Autoimmune Encephalopathies: PANDAS/PANS and Antineuronal Antibody Testing

Academy of Nutritional Medicine (AONM)
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Co-founder & CEO,
Moleculera Labs
1. **Autoimmune Neurology-based Disorders**
   - (Re) emergence of medical and clinical relevance
   - The role of *molecular mimicry* in triggering these disorders

2. **Definition and Clinical Presentation of Autoimmune Encephalopathies**
   - *PANDAS/PANS* nomenclature and alternative nomenclature
   - Proposed mechanism for these conditions
   - Some common infectious triggers

3. **Anti-neuronal Antibody Targets in the Cunningham Panel**
   - Why these biomarkers were selected
   - Patient case studies
   - Patient population study

4. **Summary**
Autoimmune Neurology

The interaction between: Immune System + Nervous System (brain)
Autoimmune Neurology

The interaction between: Immune System + Nervous System (brain)

Autoimmune Central Nervous System Disorders
  • *Multiple sclerosis*

Paraneoplastic Disorders (associated with cancer)
  • *Limbic Encephalitis*

Neuromuscular Syndromes
  • *Myasthenia gravis (acetylcholine receptor target)*

Autoimmune Encephalopathies
  • *NMDA receptor encephalitis*
  • *VGKC*
  • *GABA*
  • *PANDAS/PANS*

• Autoimmune Neurology
• Neuroimmunology
• Neuroinflammatory Disorders
Autoimmune Disorders Involving the Basal Ganglia

Baseline Ganglia is Responsible for:

- Voluntary motor control
- Procedural learning
- Cognitive functions
- Emotional functions
- Eye movement

Two disorders of the Basal Ganglia are Parkinson's Disease and Huntington's Disease

- Infectious Autoimmune Encephalopathy
- Infectious Autoimmune Encephalitis
- Infectious Autoimmune Disorder of the Brain (Basal Ganglia)
### Danish study of ~4,500 individuals revealed a relationship between inflammatory markers and neuropsychiatric disorders\(^{(2)}\)

<table>
<thead>
<tr>
<th>Description</th>
<th>Risk Increase</th>
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<tbody>
<tr>
<td>Patients with elevated Interleukin-6 (IL-6) were more likely to be depressed at age 18 years</td>
<td>+55%</td>
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<tr>
<td>Higher IL-6 baseline levels increased the risks of psychotic experiences and psychotic disorder at age 18</td>
<td>+81%</td>
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</tbody>
</table>

### Danish study of 3.6 million individuals revealed an increased risk of mental illness associated with infections\(^{(1)}\)

<table>
<thead>
<tr>
<th>Description</th>
<th>Risk Increase</th>
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</thead>
<tbody>
<tr>
<td>History of hospitalization for infection increased the risk of mood disorders (bipolar affective disorder or depression)</td>
<td>+62%</td>
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<tr>
<td>Hospitalization for autoimmune disease increased the risk of a mood disorder diagnosis</td>
<td>+45%</td>
</tr>
<tr>
<td>The two risk factors together increased the risk of subsequent mood disorders</td>
<td>+135%</td>
</tr>
</tbody>
</table>

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2. “Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life” JAMA Psychiatry. 2014;71(10):1121-1128
A Portion of Autism Diagnosed Children Are Associated with Family History of Autoimmune Disorders – Immune Dysfunction

Table 1. Epidemiological Studies of Autoimmunity and Immune dysfunction in Families of Children with ASD

<table>
<thead>
<tr>
<th>References</th>
<th>Study population, no.</th>
<th>Reporting</th>
<th>Association with ASD?</th>
<th>Autoimmune diseases and immune dysfunction</th>
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<tbody>
<tr>
<td>Comi et al.(^5) (1999)</td>
<td>107</td>
<td>Self-report</td>
<td>Yes</td>
<td>Rheumatoid arthritis (mat); general autoimmunity (mat, pat)</td>
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<td>Sweeten et al.(^6) (2003)</td>
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<td>Self-report</td>
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<td>Hypothyroidism and Hashimoto’s thyroiditis (mat, pat); rheumatic fever (mat, pat)</td>
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<td>Micali et al.(^7) (2004)</td>
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<td>Self-report</td>
<td>No</td>
<td>Psoriasis (mat), asthma and allergies</td>
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<td>Croen et al.(^3) (2005)</td>
<td>2,520</td>
<td>Medical records</td>
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<td>Autoimmune thyroid disease (mat, pat)*</td>
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<td>Molloy et al.(^8) (2006)</td>
<td>308</td>
<td>Self-report</td>
<td>Yes</td>
<td>Ulcerative colitis (mat); type 1 diabetes</td>
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<td>Mouridsen et al.(^9) (2007)</td>
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<td>Valicenti-McDermott et al.(^10) (2008)</td>
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<td>Atladóttir et al.(^2) (2009)</td>
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<td>Medical records</td>
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ASD = autism spectrum disorder; mat = maternal (autoimmunity link in mothers); pat = paternal (autoimmunity link in fathers).

*Autoimmune thyroid disease was found to be associated with the families of children with regressive ASD. †Rheumatoid arthritis and celiac disease in this study were associated with language regression.


Over 650,000 Autism Spectrum Disorder Patients Studied had Family History of Autoimmune Disorders
Numerous Studies Demonstrate that Autism has an Etiology of Immune Dysregulation

Table 3  Abnormalities in biomarkers of immune dysregulation or inflammation in ASD

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Number of studies</th>
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<tr>
<td>Cytokine abnormalities</td>
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<td>Autoantibodies to brain tissue</td>
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<tr>
<td>Abnormal brain or CSF biomarkers</td>
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<tr>
<td>Abnormal number of CD4 or CD8 cells</td>
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<tr>
<td>Alterations in MHC</td>
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<tr>
<td>Antibodies to foods</td>
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<td>Abnormalities in immunoglobulins</td>
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<td>Abnormalities in certain growth factors</td>
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<tr>
<td>Genetic mutations affecting immune function</td>
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<tr>
<td>Maternal antibodies to fetal brain tissue or lymphocytes</td>
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<td>Decreased Bcl-2 expression</td>
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<tr>
<td>Alterations in BDNF</td>
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<td>Microglial activation</td>
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<td>Abnormalities in natural killer cells</td>
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<td>Abnormal leptin levels</td>
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</tbody>
</table>

As of 2012 there were **127 published studies** demonstrating immune dysregulation in autism patients


Published studies demonstrate a correlation between autoimmune dysfunction and Autism Spectrum Disorder
Infection, Immune, Brain Connection to Neuropsychiatric Disorders

**Brain Function**
(Neurological and Neuropsychiatric symptoms)

**GENETIC PREDISPOSITION**

**Axis**

**IMMUNE SYSTEM DYSFUNCTION**

**Infectious/Non-Infectious Triggers**
(Enviornmental, bacteria, microbiome, viruses, parasites)

**Immune System**
(inflammation, microglia activation, cytokines, mast cell activation, autoimmune antibodies)
In 1894, Sir William Osler described “bizarre” and “perseverative behaviors” of children with “chorea minor,” and first made the relationship between obsessive-compulsive OCD symptoms and Sydenham’s chorea (SC).
Chorea: “Dance-like,” otherwise known as St. Vitus' dance
- abnormal movements
- Loss of fine-motor control
- Loss of emotional control

Group A Streptococcus-triggered (GAS) autoimmune reaction involving the brain

Sydenham Chorea is the neurological manifestation of Acute Rheumatic Fever
Molecular Mimicry Between Strep and Self-Antigens
Similar antigenic determinants between host and infecting microorganisms

Martin, W. J., Steer, A. C., Smeesters, P. R., Keeble, J., Inouye, M., Carapetis, J., & Wicks, I. P. (2015). Post-infectious group A streptococcal autoimmune syndromes and the heart. Autoimmunity Reviews, 14(8), 710-725
Molecular Mimicry is a Well-Established Mechanism of Autoimmune Dysfunction

Many conditions are believed to have mimicry at the core\(^{(1)}\)

<table>
<thead>
<tr>
<th>Neurologic or CNS Conditions</th>
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<tbody>
<tr>
<td>Guillain-Barré Syndrome</td>
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<td>Multiple Sclerosis</td>
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<td>Anti-NMDA Receptor Encephalitis</td>
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</table>

Guillain-Barré Syndrome occurs after a gut or respiratory infection and involves antibody attack on nerve tissue\(^{(2)}\)


Conditions Affecting Other Systems

<table>
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<tr>
<th>Conditions Affecting Other Systems</th>
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<tbody>
<tr>
<td>Lupus</td>
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<tr>
<td>Myocarditis</td>
<td>Crohn’s Disease</td>
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<tr>
<td>Lyme Arthritis</td>
<td>Type 1 Diabetes</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>Rheumatoid Arthritis</td>
</tr>
</tbody>
</table>

Inflammation and destruction of tissues and organs impacts over 100 million people afflicted with more than 80 different autoimmune diseases\(^{1}\)
Infection-Triggered Autoimmune Response through Molecular Mimicry*

Infection-Triggers that affect the CNS and other Systems

- Guillain-Barré Syndrome
  - Campylobacter jejuni
- Sydenham Chorea
  - Group A Streptococcus
- Systemic Lupus Erythematosus (Lupus)
  - Epstein-Barr virus (EBV nuclear antigen -1)
- Multiple Sclerosis
  - EBV, measles and HHV-6
- Myasthenia Gravis
  - Herpes Simplex Virus Type 1 (gpD)
- Cardiomyopathy (myocarditis)
  - Coxsackie virus, Group A Streptococcus
- Crohn’s Disease
  - Gram-positive bacterial peptidoglycans
- Diabetes Type 1
  - Coxsackie B virus, rubella, herpesvirus, rotavirus
- Psoriasis
  - Streptococcus pyogenes (Streptococcal M Protein)

PANDAS: Another Manifestation of Autoimmune Neurology-Based Syndrome

*Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection*

The Evolution of PANS Nomenclature and Hierarchy

1. Infection-Triggered
   - Bacterial, Viral, Parasitic, Fungal or possibly environmental?

2. Autoimmune
   - Immune dysfunction or Immune-mediated

3. Neuropsychiatric Syndrome or Symptoms
   - Multiple symptoms

4. Directed against portions of the brain
   - Basal ganglia

5. Acute-Onset
   - (Criteria for PANDAS/PANS but not observed in all conditions)

Estimated that 1 out of 150 to 200 children in the US have PANS/PANDAS

**PANDAS DIAGNOSIS CRITERIA**

Abrupt onset of OCD or severely restricted food intake and the presence of at least two of the following:

1. anxiety
2. emotional lability and/or depression
3. irritability, aggression, and/or severely oppositional behaviors
4. behavioral (developmental) regression
5. deterioration in school performance (related to attention deficit hyperactivity disorder ADHD-like symptoms, memory deficits, cognitive changes)
6. sensory or motor abnormalities
7. somatic signs and symptoms, including sleep disturbances, enuresis, or increased urinary frequency; or symptoms which could not be explained by another neurological or medical disorder such as Sydenham chorea

- Young age at onset
  - 6.5 +/- 3.0 years for tics
  - 7.4 +/- 2.7 years for OCD
- Boys out number girls 2.6 to 1
Symptoms found in National Institute of Mental Health Samples (NIMH)

Symptoms During Exacerbations

- Choreiform movements 95%
- Emotional lability 66%
- School changes 60%
- Personality changes 54%
- Bedtime fears 50%
- Fidgetiness 50%
- Separation fears 40%
- Sensory defensiveness 40%
- Irritability 40%
- Impulsivity and distraction 38%

Comorbid Diagnoses

- ADHD 40%
- ADD 40%
- Depression 36%
- Overanxious 28%
- Enuresis 20%
- Anorexia 17%
A Mechanism for Infection-Triggered Autoimmune Neuropsychiatric Disorders

1. **Microbial, Viral, Fungal Infection Occurs**

2. **Body Produces Antibodies That Recognize Infectious Agent**

3. **Antibodies Cross-React With Neurologic Receptors (molecular mimicry)**

4. **Reaction Disrupts Brain Function (friendly fire)**
CSF and Serum Autoantibody Binding to the Brain

Autoantibodies in CSF bind to Human Brain Caudate-Putamen in Children with Movement Disorders


Antibody-Mediated Neuronal Cell Signaling in Behavior and Movement Disorders

Christine A. Kirvan, Susan E. Swedo, Lisa A Snider, Madeline W. Cunningham

Sydenham Chorea Autoantibodies Bind and Stimulate calmodulin-dependent protein kinase (CaMKII)

Mimicry and Autoantibody-Mediated Neuronal Cell Signaling on Sydenham Chorea

Christine A. Kirvan, Susan E. Swedo, Janet S Heuser, Madeline W. Cunningham

d. PANDAS e. PANDAS f. Sydenham's Chorea

g. Control h. Control i. Control j. Control

SC mAb 24.3.1 Anti-ganglioside mAb (commercial) Isotype

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The Cunningham Panel™ Biomarker Components

The 5 biomarkers were originally identified from patients with Sydenham Chorea and PANDAS/PANS children

1) Anti-Dopamine D1
   Often positive with psychiatric symptoms including psychosis\(^1\)

2) Anti-Dopamine D2L
   Often positive with movement disorders and impulsivity\(^1\)

3) Anti-Lysoganglioside GM1
   Often positive with neuropathic symptoms including tics\(^1\)

4) Anti-Tubulin
   Often positive with cognitive complaints, OCD and brain fog\(^1\)

5) CaM KII Activity
   Often positive with involuntary movements and any symptom of adrenergic activation\(^1\)

Ref: (1) Reported by Dr. Amirm Katz base upon his 112 patients studied and our patient responses
Case Studies (>200 Similar Case Studies)

Case Study #1

24 y/o Male: Presenting symptoms: OCD, tics, decreased appetite with 30 pound weight loss, inability to concentrate, sensory abnormalities, emotional lability, behavioral regression, separation anxiety, et al.

Treatment: Patient treated with IVIG and plasmapheresis resulted in symptom reduction

Case Study #2

9 y/o Female: Obsessive-compulsive behaviors, verbal tics and “stimming”, inability to concentrate, sensory and motor abnormalities, emotional lability, behavioral regression, urinary and sleep problems, dysgraphia, and aggressiveness, Relapsing and remitting in nature

Treatment: Patient was treated with azithromycin with rapid improvement in symptoms
Case Studies (>200 Similar Case Studies)

Case Study #3

9 y/o Female: Presenting with unknown origin of neuropsychiatric symptoms. Lyme disease positive by Western Blot, Child said during a bout of strep, “Mom, something happened to my brain”

Treatment: azithromax, naproxen, omnicef, and Bactrim, Tindamax (anti parasitic) 3 IVIG treatments; complete symptom regression

Case Study #4

9 y/o Male: Presenting 30 days post confirmed strep infection with OCD, Tics, inability to concentrate, sensory abnormalities, emotional lability, separation anxiety, developmental regression, urinary frequency and urgency, sleep disturbance, dysgraphia, aggressiveness, choreiform movements, relapsing and remitting symptoms.

Treatment: Patient had IVIG within one month of diagnosis with complete symptom elimination.
Autoantibodies can act as:

**Agonist:** a substance which *initiates a physiological response* when combined with a receptor

**Antagonist:** a substance that *interferes with* or *inhibits* the physiological action of another
Gangliosides are lipid components of neuronal cell membranes and found in Myelin Sheath.
Test 4) Anti-Tubulin Biological Functions and Interruption in Function

In our clinical laboratory patient population, the most frequently reported symptoms occurring include (Total N= 552):

- OCD and cognitive impairment sometimes referred to as “brain fog” (82%).
- Symptoms inattentive, disengaged, “tuned out”, or they may struggle with concentration, memory and comprehension.
- Aggressive and/or rage behaviors have also been noted (50%), Patients also report sensory or motor abnormalities (74%), Emotional lability (73%), OCD (69%), Behavioral regression (69%), Sleep disturbances (69%), Tics (53%)

Autoantibodies against Tubulin

Tubulin gene mutations result in distinct and convergent phenotypes such as: Microcephaly, Basal Ganglia Defects, Dystonia, ALS, Autism

Test 5) Autoantibodies that stimulate CAMKII in Children with neuropsychiatric syndromes
Some Infectious Triggers that are Associated with PANDAS or PANS

- Group A streptococci
- Influenza A
- Varicella (chickenpox)
- Mycoplasma
- Lyme disease
- Babesia
- Bartonella
- Coxsackie virus

Patients often have more than one infection, and can be subclinical
Retrospective Case Study: Autoantibodies Correlation with Treatment/Symptom Resolution

Patients with Results From Two or More Cunningham Panels
April 22, 2013 to December 31, 2016
(n=206)

Pre and Post-Treatment Symptom Status Reported
(n=62)

Group 1: “Improved/Resolved”
Symptoms Improved or Resolved Upon Treatment
(n=37)

Group 2: “Not-Improved/Worsened”
Symptoms Failed to Improve or Worsened Upon Treatment
(n=25)

Included in Analysis
(n=62)
### Group 1: Patients who Improved/Resolved (n=37)

#### Pre-Treatment Results

<table>
<thead>
<tr>
<th>Case #</th>
<th>D1R</th>
<th>D2R</th>
<th>Tubulin</th>
<th>llysoganglioside G_{as1}</th>
<th>CaMKII</th>
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<tbody>
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<td>6</td>
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#### Post-Treatment Results

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<th>Tubulin</th>
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#### # of Positive Tests/Pt

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<th>Case #</th>
<th>Number of Elevated Markers</th>
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<th>Post Treatment</th>
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</table>

Portion of data in submitted manuscript under review
Group 2: Patients Not Improved/Worsened (n=25)

Pre-Treatment Results

No statistical differences between Group 1 and Group 2 in age or gender distribution

No statistical differences between Group 1 and Group 2 in the time between tests

Post-Treatment Results

# of Positive Tests/Pt

Portion of data in submitted manuscript under review
CaMKII Stimulation Assay Results

Group 1

- Pre: 153.8
- Post: 115.7
- Mean: 153.8
- SD: 38.2
- P-value: 0.000003

Group 2

- Pre: 148.4
- Post: 138.6
- Mean: 148.4
- SD: 33.0
- P-value: 0.229
Sensitivity & Specificity of the Cunningham Panel: Symptom Correlation to Positive Test Results

Sensitivity/Specificity Based Upon Positive Tests Compared to Symptoms

<table>
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<th>Panel Prediction</th>
<th>Symptoms Improved</th>
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</table>

- Sensitivity: 89%
- Specificity: 84%
- PPV: 89%
- NPV: 84%
- Accuracy: 87%

Receiver Operator Curve (ROC)
Change in Number Positive Tests

Portion of data in submitted manuscript under review
Sensitivity & Specificity of the Cunningham Panel: Symptom Correlation to Magnitude of Test Result Changes

Sensitivity/Specificity Based Upon Magnitude Change in Individual Test Values (LDA)

<table>
<thead>
<tr>
<th>Symptoms Improved</th>
<th>Sensitivity 92%</th>
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<tr>
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Specificity 88%

<table>
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<tr>
<th>Panel Prediction</th>
<th>PPV 92%</th>
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<tbody>
<tr>
<td>Yes</td>
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</tr>
<tr>
<td>No</td>
<td>88%</td>
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</tbody>
</table>

NPV

Accuracy 90%

Receiver Operator Curve (ROC)
Change in Magnitude of Test Results

AUC: 95.7% (90.0%–100.0%)

Portion of data in submitted manuscript under review
In 82 patients with Autism Spectrum Disorder (ASD), 49 patients had autoantibodies (60%). IVIG was completed for 36 of these patients (73%). Cunningham Panel predicted with accuracy (81% to 88%) those patients who improved and responded to IVIG therapy.

“The majority of the ASD patients who had autoantibodies demonstrated elevations in autoantibodies measured by the Cunningham panel along with an elevation in the activation of CaMKII.”

“The Cunningham panel predicted response to IVIG treatment with an accuracy of 81% with a sensitivity of 90% and a specificity of 67% based on the ABC scores; with an accuracy of 88% with a sensitivity of 100% and a specificity of 75% based on the SRS scores; and with an accuracy of 88% with a sensitivity of 100% and a specificity of 67% based on parental scores.”
A Cunningham panel was ordered, which measures anti-neuronal IgG antibodies (Cunningham panel) directed against dopamine 1 and 2 receptors, lysoganglioside-GM1, tubulin, and calcium/calmodulin-dependent protein kinase II (CaMKII). The results of this test revealed significant elevation of the first four antibodies and a borderline increase for CaMKII.

“A Cunningham panel was ordered, which measures anti-neuronal IgG antibodies (Cunningham panel) directed against dopamine 1 and 2 receptors, lysoganglioside-GM1, tubulin, and calcium/calmodulin-dependent protein kinase II (CaMKII). The results of this test revealed significant elevation of the first four antibodies and a borderline increase for CaMKII.”

- Cincinnati Children’s Hospital
- 15-year-old female who had been diagnosed and treated unsuccessfully for schizophrenia with psychosis, severe anxiety, and depression
- In and out of treatment facilities

“After one course of plasmapheresis was administered..., the patient had complete resolution of her psychotic, OCD, and anxiety symptoms. She was able to be weaned off olanzapine and resume many of her normal activities including tennis, within 2 weeks after plasmapheresis. This response has now been sustained for over six months consistent with previous studies”
The PANS Research Consortium (PRC) Published Clinical Management and Treatment Guidelines for PANDAS

General Treatment Categories Utilized for Infection-triggered Autoimmune Neuropsychiatric Disorders of the Brain

- Anti-microbials
- Steroids and NSAIDs
- Plasmapheresis (Plasma exchange)
- Intravenous Immunoglobulins (IVIG)
- Immune modulating medications
- Symptomatic Treatment
  - Cognitive Behavioral Therapy
  - Low Dose SSRIs

Effective allopathic, integrative or natural treatments also tend to fall into these categories.
SUMMARY: Autoimmune Neuropsychiatric Disorders are Treatable but Complex as they involve Multiple Systems

Adapted from Dr. Sidney Baker

Tack Law #1

- If you are sitting on a tack, the treatment is not two Advil every 3-4 hours
- The treatment for “tack sitting” is “tack removal”
- Search for the root and treat the cause rather than the symptoms

Tack Law #2

- If you are sitting on two tacks, removing one tack does not eliminate 50% of the symptoms
- Complex conditions are “complex”
- To be effective, address all the underlying issues for resolution

Correctly diagnosing the root cause for patients with neuropsychiatric symptoms is critical to prescribing the correct treatment
Common Symptoms

- Sensory Abnormalities
- Obsessions
- Tics
- Repetitive Behavior
- Hyperactivity
- Difficulty in School
- Anxiety
- Separation
- Irritability
- Bedwetting
- Aggression / Rage
- Sleep Disturbance
- Changes in Handwriting

Diagnostic Categories

- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
- Autism Spectrum Disorders
- Developmental & Behavioral Disorders
- Neuropsychiatric Disorders
- Asperger’s Syndrome
- Tourette’s Syndrome
- Attention Deficit Hyperactivity Disorder (ADD/ADHD)
- Chronic Depression
- Pervasive Developmental Delay (PDD)

Problem: Patients May be Labeled into Symptom-Based Categories Typically Deemed “Incurable”
Many Chronic Disorders can have a Patient Segment whose Cause is an Autoimmune Etiology

Distinctly different etiologies of disease can manifest identical symptoms but resolution is only possible with an understanding of the etiology.
The Cunningham Panel™ As an Aid in the Physician’s Diagnosis of PANDAS/PANS or Other Autoimmune Encephalopathies

Can be prescribed through doctors that work with AONM

1) Anti-Dopamine D1
Often positive with psychiatric symptoms including psychosis

2) Anti-Dopamine D2L
Often positive with movement disorders and impulsivity

3) Anti-Lysoganglioside GM1
Often positive with neuropathic symptoms including tics

4) Anti-Tubulin
Often positive with cognitive complaints, OCD and brain fog

5) CaM KII Activity
Often positive with involuntary movements and any symptom of adrenergic activation

Ref: (1) Reported by Dr. Amirm Katz base upon his 112 patients studied and our patient responses
Locate a Doctor Who is Open to Working with Patients Having Autoimmune Neurologic Disorders

Can be prescribed through doctors who work with AONM

Keys to Change

1. Increase awareness of autoimmune neurological disorders
2. More education about these biology of these conditions
3. More research and clinical studies to better identify the etiology and discover more efficacious and targeted treatments
4. Perseverance!
Neuroinflammation, Autoimmunity and the Brain

Linking infection to "mental" illness, as strep antibodies are linked to the neurological Tourette's syndrome, has been rejected by many doctors since the rise of psychoanalysis, but Maloney insisted Sammy be tested for strep titers when he became unable to attend school and to walk. He was diagnosed with PANDAS. Antibiotics ended two torturous years for the family, and Sammy’s regains came as rapidly as the symptoms had overtaken him.

Susannah Cahalan is a news reporter at the New York Post who succumbed to an infection then began a painful journey to be diagnosed with an autoimmune disorder attacking her brain, and then the path to recovery after receiving the right treatment.

Dr. Bullmore is Co-Chair of Cambridge Neuroscience, Scientific Director of the Wolfson Brain Imaging Centre, and Head of the Department of Psychiatry at Cambridge University.

DVD: Documentary chronicling several families and their children suffering from PANDAS and what they went through to reach a diagnosis and begin recovery.
Our Mission is to Help Change How Medicine is Practiced for Neuropsychiatric Disorders

Thank you for helping those suffering with this disorder, to gain hope and get well!

For More Information Contact:
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shimasakic@moleculera.com
www.MoleculeraLabs.com
U.S. +1(405) 239-5250
Grace’s Story – One of Thousands we Have Tested

Grace was diagnosed with ADHD, Oppositional Defiant Disorder, and other childhood mental disorders.
We have been informed that Moleculera Labs recommend Red Top glass tubes when collecting blood for the Cunningham panel. In our study... we have used serum sampling tubes (BD Vacutainer® SST™ II Advance tubes, Gold Top) but erroneously reported sampling in “serum sampling tube (BD Vacutainer, yellow top)”... **The use of another blood collection tube than the one recommended by Moleculera could be viewed as a limitation in our study.**

Although our findings identified a moderate correlation between change in CaMKII and change in symptom severity in individuals with PANS or PANDAS, there was no indication that the Cunningham Panel can be used to diagnose PANS or PANDAS. Our results also suggest that **test-retest reliability of CaMKII may be insufficient, and that Cunningham Panel results are commonly elevated in healthy controls.**
Invalid Blood Collection Tube

- Polymer Gel for serum separation
- **Interferes with assay results**

Only validated Blood Collection Tube

- No Polymer Gel

---

**Swedish Study Conclusions of Cunningham Panel**

1. “…test-retest reliability of CaMKII may be insufficient”

2. “…results are commonly elevated in healthy controls”
Seven patient samples collected in validated glass tubes with no additives (Red Top glass tubes) tested at **random intervals** over a period of **several months for 344 individual tests**. We observed 62 readings at one dilution higher, 207 readings at the most commonly observed dilution, and 75 readings at one dilution lower.
Multiple Test-retesting of samples collected in Red Top Glass Tubes (No additives)

- First test on the X axis
- Repeat test on the Y axis
- R=0.90299
Normal ranges based upon 50 pediatric patients

- No Lifetime history of neuropsychiatric disorders
- No first degree relative with neuropsychiatric disorders
- No patient history of autoimmune diseases
- No active infections or symptoms
What is the Controversy?

Defining, Diagnosing and Treating a Cross-disciplinary Multi-symptom Neuropsychiatric Disorder

1. **PANDAS**
   - Association with Group A Streptococcus (GAS) but most all children get Strep

2. **Heterogeneous symptoms**
   - Patients present with multiple, and often different neurological and psychiatric symptoms

3. **Crosses multiple medical specialties**
   - Infectious Disease, Immunology/Rheumatology, Neurology, Psychiatry

4. **A clinically-defined disorder without identifying biological markers**
   - based upon symptoms and often a diagnosis of exclusion
Anti-Streptolysin O Titers and OCD Symptom Severity (Y-BOCS)

Credits: Dr. Susan Swedo
Other Recognized Anti-Neuronal Antibodies Account for a Portion of Autoimmune Encephalitis

A patient population unable to be identified by current autoantibodies

Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis

Figure 1  Antibody status of patients with AE

Antibodies against synaptic receptor, ion channel, or other cell surface proteins
- NMDAR
- VGKCc
- LGI1
- Aquaporin 4

Antibodies against intracellular antigens
- GAD65
- Ma2/Ta
- Hu (ANNA-1)
- CV2/CRMP5

Antibodies against other neuronal or muscle antigens
- AChR
- Striational
- Antibody negative
Our Mission is to Help Change How Medicine is Practiced for Neuropsychiatric Disorders

We are here to help provide some answers!

For more information contact:
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Email: cunninghampanel@aonm.org
Phone: 0044 3331 210 305