Autoimmune Movement Disorders

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Immune System
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>
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<tbody>
<tr>
<td><strong>Intracellular antigens-antibodies</strong>&lt;sup&gt;(Commonly paraneoplastic)&lt;/sup&gt;</td>
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<tr>
<td>Hu (ANNA1)</td>
<td>SCLC, other</td>
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<td>Ma2</td>
<td>Testis (germ-cell); SCLC, breast</td>
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<td>CV2/CRMP5</td>
<td>SCLC, thymoma, non-Hodgkin's lymphoma</td>
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<td>Amphiphysin</td>
<td>Breast, SCLC</td>
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<td>Yo</td>
<td>Ovary, breast</td>
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<tr>
<td>Ri (ANNA2)</td>
<td>Breast, SCLC</td>
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<td>Tr</td>
<td>Hodgkin's lymphoma</td>
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<td><strong>Membrane antigens-antibodies</strong>&lt;sup&gt;(Less commonly paraneoplastic)&lt;/sup&gt;</td>
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<tr>
<td>LGI1 (VGKC)</td>
<td>SCLC, thymoma</td>
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<td>CASPR2</td>
<td>SCLC, thymoma</td>
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<tr>
<td>NMDAR</td>
<td>Ovarian teratoma</td>
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<tr>
<td>AMPAR</td>
<td>SCLC, thymoma, breast</td>
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<tr>
<td>(GluR1 and GluR2)</td>
<td>SCLC</td>
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<tr>
<td>GABA</td>
<td>Hodgkin disease</td>
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<tr>
<td>mGluR1</td>
<td>SCLC</td>
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<tr>
<td>VGCC</td>
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<td><strong>Inflammatory infiltrates – reversible</strong></td>
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<tr>
<td>Glycine R(α1 subunit)</td>
<td>Lung</td>
</tr>
<tr>
<td>AMPAR (GluR3)</td>
<td>Rarely paraneoplastic</td>
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<tr>
<td>GAD65</td>
<td>Thymoma</td>
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<td>GABA</td>
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<td>LG11 (AMPAR, ADAM)</td>
<td>Thymoma</td>
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<tr>
<td>Homer-3</td>
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<td>Anti-Neurexin-3α</td>
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### Autoimmune disorders associated with movement disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Relevant antibodies</th>
<th>Movement disorders</th>
</tr>
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<tbody>
<tr>
<td>Anti-NMDAR encephalitis</td>
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<td>Stereotypies, dystonia, chorea, myorhythmia, other dyskinesias</td>
</tr>
<tr>
<td>Sydenham disease</td>
<td>ASO, Anti-DNAse B</td>
<td>Chorea, tics, OCD</td>
</tr>
<tr>
<td>SLE and APS</td>
<td>ANA, anti-dsDNA, aCL, LA, anti-B2 GP1</td>
<td>Chorea</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td>Anti-Ro/52, anti-La/SSB</td>
<td>Parkinsonism and chorea</td>
</tr>
<tr>
<td>Hashimoto's disease</td>
<td>Anti-GAD65, anti-GAD67, anti-ampiphysin, anti-gephryn, anti-Ri</td>
<td>Axial and limb stiffness, myoclonus, hyperekplexia</td>
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<tr>
<td>Stiff person syndrome (SPS)</td>
<td>Anti-GlyR</td>
<td>Rigidly, myoclonus, tremor, ataxia, hyperekplexia</td>
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<td>Progressive encephalomyelitis</td>
<td>Anti-HU, anti-Ma2, anti-CRMP5, anti-VGKC complex (anti-LGI1, anti-CASPR2), anti-AMPAR, anti-GABA, anti-IGLON5</td>
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<td>Limbic encephalitis</td>
<td>Anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-mGlur1, anti-VGCC, anti-GAD65</td>
<td>Progressive cerebellar syndrome</td>
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<td>Paraneoplastic cerebellar ataxias</td>
<td>Anti-FR</td>
<td>Ataxia</td>
</tr>
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<td>AGA, anti-TG2, anti-TG6</td>
<td>Ataxia, choreoathetosis, dystonia</td>
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<tr>
<td>Cerebral folate deficiency syndrome</td>
<td>Anti-Ri</td>
<td>Opoclonus, axial and limb myoclonus, ataxia, tremor</td>
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<tr>
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<td>Myoclonus, painful cramps, myokymia, and neumyotonia</td>
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**Keywords:** Autoimmune, Movement disorders, Chorea, Stiff person syndrome, Sjögren's syndrome, Sydenham disease, Hashimoto's disease.
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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, plasma exchange, rituximab, anti-CD20 monoclonal antibodies and other emerging immunotherapies
Anti-NMDAR Encephalitis

• Unrecognized until 2007, anti-NMDAR encephalitis is a potentially devastating neuronal autoimmune condition affecting children and adults

• The classic clinical phenotype is subacute onset of:
  – Headache, fever
  – Seizures
  – Behavioral/neurocognitive changes
  – Encephalopathy somnolence/insomnia → coma
  – Dysautonomia
  – Abnormal movements (oromandibular-lingual stereotypies, myorhythmia, chorea, dystonia, tremor)

Anti-NMDAR Encephalitis

• 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 action potential

• If not detected in serum, test CSF
  – NMDAR antibodies are not detected in the serum of 15% of the patients with anti-NMDAR encephalitis documented by positive CSF antibodies.
  – 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 or cerebellar cortex, basal ganglia, brainstem, and spinal cord

• 2 known immunologic triggers: ovarian teratoma and prior herpes simplex virus encephalitis

• Earlier diagnosis, tumor removal, and immunotherapy may be life-saving and decrease relapse rates and neurologic morbidity
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.

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.
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

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age at onset</th>
<th>Myorhythmia (facial)</th>
<th>Myorhythmia (limb)</th>
<th>Chorea</th>
<th>Athetosis</th>
<th>Cranial dystonia</th>
<th>Opisthotonus</th>
<th>Limb dystonia</th>
<th>Stereotypic movements</th>
<th>Ataxia</th>
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<tbody>
<tr>
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<td>F/13 years old</td>
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<td>9</td>
<td>F/10 years old2</td>
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Myorhythmia: Phenomenology, Etiology, and Treatment
José Fidel Baizabal- Carvallo, MD, MSc,1 Francisco Cardoso, MD, PhD,2 and Joseph Jankovic, MD2

1Parkinson’s Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA
2Movement 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, lassos 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
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

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
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]

**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

NMDAR Encephalitis – MRI

3 y/o boy presenting with seizures

Gorman et al. NEJM 2018;379:870-8
Flair
Treatment of NMDAR Encephalitis

- Removal of tumor (ovarian > testicular teratoma)
- 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)

- 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.
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

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.
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.
- Antigenic target within the central nervous system has not yet been identified.
- In patients with SLE chorea aPL antibodies may contribute to BBB dysfunction leading to passage of other pathogenic antibodies into the CNS.
- Complement activation could also play an important role in BBB dysfunction by means of the C5a fraction.
- The anticomplement properties of heparin may play a role in the clinical amelioration of patients with SLE and APS chorea.

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
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)

Hashimoto encephalopathy in the 21st century.
Mattozzi et al. Neurology 2020;94:e217-e224

- Symptoms and steroid responsiveness was assessed in 24 patients (14 women) with pretreatment criteria of HE: (1) subacute onset of cognitive impairment, psychiatric symptoms, or seizures; (2) euthyroid status or mild hypothyroidism; (3) serum thyroid peroxidase antibodies (TPOAb) >200 IU/mL; (4) absent neuronal antibodies in serum/CSF; and (5) no other etiologies.
- 4 syndromes were identified: psychiatric (7, 29%), encephalopathy (7, 29%), new-onset refractory status epilepticus (6, 25%), and limbic encephalitis (4, 17%).
- Only 6 of 19 (31.6%) patients completely responded to steroids.
- CONCLUSION: The findings of our study challenge the concept of HE. All pretreatment features usually considered in this disorder (encephalopathy, elevated levels of TPOAb, nonspecific MRI, EEG, or CSF findings) are not specific and do not help to predict whether patients will respond to steroids.
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
- 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)
- A characteristic aggregate of tau protein in the tegmentum and brainstem observed in pathological samples of 2 individuals
- Poor response to immunosuppressive therapy; may die of sudden death during sleep or wakefulness
- Brainstem, hypothalamic manifestations associated with antibodies against the neuronal cell adhesion protein IgLON5

Graus F, Santamaría J. Neurol Neuroimmunol Neuroinflamm 2017;4:e393

MRI Findings in IgLON5 Antibody Disease

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 2019 (in press)
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%**

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

Brain 2018;141(11), November – Cover
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

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”), associated with right facial movements 2 weeks prior to hospital admission. She became less interactive, had slurred speech; followed by abnormal movements in the right face, left shoulder and leg. EEG during the events – non-epileptiform. CSF was positive for LGI1-antibodies.
Neuromyotonia

- Also known as Isaacs Syndrome (Isaacs 1961), Isaacs-Mertens Syndrome, Armadillo syndrome, Quantal squander syndrome, Pseudomyotonia
- M>F, median age 55 (12-85) years
- LGI1 and CASPR2 antibodies
- 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)
- 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

Vincent et al. JAMA Neurol 2018;75:1519-27
Morvan Syndrome
Morvan’s fibrillary chorea or “la chorée fibrillaire”

- M > F
- Characterized by generalized myokymia, burning pain, cramping, weakness, pruritis, hyperhidrosis, weight loss, sleeplessness, hallucinations, encephalopathy and dysautonomia
- 1/3 have tumors
- Most cases are associated with increased antibodies to voltage gated potassium channel complex (VGKC) > CASPR2, LGI1, contactin-2 antibodies
- Treatment: Carbamazepine, phenytoin, plasmapheresis or IVIG

Voltage-gated potassium channel-complex

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.
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
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
- 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/SLCA5 (GlyT2)
- Anti-Ri, cardiolipin and β2 glycoprotein 1

Stiff-person syndrome: Treatment

- Symptomatic
  - Diazepam, baclofen, botulinum toxin, physical therapy
- Etiologic
  - Steroids, plasmapheresis, IVlg (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
    Lümemann 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
Anti-GAD65 antibody-associated hemiataxia.

<table>
<thead>
<tr>
<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>
</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>
</tr>
<tr>
<td>44/man</td>
<td>6 yrs; left-sided</td>
<td>IDDM, generalized epilepsy</td>
<td>“positive”</td>
<td>Mycophenolate mofetil</td>
<td>Symptoms stabilized</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>
</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>
</tr>
</tbody>
</table>
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)

PERM with anti-GlyR antibodies

Courtesy Prof. Angela Vincent
Paraneoplastic Movement Disorders

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**
Movement disorders in multiple sclerosis and other demyelinating diseases.
Mehanna R, Jankovic J. J Neurol Sci 2013;328:1-8

<table>
<thead>
<tr>
<th>Movement disorders in demyelinating diseases</th>
<th>Movement disorder</th>
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<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Tremor</td>
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<td></td>
<td>Paroxysmal dystonia</td>
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<td>Dystonia</td>
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<td>Tic and Dystonic Dystonia (PdD)</td>
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<td>Parkinsonism</td>
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<td>Myoclonus</td>
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<td>Hemifacial spasm and continuous facial myokymia</td>
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<td>Tics and taurism</td>
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<td>Benign essential movement disorders</td>
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<td>Complex hyperkinetic movement disorders</td>
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<td>Neuremyelitis optica</td>
<td>Paroxysmal dystonia after induction of treatment and during the recovery phase</td>
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<td>Prophylactic use of carbamazepine</td>
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<td>Acute disseminated encephalitis</td>
<td>Acute ataxia [509] [112]</td>
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<td></td>
<td>Acute encephalitis, hemiplegia, opsoclonus, opsoclonus plus dystonia [170] [172]</td>
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<td></td>
<td>Fatigue [134]</td>
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<td>Segmental myelination [135]</td>
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<tr>
<td>Central pontine myelinolysis and exoptopic myelinolysis</td>
<td>Paroxysmal, frequently responsive to levodopa [135,156,141]</td>
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<tr>
<td></td>
<td>Optic ataxia, multiblinded, segmental or generalized, symptoms well localized [142]</td>
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<td>Truncal ataxia [147]</td>
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<td></td>
<td>Paroxysmal dystonia [147]</td>
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<tr>
<td></td>
<td>Choreoathetosis [130]</td>
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<td></td>
<td>Phenomenology can evolve from one movement to another over time [145]</td>
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<td></td>
<td>These movement disorders can be transient or permanent and can start as early as within a week of the initial insult, or be delayed by up to 5 months [138,139] [142,143]</td>
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Post-acute encephalopathy

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<th>Post-acute encephalopathy</th>
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<tr>
<td>Encephalomyelitis</td>
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<tr>
<td>Hypomyelination with atrophy of the basal ganglia and cerebellum</td>
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The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings.
Paterson et al. Brain 2020 (on line)

- 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.
Parkinson disease and the immune system -- associations, mechanisms and therapeutics

Eng-King Tan1,2,3, Yin-Xia Chao1,2,3, Andrew West4, Ling-Ling Chan5,6, Werner Poewe6 and Joseph Janovetz7

Nat Rev Neurol 2020

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 potential 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.

Association of Stress-Related Disorders With Subsequent Autoimmune Disease


The median age at diagnosis of stress-related disorders was 15 years (range, 5.5-60 years) and 47 of the 100 patients were male. During a mean follow-up of 10 years, the incidence rate of autoimmune disease was 1.6% and 4.4% per 1000 person-years among untreated patients with stress-related disorders and without controls, respectively (Kaplan-Meier incidence rate, 2.3% and 18.3% per 1000 person-years). In a multivariate Cox regression model, the risk of autoimmune disease was significantly higher in patients with stress-related disorders compared with the matched controls (hazard ratio, 2.77; 95% confidence interval, 1.21-6.39). The risk of autoimmune disease was also significantly higher in patients with stress-related disorders compared with the matched controls (hazard ratio, 2.77; 95% confidence interval, 1.21-6.39). These results suggest that stress-related disorders are associated with an increased risk of autoimmune disease.
Parkinson’s Disease Center and Movement Disorders Clinic

THANKS