Autoimmune Movement Disorders

Joseph Jankovic, MD
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Our bodies are confused by this 21st-century world.


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.

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.

Movement Disorders in Autoimmune Diseases

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

<table>
<thead>
<tr>
<th>Main Antigen</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular antigens</td>
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<tr>
<td>(Commonly paraneoplastic)</td>
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<tr>
<td>HU (ANNA1)</td>
<td>Lung (rarely paraneoplastic)</td>
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<tr>
<td>Ma2</td>
<td>SCLC, other</td>
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<tr>
<td>Cytotoxic – neuronal damage</td>
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<tr>
<td>CV2/CRMP5</td>
<td>SCLC, thymoma, non-Hodgkin’s lymphoma</td>
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<tr>
<td>Amphiphysin</td>
<td>Ovary, breast</td>
</tr>
<tr>
<td>Yo (ANNA2)</td>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Tr</td>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Surface (membrane) antigens</td>
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<tr>
<td>(Less commonly paraneoplastic)</td>
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<tr>
<td>LGI1</td>
<td>SCLC, thymoma</td>
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<tr>
<td>NMDAR</td>
<td>SCLC, thymoma, breast</td>
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<tr>
<td>AMPAR (Glur1 and Glur2)</td>
<td>Ovarian teratoma</td>
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<tr>
<td>GABA</td>
<td>SCLC</td>
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<tr>
<td>mGluR1</td>
<td>Hodgkin disease</td>
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<td>VGCC</td>
<td>SCLC</td>
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<tr>
<td>Synaptic antigens</td>
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<tr>
<td>(Rarely paraneoplastic)</td>
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<tr>
<td>Glycine R (of subunit)</td>
<td>Lung</td>
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<tr>
<td>AMPAR (Glur3)</td>
<td>Rarely paraneoplastic</td>
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<tr>
<td>GABA</td>
<td>Thymoma</td>
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**Three groups of neuronal antibodies and their pathogenic roles**

<table>
<thead>
<tr>
<th>Autoimmune conditions associated with movement disorders</th>
<th>Relevant antibodies</th>
<th>Movement disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorder</strong></td>
<td><strong>Anti-NMDAR</strong></td>
<td><strong>Movement disorders</strong></td>
</tr>
<tr>
<td>autoimmune encephalitis</td>
<td>Anti-NMDAR</td>
<td>chorea, dyskinesia, dystonia, myokymia, other dyskinesias</td>
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<tr>
<td>Sydenham disease</td>
<td>Anti-NMDAR, Anti-DNAase B</td>
<td>hyperekplexia, opsoklonus</td>
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<tr>
<td>SLE and MPPE</td>
<td>Anti-Ro/SSA, anti-La/SSB</td>
<td>myokymia, opsoklonus, ataxia</td>
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<tr>
<td>Hashimoto’s disease</td>
<td>Anti-TPO, anti-NAE</td>
<td>hyperekplexia, opsoklonus</td>
</tr>
<tr>
<td>stiff person syndrome (SPS)</td>
<td>Anti-GAD65, anti-GAD67</td>
<td>myokymia, opsoklonus</td>
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<tr>
<td>Progressive encephalomyelitis with rigidity and myoclonus (PERM)</td>
<td>Anti-GlyR</td>
<td>myokymia, opsoklonus</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Anti-Hu, anti-Ma2, anti-CRMP5, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPA, anti-GABA, anti-IgL0N5, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPA, anti-GABA, anti-IgL0N5</td>
<td>hyperekplexia, opsoklonus</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar ataxias</td>
<td>Anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-mGluR1, anti-YGCC, anti-GAD65</td>
<td>myokymia, opsoklonus</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Anti-AGA, anti-TTG, anti-TG6</td>
<td>opsoklonus, ataxia, opsoklonus</td>
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<tr>
<td>Cerebral folate deficiency syndrome</td>
<td>Anti-IFN</td>
<td>opsoklonus, ataxia, opsoklonus</td>
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<td>Opsoclonus-myoclonus syndrome</td>
<td>Anti-VGKC complex (LGI1 and CASPR2)</td>
<td>opsoklonus, ataxia, opsoklonus</td>
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<tr>
<td>Neuromyotonia</td>
<td>Anti-VGKC complex (LGI1 and CASPR2)</td>
<td>opsoklonus, ataxia, opsoklonus</td>
</tr>
</tbody>
</table>

**Autoimmune and paraneoplastic movement disorders: An update**

Balint B. Practical Neurology 2020 September:30-40

Balint B. Practical Neurology 2020 September:30-40
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

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

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

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NMDAR Encephalitis – MRI
3 y/o boy presenting with seizures

Leptomenigeal enhancement is a common early finding

Left temporal lobe, right superior frontal gyrus and bilateral cingulate gyrus

Symmetric restricted diffusion

Hyperintensity in the basal ganglia

Gorman et al. NEJM 2018;379:870-8
3 y/o boy with subacute onset of myalgias, frontal headaches, malaise, and vomiting; followed by confusional state, hallucinations, dysarthria and motor aphasia. Admitted with diagnosis of “viral encephalitis”. During the hospitalization he developed generalized seizures, dysautonomia, repetitive orofacial stereotypes, dystonic contractions of the left side of his face, blepharospasm, dystonic flexion of the right hand and generalized chorea. Improved with tetrabenazine.

13 y/o presented to the ER with recent onset ataxic gait, rapidly followed by altered mental status with perseveration, 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.

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

Mov Disord 2015;30:171-9

Myorhythmia: Phenomenology, Etiology, and Treatment

José Federico Baizabal-Carvallo, MD, MS,1 Francisco Gantoso, MD, PhD,2 and Joseph Jankovic, MD3

Parkinson’s Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

Movement Disorders Clinic, Neurology Service, Department of Internal Medicine, The Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

ABSTRACT: Myorhythmia is defined as repetitive, rhythmic, slow (1.4 Hz) movements affecting 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 slower, repetitive, often asymmetrical, facial and ocular movement. Thus, myorhythmia overlaps phenomenologically with tremor and segmental myoclonus. Although often present as well, it must be differentiated from paroxysmal or dys tonic tremor. Recognition of this movement disorder is important because it is typically associated with various underlying conditions, including Whipple’s disease, tremor-related encephalitis, and other dementia. Myorhythmia is a rare condition that requires a high index of suspicion for its accurate diagnosis. In addition to Whipple’s disease, myorhythmia has been described in patients with cerebrovascular disease, idiopathic encephalitis, anti-NMDAR encephalitis, and other conditions. Myorhythmia is a distinct entity that should be recognized as a separate clinical entity. © 2014 International Parkinson and Movement Disorder Society.
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

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

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

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

Immunologic triggers in anti–NMDAR encephalitis

Ovarian teratoma
Herpes encephalitis
27% develop autoimmune encephalitis

20% have ovarian teratoma
Dense infiltration of T cells and B cells

Dalmau J. Neurology 2016;87:2471-82

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

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)
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.

Autoimmune chorea in adults

- 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)

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

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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  - 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

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 hypoventilation
- 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
Presenting symptoms and disease course in 38 patients with anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis and disease course.

- 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%

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)

Pathogenic effects of LGI1 autoantibodies in the brain, showing that patients' autoantibodies alter presynaptic and postsynaptic pathways related to K,1.1 potassium channels and AMPA receptors

Abnormalities in the mediotemporal lobe and the hippocampus

74% hippocampal T2 hyperintensity
Faciobrachial dystonic seizures with LGI1 limbic encephalitis

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.

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)

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

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
Syndromes associated with VGKC antibodies

Central Nervous System (CNS)

- Dysesthesia and insomnia
- Neuromyotonia
- Morvan Encephalopathy
- Collagen-vascular diseases
- Other Epilepsies/Non-immune

Cranio-fasciculation syndrome-neuromyotonia

Abnormal MRI / CSF

LG1

CASPR2


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

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

Neuromyotonia

Courtesy of Prof. A. Vincent

Stiff-Person Syndrome: An Autoimmune Disease

Philip Been and Joseph Zabramski
Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.

Stiff-person syndrome was first described by Eudevant and Winter in 1950 as a syndrome caused by high levels of anti-NMDA receptor antibodies. Since then, several other autoimmune disorders have been described that target the motor system. The hallmark of the disease is a progressive, spastic, muscular rigidity in the affected muscles despite the patient’s awareness to move. Both the rigidity and the spasms are often dramatically relieved by sleep, general anesthesia, or typical muscle relaxants. In severe cases, respiratory compromise, and ultimately death, can occur. The disease can be associated with a variety of other autoimmune disorders, including diabetes mellitus, thyroid disorders, and inflammatory bowel disease. The presence of an autoantibody to the P/Q-type voltage-gated calcium channel is a marker of an autoimmune disorder of the motor system. In case of persistent symptoms or severe autoimmunity, referral to an immunologist is recommended.
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.

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


- 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

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
- Glycine α subunit receptor (GLRA)
- Amphiphysin – often paraneoplastic
- Gephyrin
- Dipeptidyl-peptidase-like protein-6 (DPPX)
- Gamma-aminobutyric acid type A receptor (GABA_A R > GABA_B R)
- Glycine receptor β subunit (GlyR)
- Glycine transporter 2/SLC5A (GlyT2)
- Anti-Ri, cardioliopin and β2 glycoprotein 1
### 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

- In a placebo-controlled crossover study in 16 patients with SPS, IVlg significantly decreased stiffness scores and substantially increased walking and functions of daily activities
- 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

### 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)

### Clinical spectrum of high-titre GAD65 antibodies.

- **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.**
### Anti-GAD65 antibody-associated hemiataxia.

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

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

### 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

### 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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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 tetrabenzine.
Antiphospholipid 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

Other Autoimmune Movement Disorders

- Behcet’s syndrome – tremor, myoclonus, chorea
- Sjogren’s syndrome – parkinsonism, dystonia, chorea
- Celiac disease – ataxia, cortical myoclonus (leg), cerebellum
- CLIPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) – ataxia, dystonia, myoclonus
- Rasmussen’s encephalitis – myoclonus, anti-AMPA
- Cerebellar ataxia – anti-Yo, anti-Hu, anti-GAD65, anti-gliadin, paraneoplastic
- Neuropsychiatric tremor – associated with IgM monoclonal gammopathy
- Multiple sclerosis

Paraneoplastic Movement Disorders

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<tr>
<th>Paraneoplastic Movement Disorders</th>
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- Diagnostic criteria include at least three of the following:
  1) opsonoclonus; 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)

Movement disorders in multiple sclerosis and other demyelinating diseases.

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

COVID-19 Related Cases of Parkinsonism
Makhoul K, Jankovic J. J Neurol Sci 2021;422:117331

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age</th>
<th>COVID-19 severity</th>
<th>Days to Parkinsonian features after initial COVID symptoms</th>
<th>Parkinsonian features</th>
<th>Imaging of dopaminergic uptake</th>
<th>Prodromal symptoms</th>
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<tbody>
<tr>
<td>Cohen et al.</td>
<td>45</td>
<td>Moderate requiring hospitalization</td>
<td>2 to 3 weeks</td>
<td>Right more than left tremor, bradykinesia, rigidity</td>
<td>Decreased uptake in bilateral putamen more apparent on the left</td>
<td>None</td>
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<tr>
<td>Mendez-Guerrero et al.</td>
<td>58</td>
<td>Severe with desaturation requiring ICU admission</td>
<td>32 days</td>
<td>Right hypokinetic-rigid syndrome with rest and postural tremor, hypomimia, slow saccades and gait impairment</td>
<td>Decreased left putamen uptake</td>
<td>None</td>
</tr>
<tr>
<td>Faber et al.</td>
<td>55</td>
<td>Mild</td>
<td>10-days</td>
<td>Right rigidity, bradykinesia and postural hypokinesia, hypomimia, slow saccades and gait impairment</td>
<td>Decreased left putamen uptake</td>
<td>None</td>
</tr>
<tr>
<td>Baylor Case</td>
<td>64</td>
<td>Mild</td>
<td>5-days</td>
<td>Left bradykinesia, rigidity and rest tremor with hypomimia</td>
<td>Decreased right putamen uptake</td>
<td>Constipation</td>
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</tbody>
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Until clinical-etiopathogenic correlation can be established, the reports of COVID-19 related PD must be interpreted with caution.

Parkinson disease and the immune system — associations, mechanisms and therapeutics
Eng-King Tong, Yin-Xia Chang, Andrew West, Eng-Ling Chan
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 a-synuclein and the targeting of immune mediators such as inflammatory cytokines. We also consider future research and clinical trials necessary to maximize the potential of targeting the immune system.
THANKS