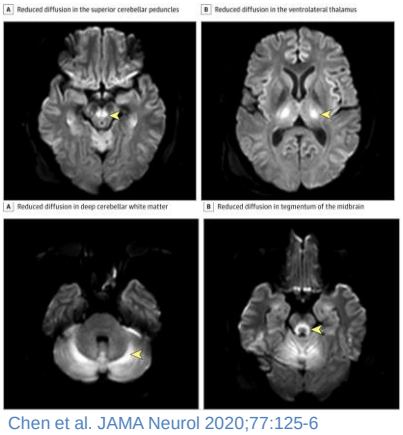
MRI in IgLON5 is usually normal, but …



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

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

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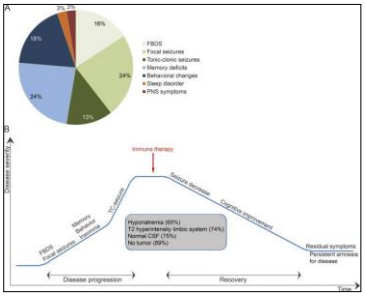
Anti-LGI1 Encephalitis

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**
- **Residual cognitive deficit and relapses were common (and presented up to 8 years after initial disease)**
- **Two-year case fatality rate was 19%**

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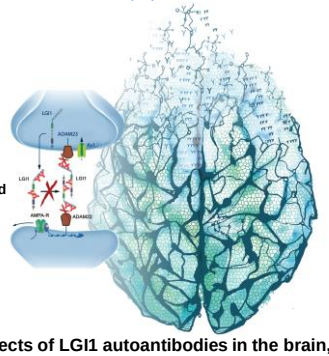
Brain 2018;141(11), November – Cover

IgG from 25, but not from 20 healthy participants, prevented the binding of LGI1 to ADAM23 and ADAM22



Background of mosaics inspired by Antoni Gaudí

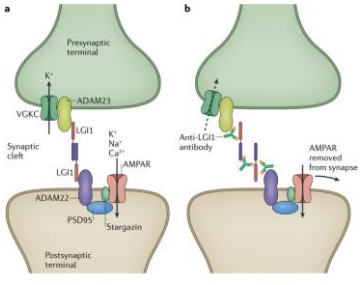
Pathogenic effects of LGI1 autoantibodies in the brain, showing that patients' autoantibodies alter presynaptic and postsynaptic pathways related to K_v1.1 potassium channels and AMPA receptors

Petit-Pedrol et al. Brain 2018;141:3144-59

49

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)

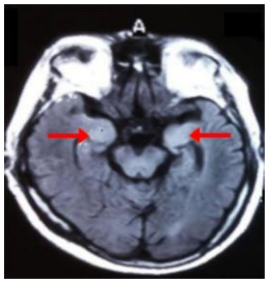


van Sonderen et al.
Nat Rev Neurol 2017;13:290-301

50

Limbic encephalitis with LGI1 antibody

Abnormalities in the mediotemporal lobe and the hippocampus

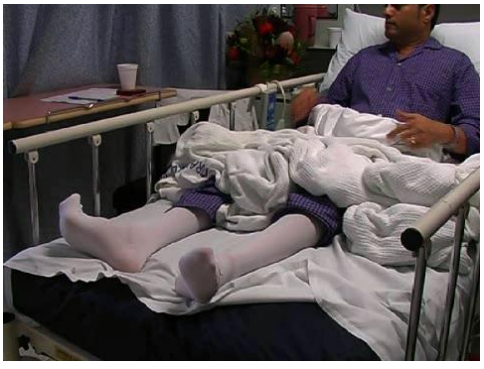


74% hippocampal T2 hyperintensity

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

52

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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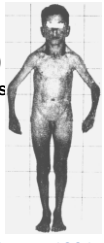
Morvan syndrome (Neuromyotonia)

- Morvan syndrome (fibrillary chorea or "la chorée fibrillaire") – 1890 Isaacs Syndrome (Isaacs 1961), 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
- Most cases are associated with voltage-gated potassium channel (VGKC)-complex antibodies
  CASPR2 > LGI1, contactin-2 antibodies
- Treatment: Carbamazepine, phenytoin, plasmapheresis or IVIG

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

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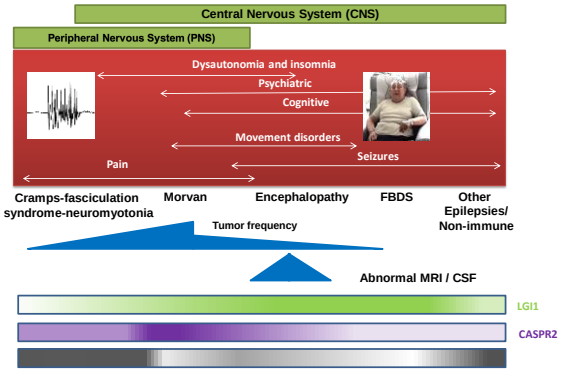
Syndromes associated with VGKC antibodies



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

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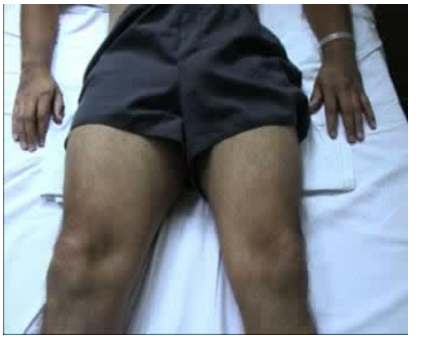
Neuromyotonia



Courtesy of Prof. A. Vincent

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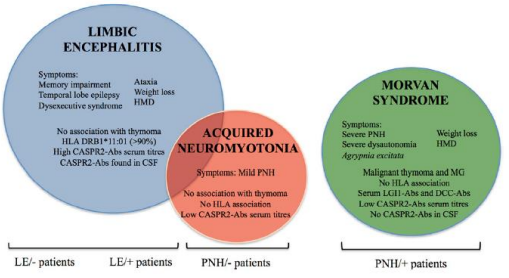
Clinical and immunogenetic features of three major anti-CASPR2 antibodies diseases



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

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Movement Disorders
Vol. 6, No. 1, 1991, pp. 12-20

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, startling noises, and emotional stimuli. Electromyography demonstrates continuous normal motor unit potentials in the affected 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.

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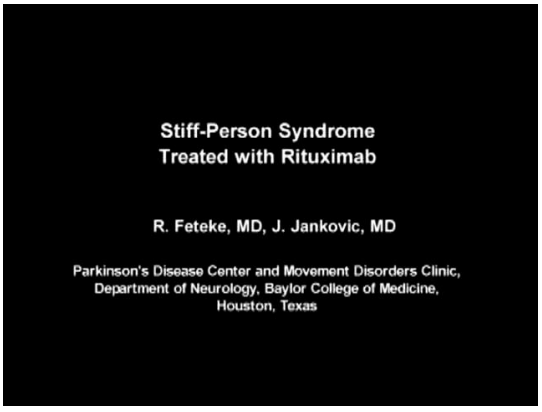
61 y/o woman with a long hx of insulin-dependent DM presented with a 6-month hx of progressive stiffness in both legs. On examination she had spasticity and peripheral neuropathy. Her anti-GAD65 antibody titer was >30U/cc (normal <1.2). She improved with diazepam and IVIG infusions with initial induction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

69

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 and inability to move the head; asymmetrical limb rigidity associated with limb-kinetic and ideomotor apraxia
- Paroxysms of transient but intense muscle spasms, frequently triggered by emotional upset, sudden movements, or external stimuli, may be accompanied by profuse diaphoresis, hypertension, tachycardia, and extreme dysphoria
- Hyperreflexia, stiff gait, downbeat nystagmus, ophthalmoplegia
- Many patients with functional neurological disorder are misdiagnosed as SPS

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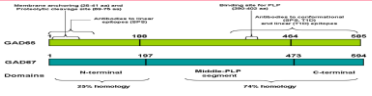
Antibodies associated with SPS

- **GAD65**>>GAD67



  - Serum negative result is 0-5.0 U/mL; positive result is >25.0 U/mL
  - The mean anti-GAD antibody titer in the serum was 51,500 U/mL (range: 24,000-200,000 U/mL); CSF: 181 U/mL (range: 30-400 U/mL)
    - a 10-fold increased intrathecal production of GAD-specific IgG antibodies

    Rakocevic et al. Arch Neurol 2004;61:902-4
- **Glycine α subunit receptor (GLRA)**
- **Amphiphysin** – often paraneoplastic
- Gephyrin
- Dipeptidyl-peptidase-like protein-6 (DPPX)
- Gamma-aminobutyric acid type A receptor ($GABA_AR$ > $GABA_BR$)
- Glycine receptor β subunit (GlyR)
- Glycine transporter 2/SLCA5 (GlyT2)
- Anti-Ri, cardiolipin and β2 glycoprotein 1

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Stiff-person syndrome: Treatment

- **Symptomatic**
  - **Diazepam, baclofen, 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 is not effective**
  Dalakas et al. Ann Neurol 2017;82:271–7
  - **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
  - **Tacrolimus (Prograf, FK506) similar to cyclosporine**
    Nakane et al. JNNP 2013;84:1177-80

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Progressive Encephalomyelitis with Rigidity (PERM)

- **Progressive course, with the emergence of rigidity, myoclonus, cranial nerve dysfunction producing bulbar symptoms and disorders of eye movement, cognitive impairment and long tract signs**
- **Pathology: Widespread encephalomyelitis with perivascular lymphocytic cuffing and infiltration, associated with neuronal loss throughout the brainstem and spinal cord, mainly involving interneurons**
- **Antibodies:**
  - **Anti-GAD antibodies**
  - **Anti-glycine receptor antibodies**
  - **Both anti-glycine receptor and anti-NMDAR antibodies**
  - **DPPX antibodies (a subunit of neuronal K-channel)**

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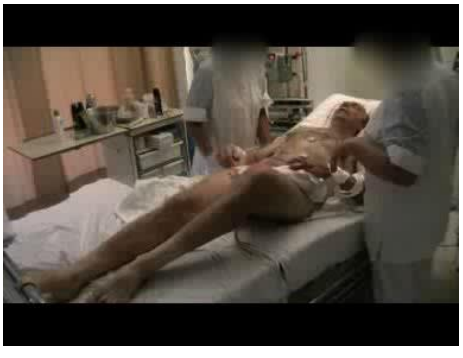
PERM with anti-GlyR antibodies



Courtesy Prof. Angela Vincent

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Clinical spectrum of high-titre GAD65 antibodies.

Budhram et al. J Neurol Neurosurg Psychiatry 2021;92:645–54

- **323 patients from Mayo Clinic with high-titer (>20 nmol/L in serum) GAD65 antibodies out of 380,514 submitted anti-GAD65 samples (2003-2018).**
- **108 patients were classified as not having GAD65 neurological autoimmunity and 3 patients had no more likely alternative diagnoses but atypical presentations (hyperkinetic movement disorders).**
- **Of remaining 212 patients with GAD65 neurological autoimmunity, median age at symptom onset was 46 years (range: 5-83 years); 163/212 (77%) were female.**
- **Stiff-person spectrum disorders (SPSD) (N=71;33%), cerebellar ataxia (N=55;26%), epilepsy (N=35) and limbic encephalitis (N=7) could occur either in isolation or as part of an overlap syndrome (N=44), and were designated core manifestations.**
- **Sustained response to immunotherapy ranged from 5/20 (25%) in epilepsy to 32/44 (73%) in SPSD (p=0.002). Cerebellar ataxia and serum GAD65 antibody titer >500 nmol/L predicted poor outcome.**

85

Anti-GAD65 antibody-associated hemiataxia.

Hill EJ, Jankovic J. Mov Disord Clin Pract 2021 (in press)

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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Complications of Systemic Autoimmune Disorders

- Systemic Lupus Erythematosus (SLE)
- Antiphospholipid syndrome (APL)
- Hashimoto's Encephalopathy (HE)
- 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

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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.

91

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.
- The anticomplement properties of heparin may play a role in the clinical amelioration of patients with SLE and APS chorea.

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Antiphosholipid syndrome

- **aPL antibodies are a heterogeneous population of antibodies directed against phospholipid binding proteins, phospholipids and other proteins**
  - **1. Lupus anticoagulant (LA; directed against prothrombin and β2 glycoprotein-I)**
  - **2. Anticardiolipin (aCL; directed against β2 glycoprotein-I)**
  - **3. Anti-β2 glycoprotein-I (anti-B2 GPI antibodies; may be the primary abnormality)**
- **A hypercoagulable state leading to arterial, venous, or small vessel thrombosis, associated with spontaneous abortions and increased morbidity during pregnancy**
- **Neurological manifestations include migraine, seizures, myelitis, and dementia; chorea is the most common movement disorder in APL although its prevalence is only 1.3%**
  (Baizabal-Carvallo et al. 2013; Abreu et al. Autoimmun Rev 2015;14:401-14)
- **Treatment: anticoagulants, statins, hydroxychloroquine, rituximab, tetrabenazine**

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Paraneoplastic Movement Disorders

Paraneoplastic movement disorders	Neoplastic disease	Antibody
Myoclonus	Lung cancer, breast cancer, melanoma	Anti-amphiphysin [3]
Chorea	Lung cancer, thymomas	Anti-CRMP-5 [46]; anti-Hu/ANNA-1 [47,48]; anti-$GABA_BR$, anti-NMDA-R [49].
	Non-Hodgkin lymphoma	Anti-CRMP-5 [46].
	Head and neck cancer	Anti-CRMP-5 [46].
	Ovarian teratoma	Anti-NMDA-R [49].
Dystonia	Breast cancer	Anti-Ri/ANNA-2 [50].
	Ovarian teratoma	Anti-NMDA-R [50].
Paraneoplastic parkinsonism	Testicular cancer	Anti-Ma2 [51].
	Ovarian teratoma	Anti-NMDA-R [49].
Peripheral nerve hyperexcitability	Lung cancer	Anti-CRMP-5 [52].
Stiff person syndrome	Breast cancer, Lung cancer, thymoma	Anti-amphiphysin [3]; anti-glycine receptor [53]; $GABA_AR$ [49]; Anti-Ri/ANNA-2 [49].
	Lymphoma	Anti-DPPX [49].

Onconeural antibodies: anti-Hu/ANNA-1, anti-Ri/ANNA-2, anti-CRMP-5, anti-amphiphysin, anti-Ma2. Neuronal surface antibodies: anti-glycine receptor, anti-VGKC.

Chirra et al. Eur J Intern Med 2019;67:14-23

Opsoclonus Myoclonus Ataxia Syndrome

- **Diagnostic criteria include at least three of the following: 1) opsoclonus; 2) myoclonus or ataxia; 3) behavioral change or sleep disturbance; and 4) neuroblastoma.**
- **Other clinical symptoms include dysarthria, drooling, hypotonia**
- **No specific biomarker (except for rare anti-Ri antibodies)**

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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**
- **Cerebellar ataxia – anti-Yo, anti-Hu, anti-GAD65, anti-gliadin, paraneoplastic**
- **Neuropathic tremor – associated with IgM monoclonal gammopathy**
- **Multiple sclerosis**

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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 – Paroxysmal dystonia – Dystonia – Ballism/Chorea – Paroxysmal Kinesigenic Dyskinesia (PKD) – Parkinsonism – Myoclonus – Hemifacial spasm and continuous facial myokymia – Tics-tourettism – Restless legs syndrome – Complex hyperkinetic movement disorder
Neuromyelitis optica	– Paroxysmal dystonia after initiation of treatment and during the recovery phase. Good response to carbamazepine [128–130].
Acute disseminated encephalomyelitis	– Ataxia [131]. – Acute ataxia (50%) [132]. – Acute choreoathetosis, hemidystonia, paroxysmal hemidystonia and hemichorea plus dystonia (12%) [132]. – Painless torticollis [134]. – Segmental myoclonus [135].
Central pontine myelinolysis and extrapontine myelinolysis	– Parkinsonism, frequently responsive to levodopa [138,140,141]. – Dystonia. Multifocal, segmental or generalized. Responds well to trihexyphenidyl [138,143,144]. – Truncal ataxia [147]. – Paroxysmal dystonia [137]. – Chorea [138]. – Phenomenology can evolve from one movement to another over time [145]. – 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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The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings.

Paterson et al. Brain 2020;143:3104-20

- **Of 43 patients, 29 were SARS-CoV-2 PCR positive and definite, 8 probable and 6 possible.**
- **1. Encephalopathies; 2. inflammatory CNS syndromes; 3. Ischemic strokes; 4. Peripheral neurological disorders; and 5. Miscellaneous central disorders**
- **Two cases had a probable autoimmune encephalitis, one with typical clinical features of opsoclonus and myoclonus, and another with typical radiological images as seen in 'limbic' encephalitis. These patients did not have NMDAR, LGI1 or related autoantibodies.**
- **The issue of whether SARS-CoV-2 will trigger a significant number of cases of autoimmune encephalitis, with probable antibody mediated mechanisms, will become clear in time.**

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COVID-19 Related Cases of Parkinsonism

Makhoul K, Jankovic J. J Neurol Sci 2021;422:117331

Publication	Age	COVID-19 severity	Days to Parkinsonian features after initial COVID symptoms	Parkinsonian features	Imaging of dopaminergic uptake	Prodromal symptoms
Cohen et al. [9]	45	Moderate requiring hospitalization	2 to 3 weeks	Right more than left tremor, bradykinesia, rigidity	Decreased uptake in bilateral putamen more apparent on the left	None
Mendéz-Guerrero et al. [7]	58	Severe with desaturation requiring ICU admission	32 days	Right hypokinetic-rigid syndrome with rest and postural tremor[a]	Decreased uptake in bilateral putamen more apparent on the left	None
Faber et al. [10]	35	Mild	10 days	Right rigidity, bradykinesia and hypophonia, hypomimia, slow saccades and gait impairment	Decreased left putamen uptake	None
Baylor Case	64	Mild	5 days	Left bradykinesia rigidity and rest tremor with hypomimia	Decreased right putamen uptake	Constipation

Until clinical-etiopathogenic correlation can be established, the reports of COVID-19 related PD must be interpreted with caution.

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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[5,5], 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.

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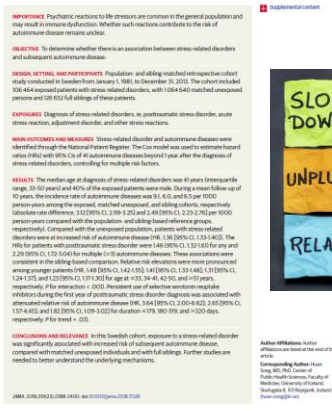
Association of Stress-Related Disorders With Subsequent Autoimmune Disease



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Parkinson's Disease Center and Movement Disorders Clinic

www.jankovic.org

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THANKS

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