Autoimmune Encephalopathies: PANDAS/PANS and Antineuronal Antibody Testing

Academy of Nutritional Medicine (AONM)
March 26, 2019

Craig Shimasaki, PhD, MBA
Co-founder & CEO,
Moleculera Labs

Topics We will Cover

1. **Autoimmune Neurology-based Disorders**
   - (Re) emergence of medical and clinical relevance
   - The role of ***molecular mimicry*** in triggering these disorders

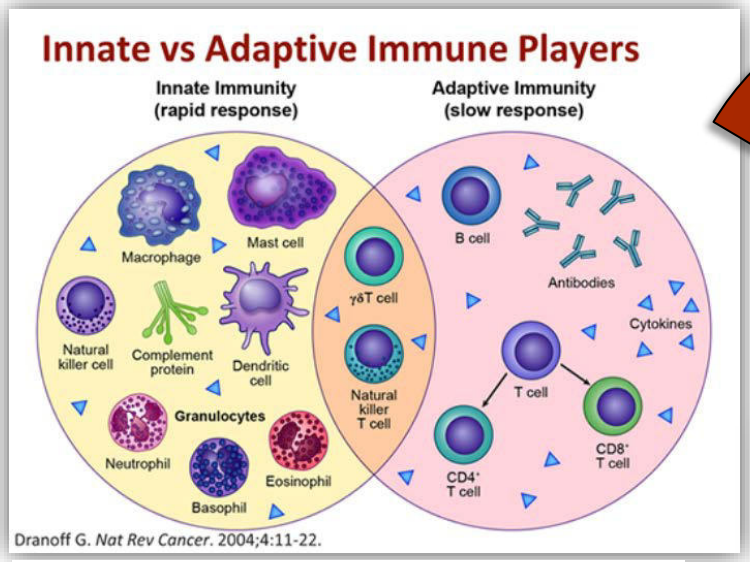
2. **Definition and Clinical Presentation of Autoimmune Encephalopathies**
   - ***PANDAS/PANS*** nomenclature and alternative nomenclature
   - Proposed mechanism for these conditions
   - Some common infectious triggers

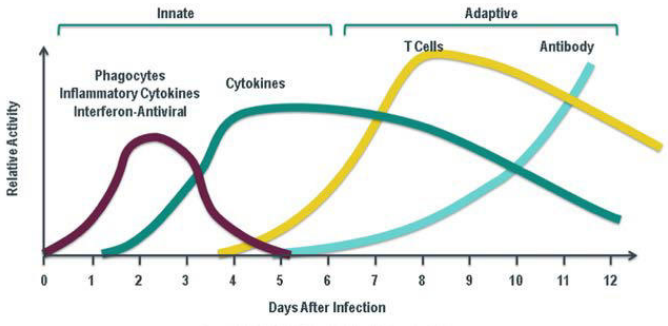
3. **Anti-neuronal Antibody Targets in the Cunningham Panel**
   - Why these biomarkers were selected
   - Patient case studies
   - Patient population study

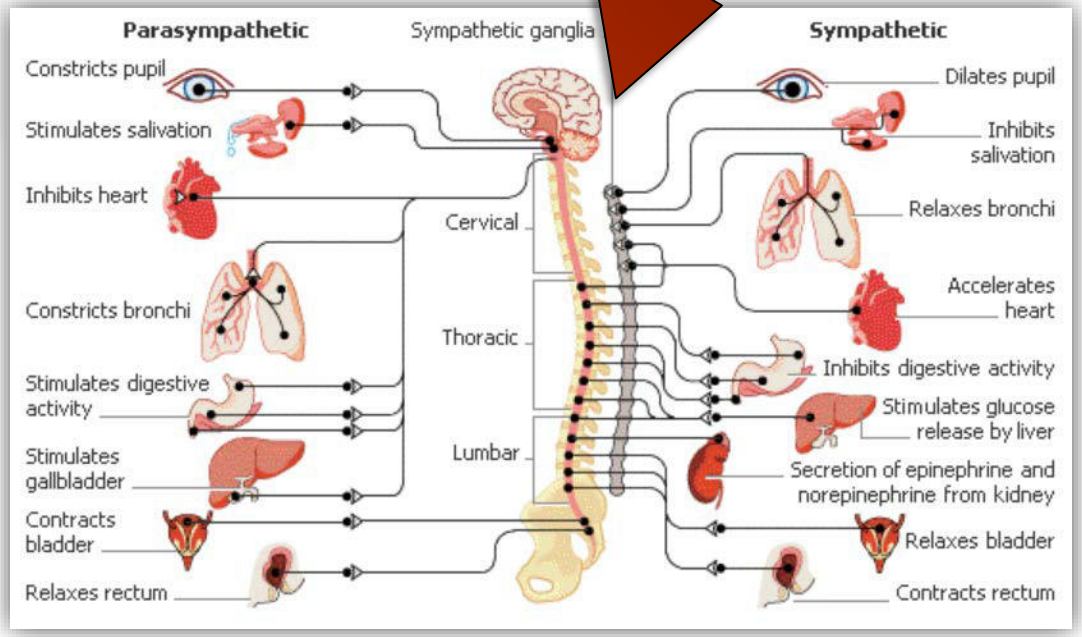
4. **Summary**

Autoimmune Neurology

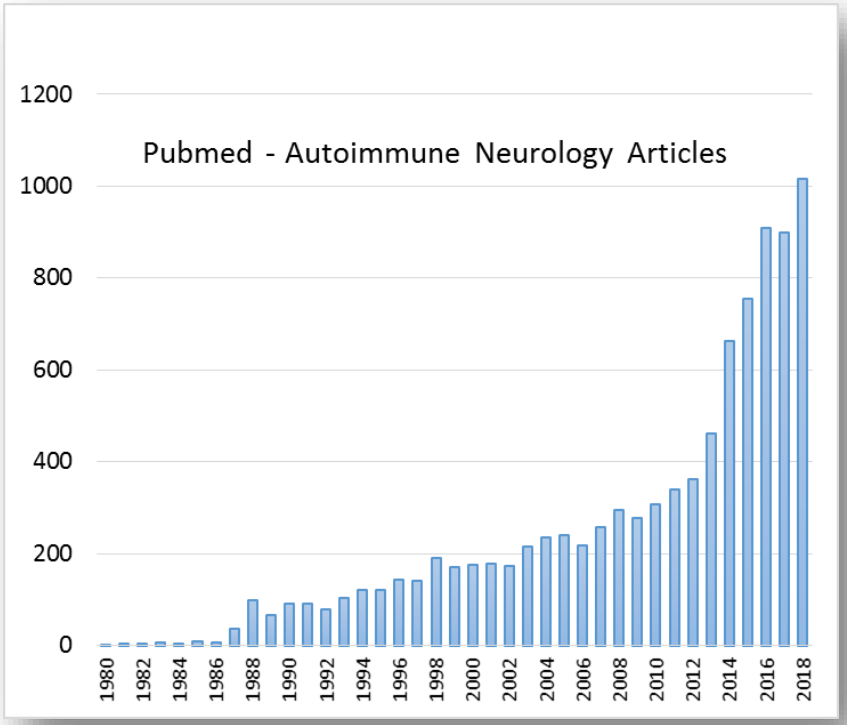
The interaction between: Immune System + Nervous System (brain)







Autoimmune Neurology



- **Autoimmune Neurology**
- **Neuroimmunology**
- **Neuroinflammatory Disorders**

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)*

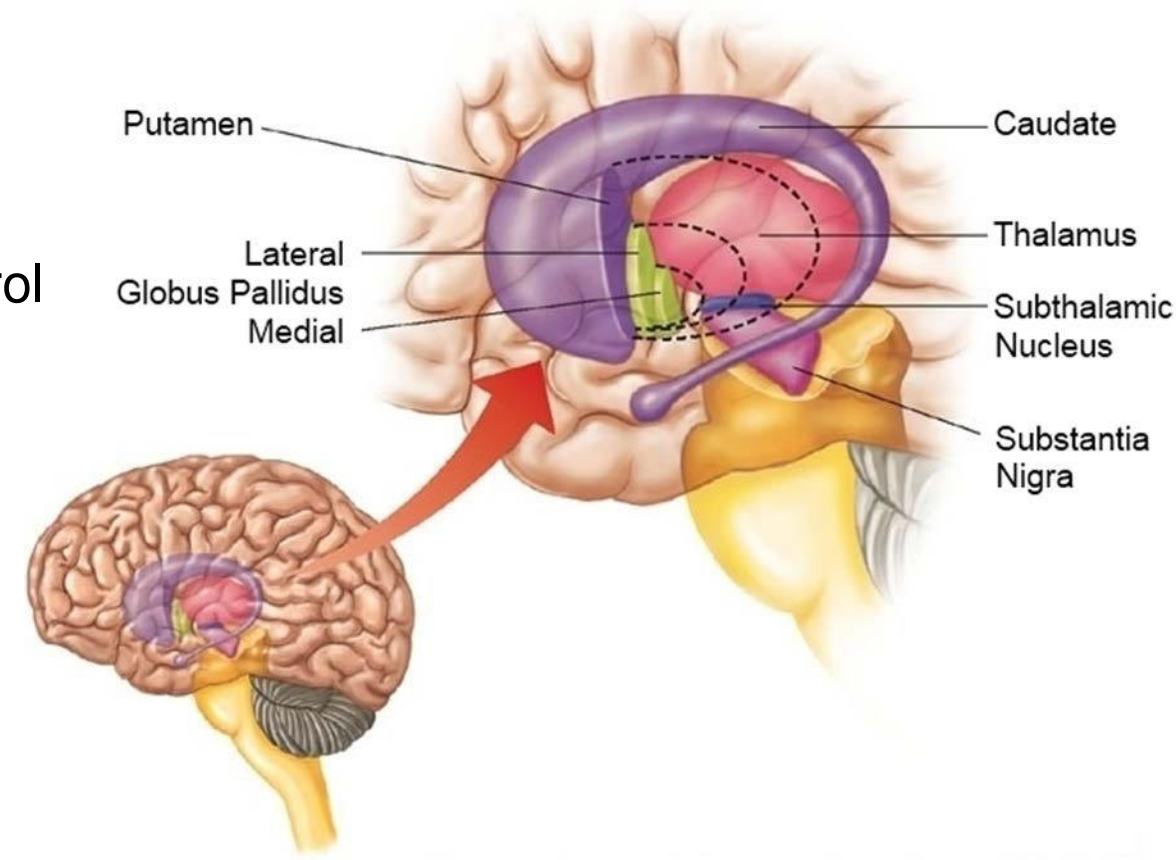
Autoimmune Encephalopathies

- *NMDA receptor encephalitis*
- *VGKC*
- *GABA*
- *PANDAS/PANS*

Autoimmune Disorders Involving the Basal Ganglia

Basal 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)**

Population-based Studies Linking Infection, the Immune System and Mental Illness

Danish study of ~4,500 individuals revealed a relationship between inflammatory markers and neuropsychiatric disorders[2]

Patients with elevated Interleukin-6 (IL-6) were more likely to be depressed at age 18 years	+55%
Higher IL-6 baseline levels increased the risks of psychotic experiences and psychotic disorder at age 18	+81%

Danish study of 3.6 million individuals revealed an increased risk of mental illness associated with infections[1]

History of hospitalization for infection increased the risk of mood disorders (bipolar affective disorder or depression)	+62%
Hospitalization for autoimmune disease increased the risk of a mood disorder diagnosis	+45%
The two risk factors together increased the risk of subsequent mood disorders	+135%

1. "Autoimmune Diseases and Severe Infections as Risk Factors for Mood Disorders" JAMA Psychiatry. 2013;70(8):812-820
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*

References	Study population, no.	Reporting	Association with ASD?	Autoimmune diseases and immune dysfunction
Comi et al.[5] (1999)	107	Self-report	Yes	Rheumatoid arthritis (mat); general autoimmunity (mat, pat)
Sweeten et al.[6] (2003)	303	Self-report	Yes	Hypothyroidism and Hashimoto's thyroiditis (mat, pat); rheumatic fever (mat, pat)
Micali et al.[7] (2004)	140	Self-report	No	—
Croen et al.[3] (2005)	2,520	Medical records	Yes	Psoriasis (mat), asthma and allergies
Molloy et al.[8] (2006)	308	Self-report	Yes	Autoimmune thyroid disease (mat, pat)*
Mouridsen et al.[9] (2007)	441	Medical records	Yes	Ulcerative colitis (mat); type 1 diabetes
Valicenti-McDermott et al.[10] (2008)	100	Self-report	Yes	Rheumatoid arthritis (mat)†; celiac disease (mat)†
Atladóttir et al.[2] (2009)	689,196	Medical records	Yes	Rheumatoid arthritis (mat); celiac disease (mat); type 1 diabetes (mat, pat)

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.

Ref: Mol Psychiatry. 2012 Apr; 17(4): 389–401 "A Review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, etc." DA Rossignol and RE Frye

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

Abnormality	*Number of studies*
Cytokine abnormalities	30
Autoantibodies to brain tissue	23
Abnormal brain or CSF biomarkers	20
Abnormal number of CD4 or CD8 cells	16
Alterations in MHC	15
Antibodies to foods	12
Abnormalities in immunoglobulins	11
Abnormalities in certain growth factors	9
Genetic mutations affecting immune function	7
Maternal antibodies to fetal brain tissue or lymphocytes	7
Decreased Bcl-2 expression	6
Alterations in BDNF	6
Microglial activation	3
Abnormalities in natural killer cells	3
Abnormal leptin levels	2

Abbreviations: ASD, autism spectrum disorders; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; MHC, major histocompatibility complex.

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

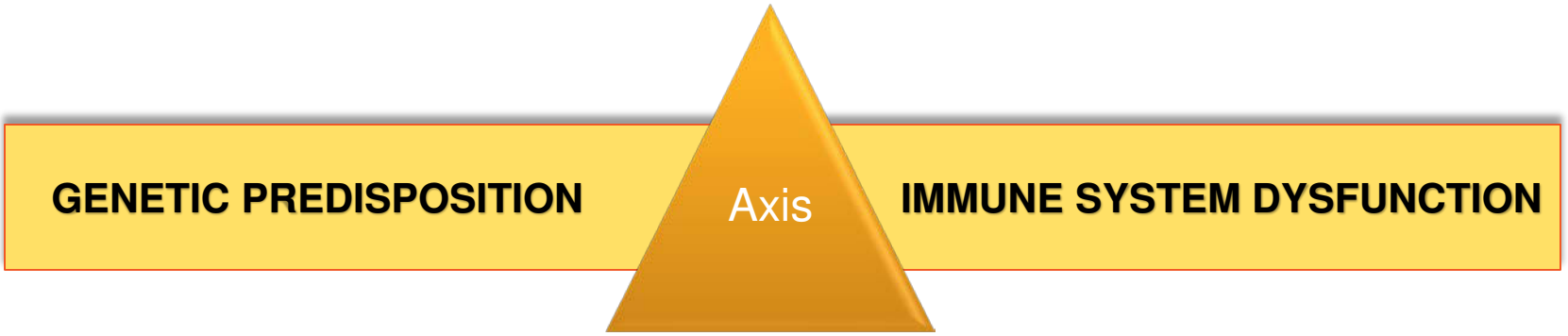
Ref: Mol Psychiatry. 2012 Apr; 17(4): 389–401 "A Review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, etc." DA Rossignol and RE Frye

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)



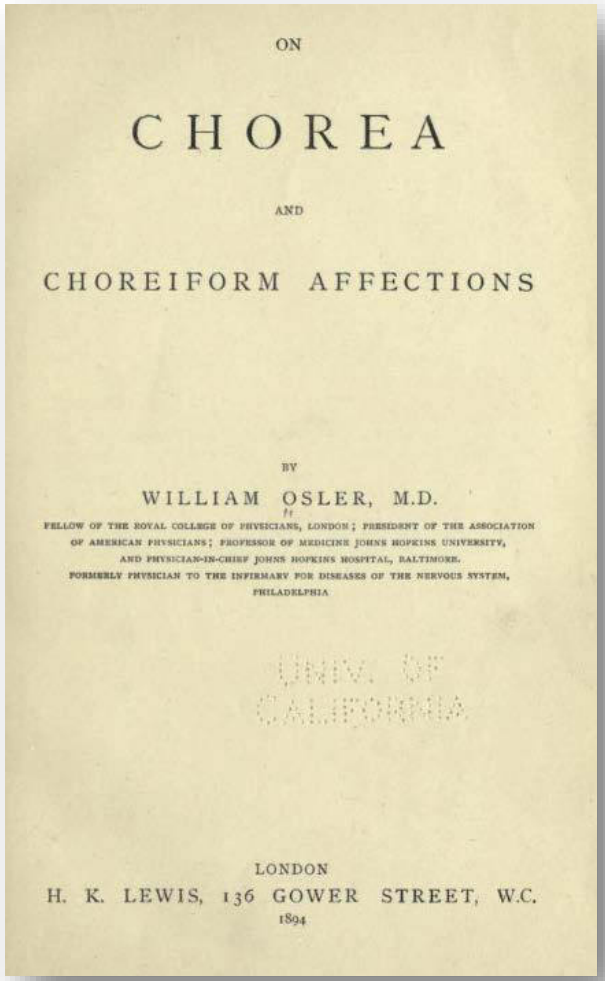
Infectious/Non-Infectious Triggers

(Environmental, bacteria, microbiome, viruses, parasites)

Immune System

(inflammation, microglia activation, cytokines, mast cell activation, autoimmune antibodies)

History of Infection-Triggered Neuropsychiatric Disorder



ON

CHOREA

AND

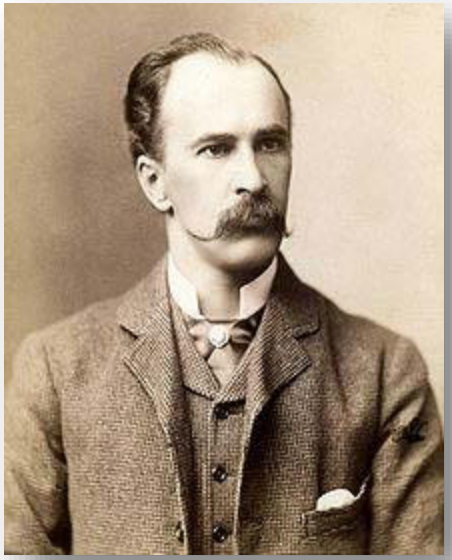
CHOREIFORM AFFECTIONS

BY

WILLIAM OSLER, M.D.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON; PRESIDENT OF THE ASSOCIATION OF AMERICAN PHYSICIANS; PROFESSOR OF MEDICINE JOHNS HOPKINS UNIVERSITY, AND PHYSICIAN-IN-CHIEF JOHNS HOPKINS HOSPITAL, BALTIMORE. FORMERLY PHYSICIAN TO THE INFIRMARY FOR DISEASES OF THE NERVOUS SYSTEM, PHILADELPHIA

LONDON
H. K. LEWIS, 136 GOWER STREET, W.C.
1894



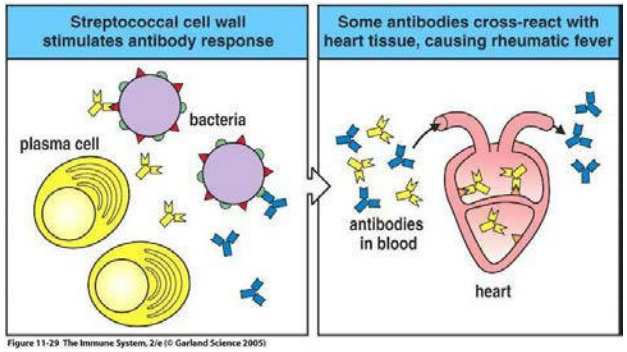
In 1894, Sir William Osler described ***"bizarre"*** and ***"perseverative behaviors"*** of children with ***"chorea minor,"*** and first made the relationship between obsessive-compulsive OCD symptoms and Sydenham's chorea (SC)

Sydenham Chorea is a Medical Model for Other Autoimmune Neuropsychiatric Disorders

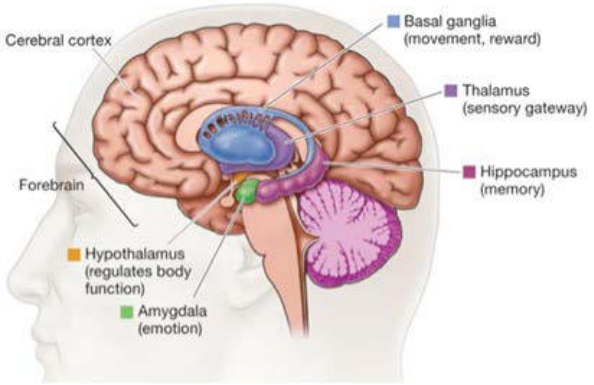
Chorea: "Dance-like," otherwise known as St. Vitus' dance"

- **abnormal movements**
- **Loss of fine-motor control**
- **Loss of emotional control**

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

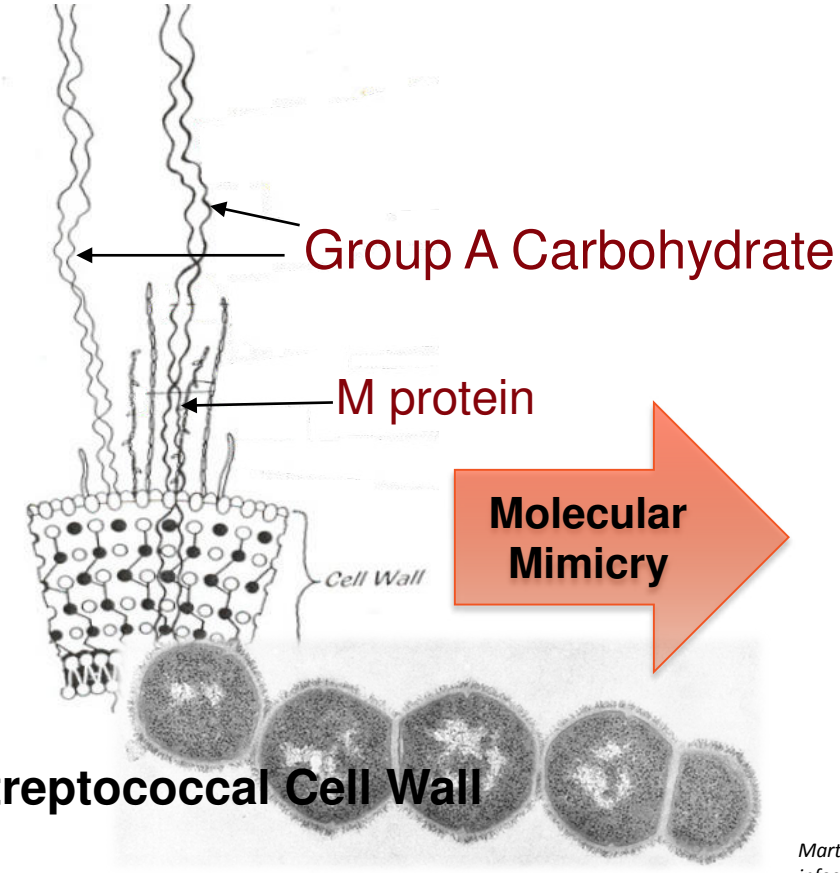


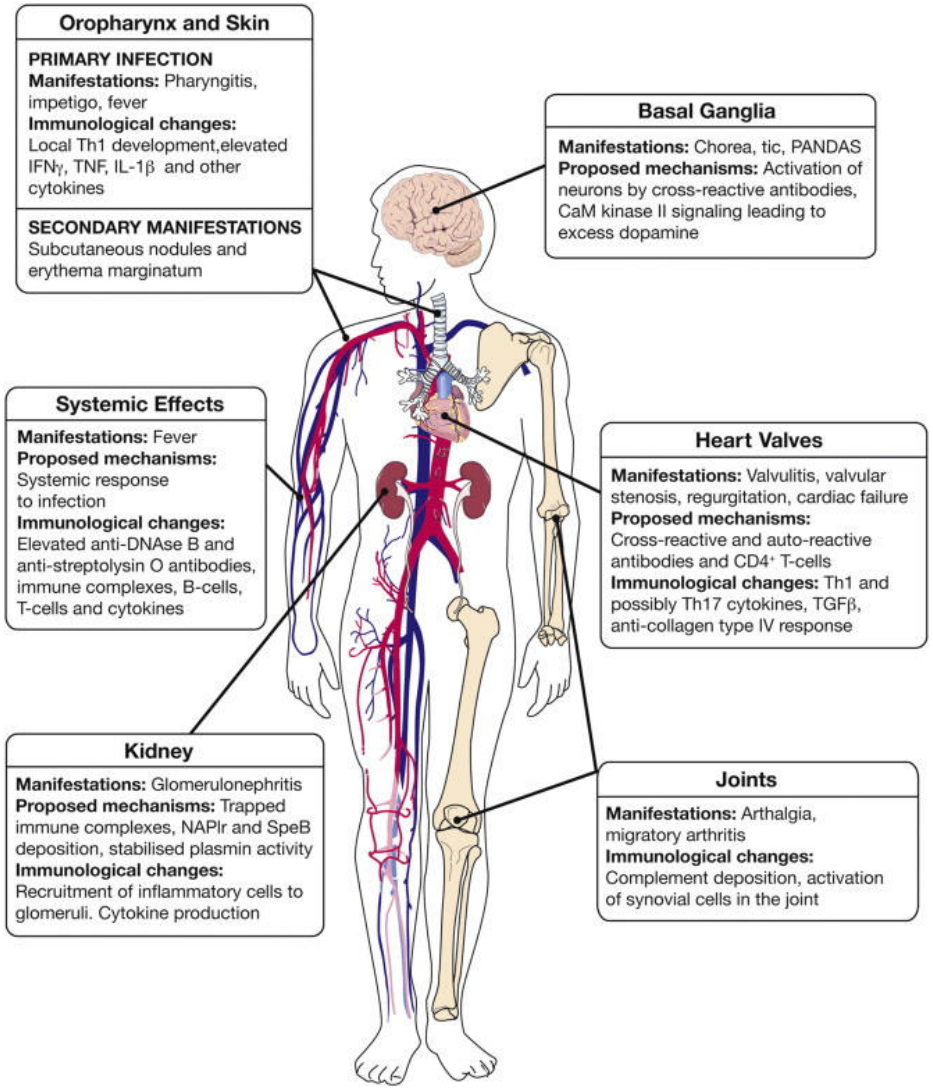
Sydenham Chorea is the neurological manifestation of Acute Rheumatic Fever



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

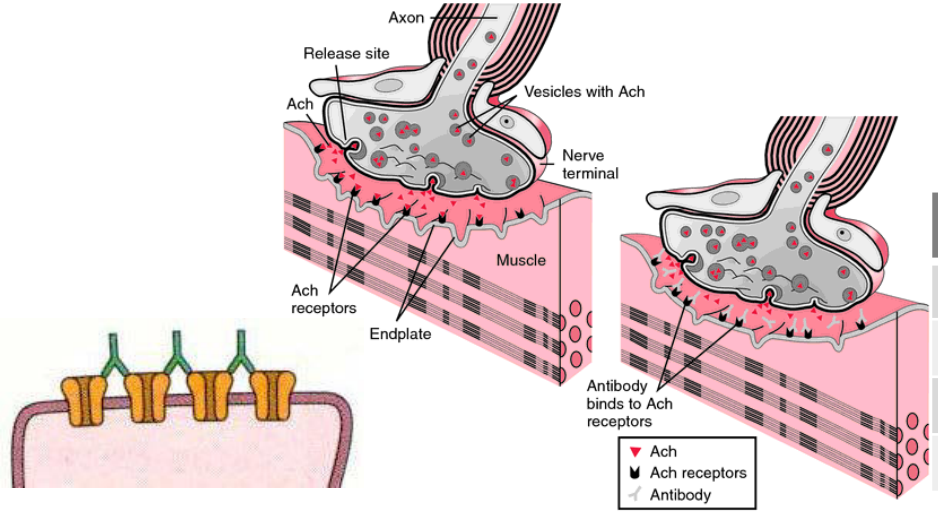
Molecular Mimicry is a Well-Established Mechanism of Autoimmune Dysfunction

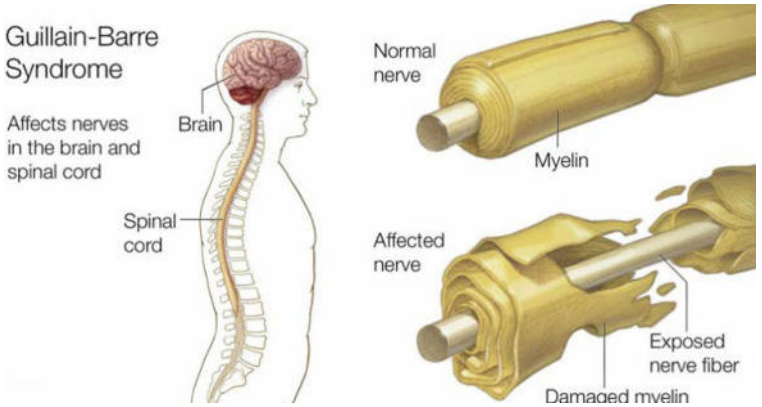
Many conditions are believed to have mimicry at the core(1)

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

Neurologic or CNS Conditions

Guillain-Barré Syndrome	**Sydenham Chorea**
Multiple Sclerosis	**Myasthenia Gravis**
Anti-NMDA Receptor Encephalitis	**Schizophrenia and Portions of Autism**





1. Ref: *M.F. Cusick, et. al., Clin Rev Allergy Immunol. 2012 February, 42(1): 102-111

Conditions Affecting Other Systems

Lupus	**Rheumatic Fever**
Myocarditis	**Crohn's Disease**
Lyme Arthritis	**Type 1 Diabetes**
Inflammatory Bowel Disease	**Rheumatoid Arthritis**

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)

**M.F. Cusick, et. al., Clin Rev Allergy Immunol. 2012 February, 42(1): 102-111*

PANDAS: Another Manifestation of Autoimmune Neurology-Based Syndrome

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections: Clinical Description of the First 50 Cases

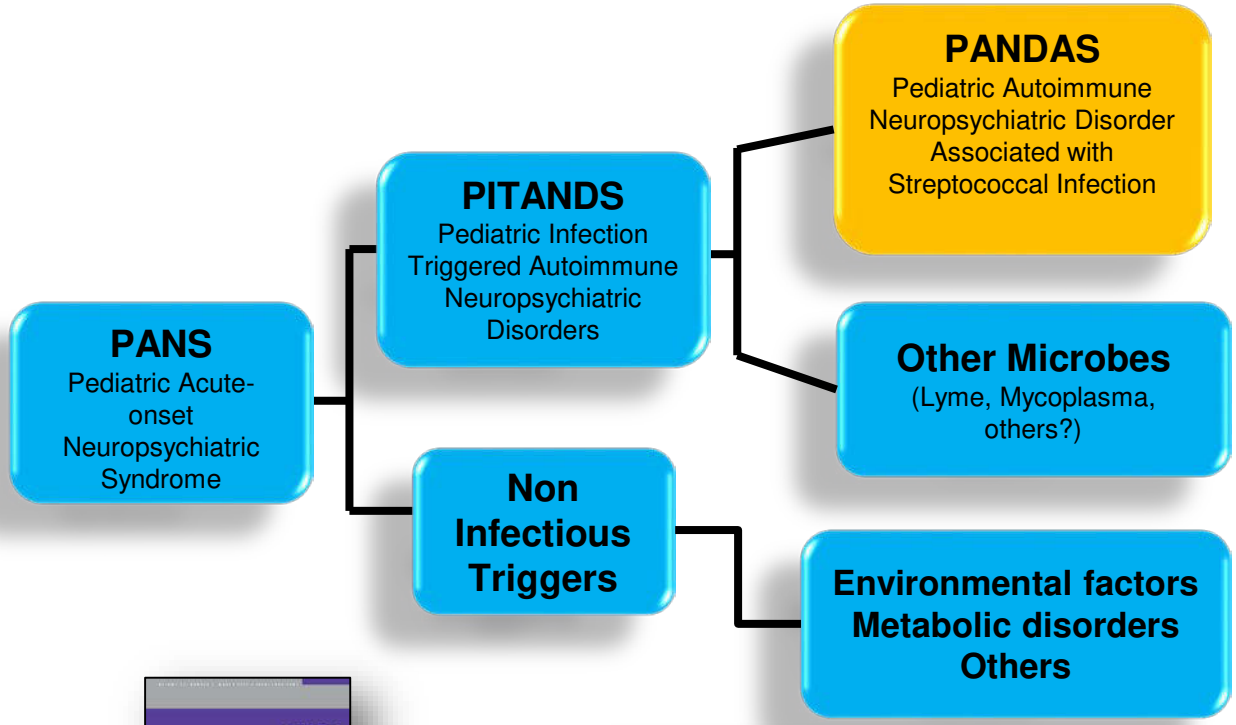
Susan E. Swedo, M.D., Henrietta L. Leonard, M.D., Marjorie Garvey, M.D., Barbara Mittleman, M.D., Albert J. Allen, M.D., Ph.D., Susan Perlmutter, M.D., Lorraine Lougee, L.C.S.W., Sara Dow, B.A., Jason Zamkoff, B.A., and Billinda K. Dubbert, M.S.N.

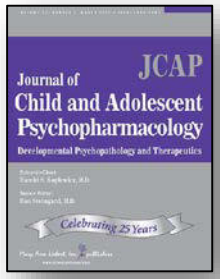
(1998) Am J Psychiatry **155**(2): 264-271.

THE AMERICAN JOURNAL OF PSYCHIATRY

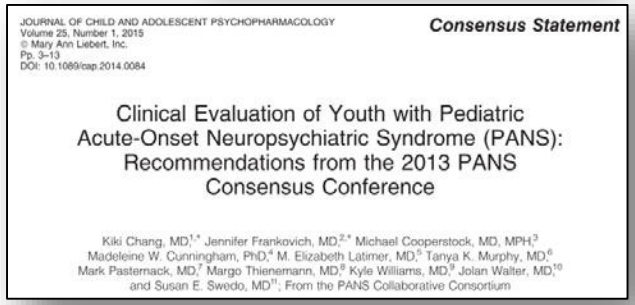
The Evolution of PANS Nomenclature and Hierarchy

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)





2015 Chang, K. et al. J Child Adolesc Psychopharmacol **25**(1): 3-13.


JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015
© Mary Ann Liebert, Inc.
Pp. 3–13
DOI: 10.1089/cap.2014.0084

Consensus Statement

Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference

Kiki Chang, MD,[1,*] Jennifer Frankovich, MD,[2,*] Michael Cooperstock, MD, MPH,[3] Madeleine W. Cunningham, PhD,[4] M. Elizabeth Latimer, MD,[5] Tanya K. Murphy, MD,[6] Mark Pasternack, MD,[7] Margo Thienemann, MD,[8] Kyle Williams, MD,[9] Jolan Walter, MD,[10] and Susan E. Swedo, MD[11]; From the PANS Collaborative Consortium

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

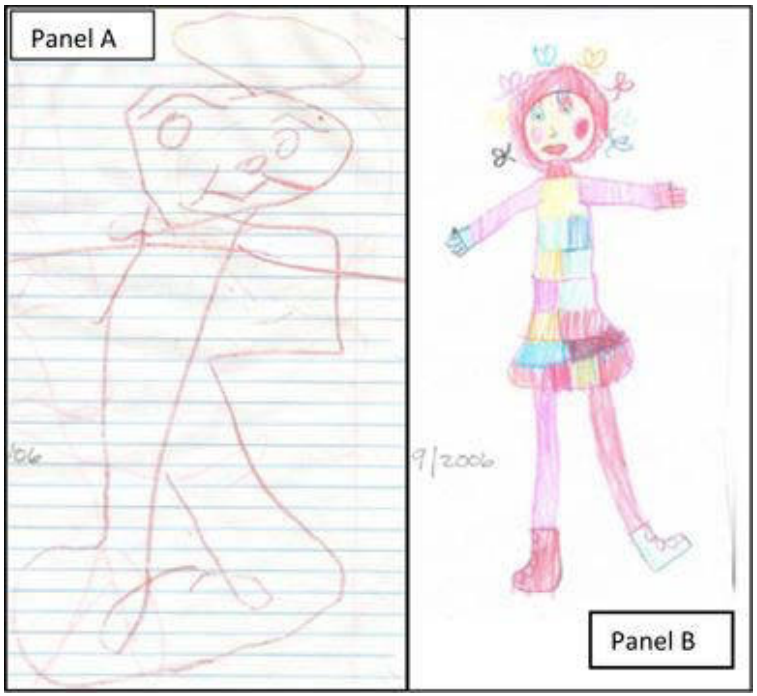
(3) irritability, aggression, and/or severely oppositional behaviors

(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%
- Separation anxiety 20%
- Overanxious 28%
- Enuresis 20%
- Anorexia 17%

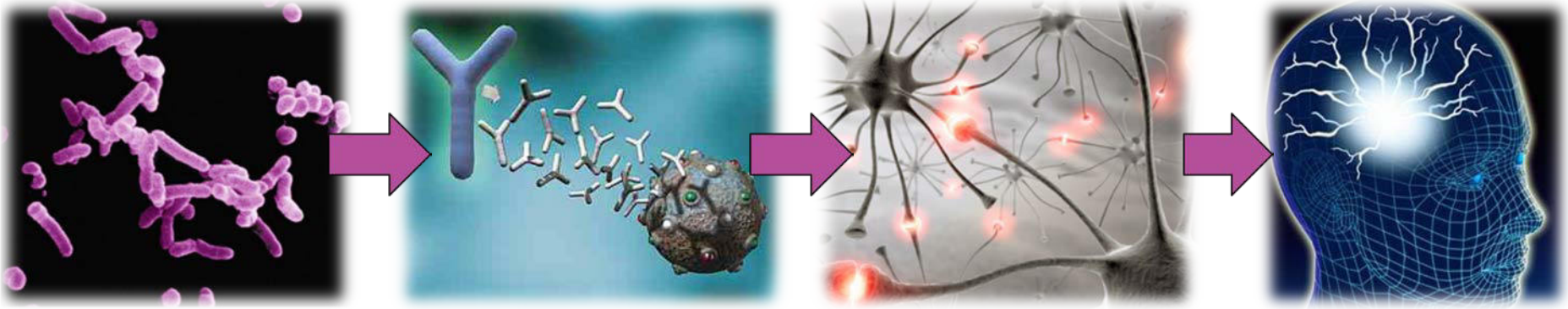
A Mechanism for Infection-Triggered Autoimmune Neuropsychiatric Disorders

Microbial, Viral, Fungal Infection Occurs

Body Produces Antibodies That Recognize Infectious Agent

Antibodies Cross-React With Neurologic Receptors (molecular mimicry)

Reaction Disrupts Brain Function (friendly fire)



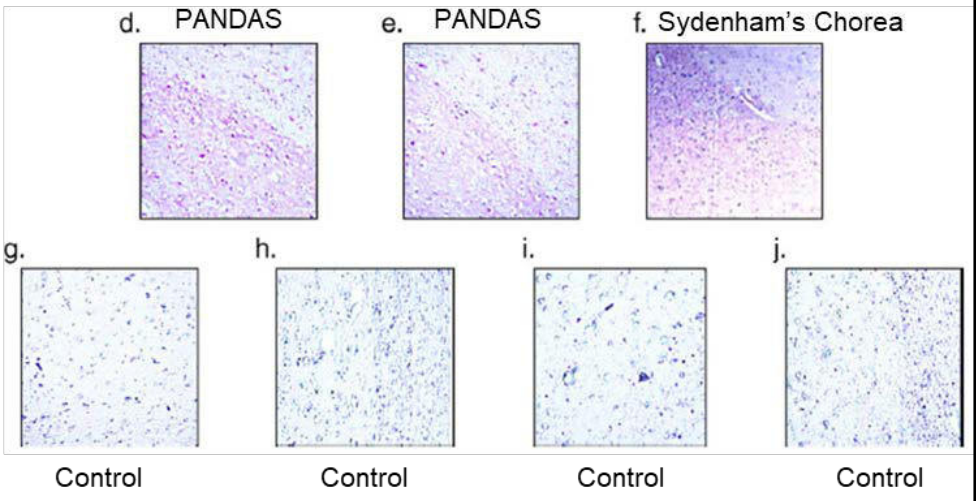
CSF and Serum Autoantibody Binding to the Brain

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

Journal of Neuroimmunology 2006 Oct;179(1-2):173-9

Antibody-Mediated Neuronal Cell Signaling in Behavior and Movement Disorders

Christine A. Kirvan[a], Susan E. Swedo[b], Lisa A Snider[b], Madeline W. Cunningham

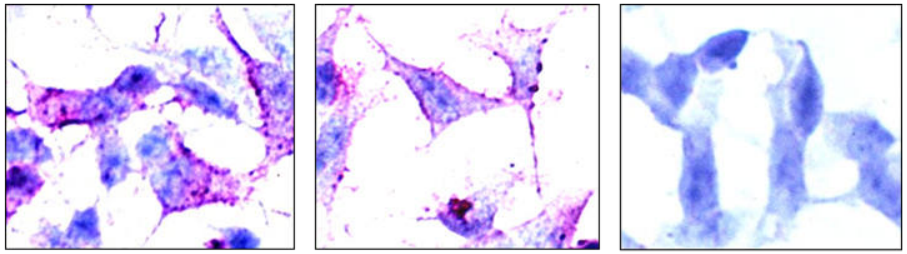


Sydenham Chorea Autoantibodies Bind and Stimulate calmodulin-dependent protein kinase (CaMKII)

nature medicine

Mimicry and Autoantibody-Mediated Neuronal Cell Signaling on Sydenham Chorea

Christine A. Kirvan[1], Susan E. Swedo[2], Janet S Heuser[1], Madeline W. Cunningham[1]

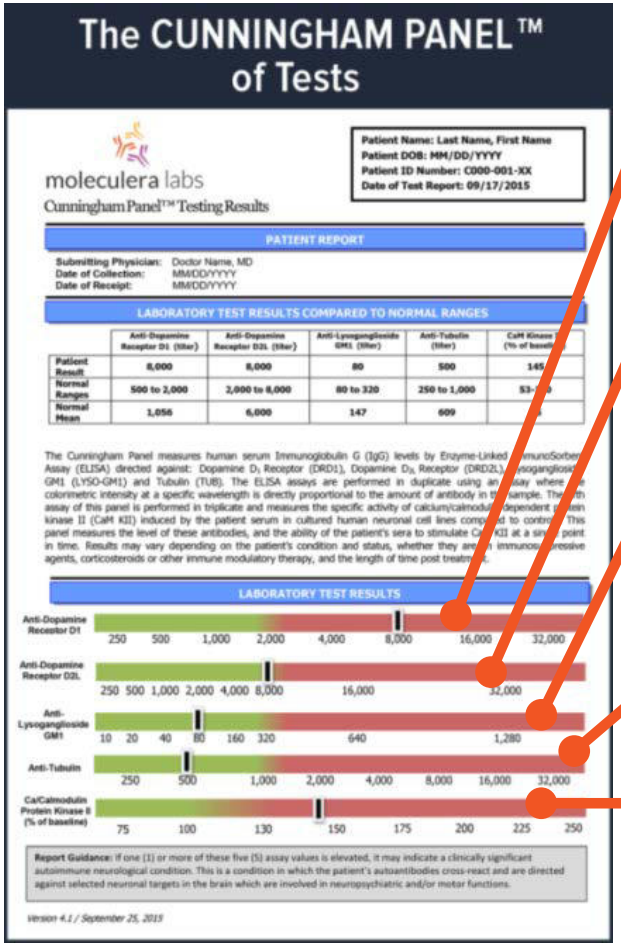


SC mAb 24.3.1 | Anti- ganglioside mAb (commercial) | Isotype

VOLUME 9 | NUMBER 7 | JULY 2003 NATURE MEDICINE

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

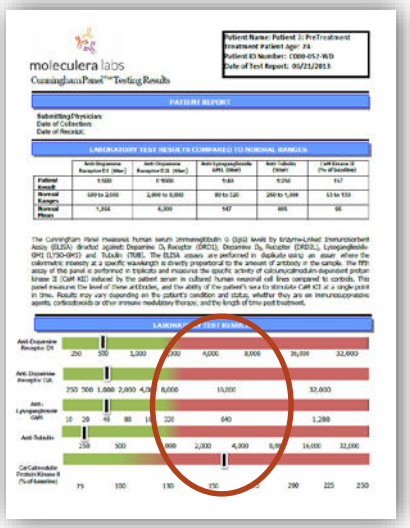
Often positive with involuntary movements and any symptom of adrenergic activation (1)

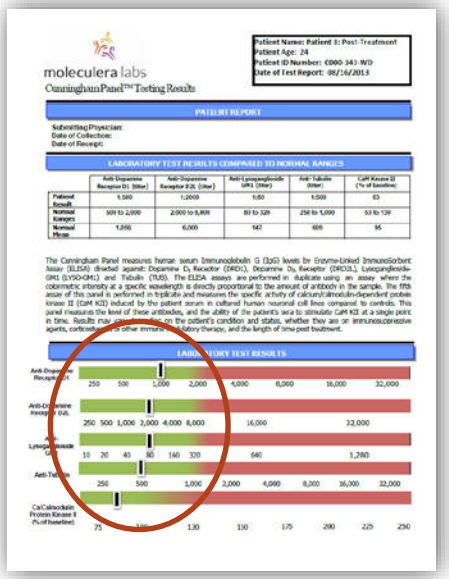
Ref: (1) Reported by Dr. Amirm Katz base upon his 112 patients studied and our patient responses

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.

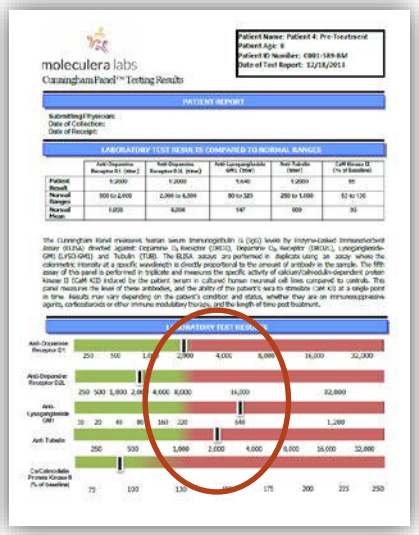


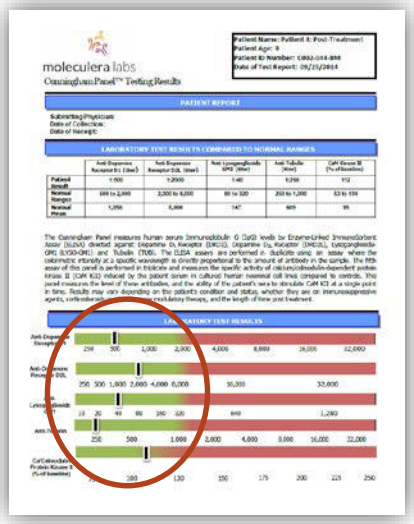


Treatment: Patient treated with IVIG and plasmapheresis resulted in symptom reduction

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



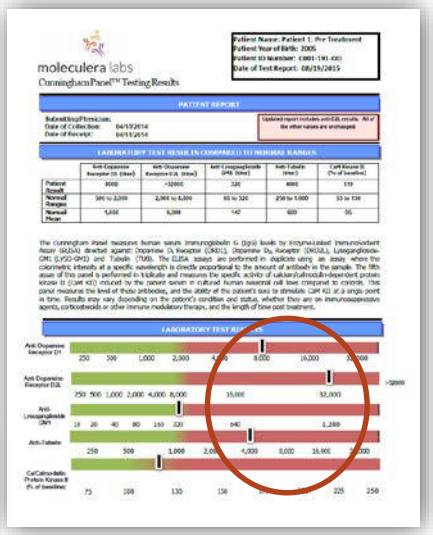


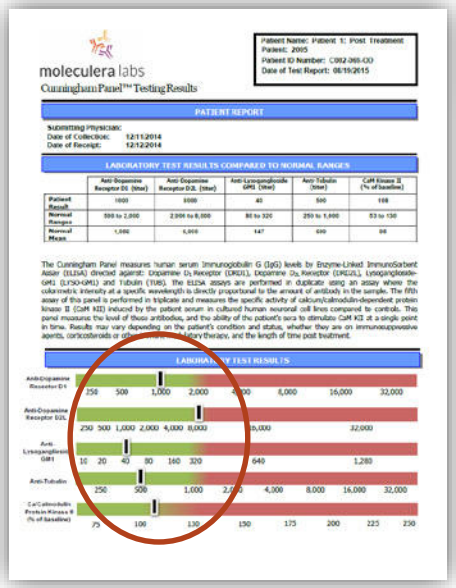
Treatment: Patient was treated with azithromycin with rapid improvement in symptoms

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"***

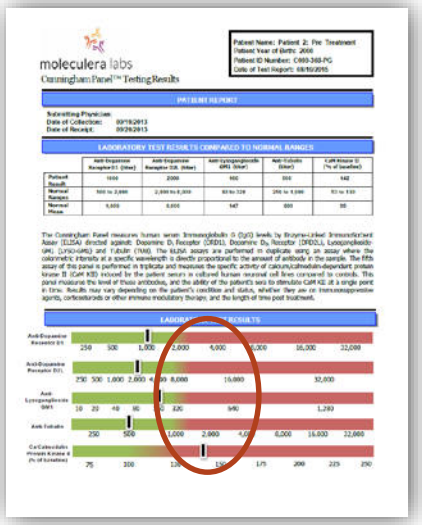

moleculera labs
Cunningham Panel™ Testing Results

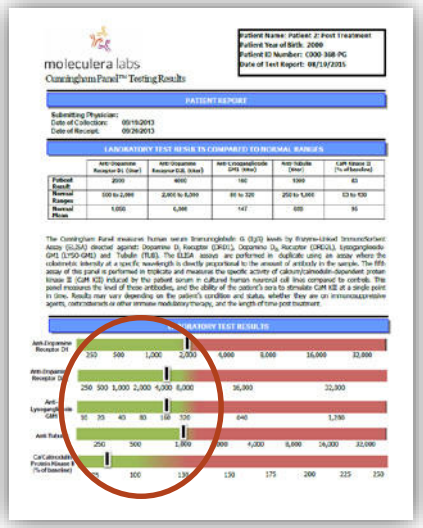

moleculera labs
Cunningham Panel™ Testing Results

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

Case Study #4

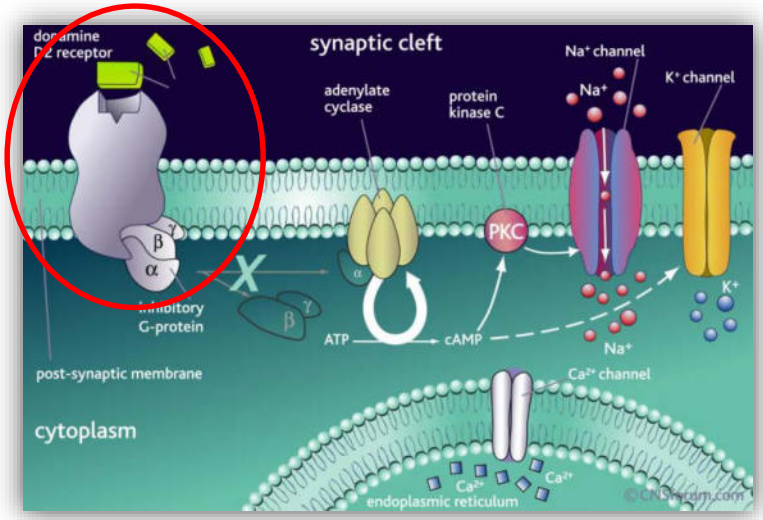
9 y/o Male: Presenting 30 days post confirmed strep infection with OCD, Tics, inability to concentrate, sensory abnormalities, emotional lability, separation anxiety, developmental regression, urinary frequency and urgency, sleep disturbance, dysgraphia, aggressiveness, choreiform movements, relapsing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

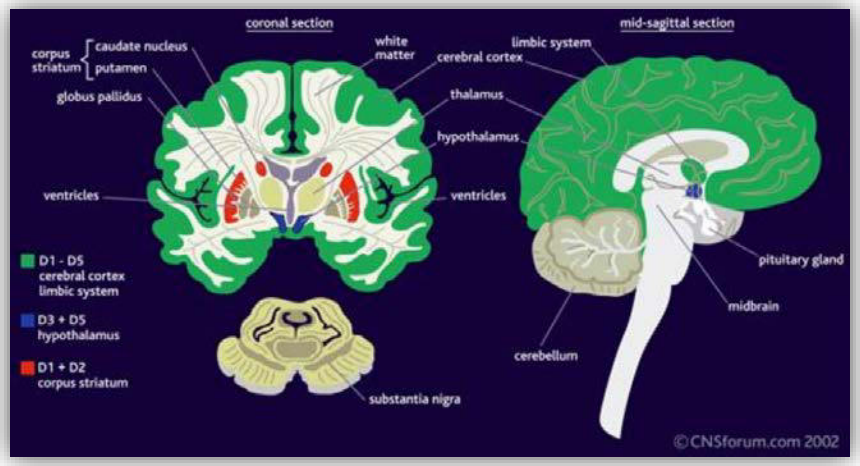

moleculera labs
Cunningham Panel™ Testing Results

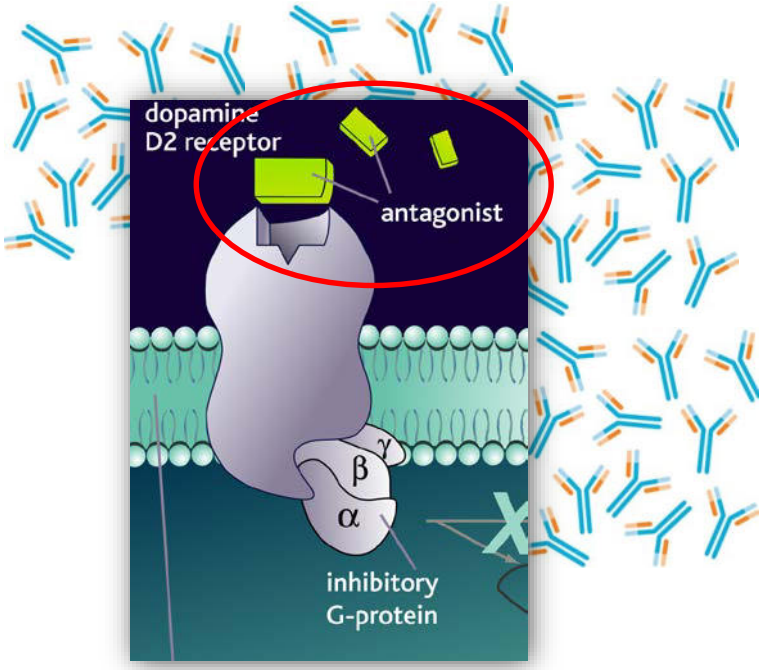

moleculera labs
Cunningham Panel™ Testing Results

Treatment: Patient had IVIG within one month of diagnosis with complete symptom elimination.

Test 1 and 2) Anti-Human Dopamine D1 and D2L Receptors







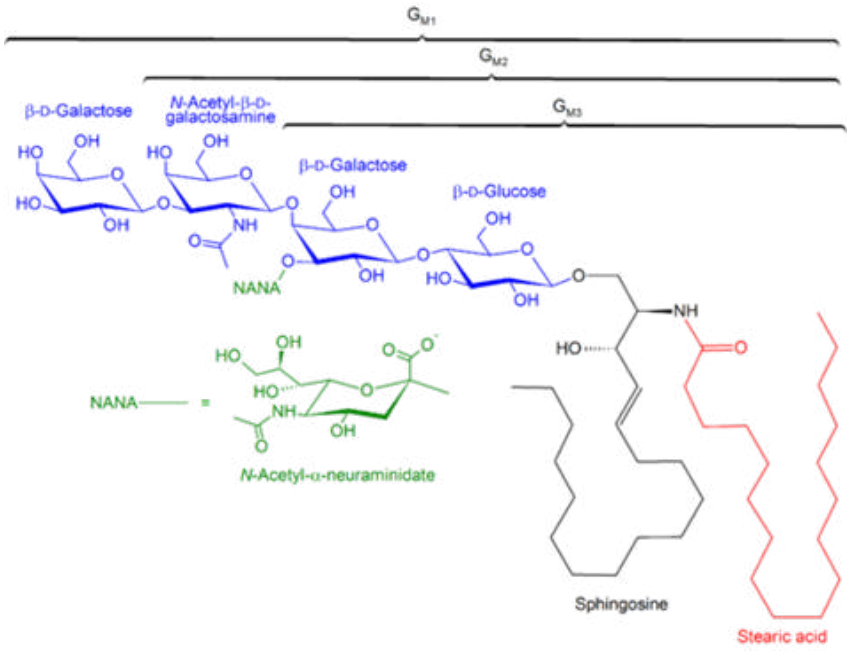
Autoantibodies can act as:

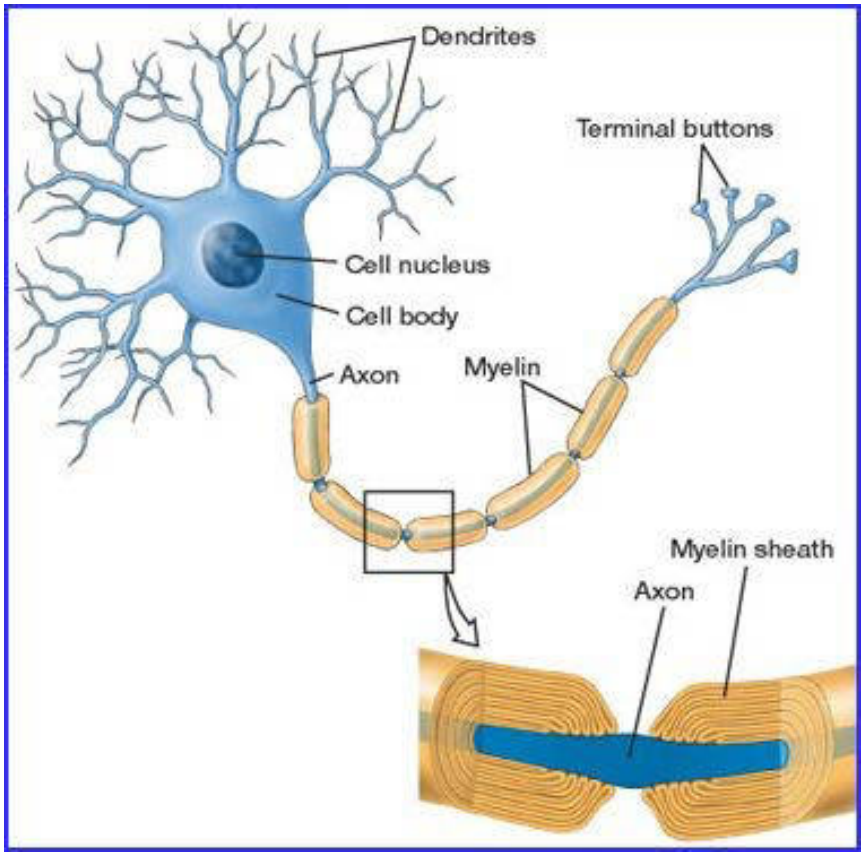
Agonist: a substance which ***initiates a physiological response*** when combined with a receptor

Antagonist: a substance that ***interferes*** with or ***inhibits*** the physiological action of another

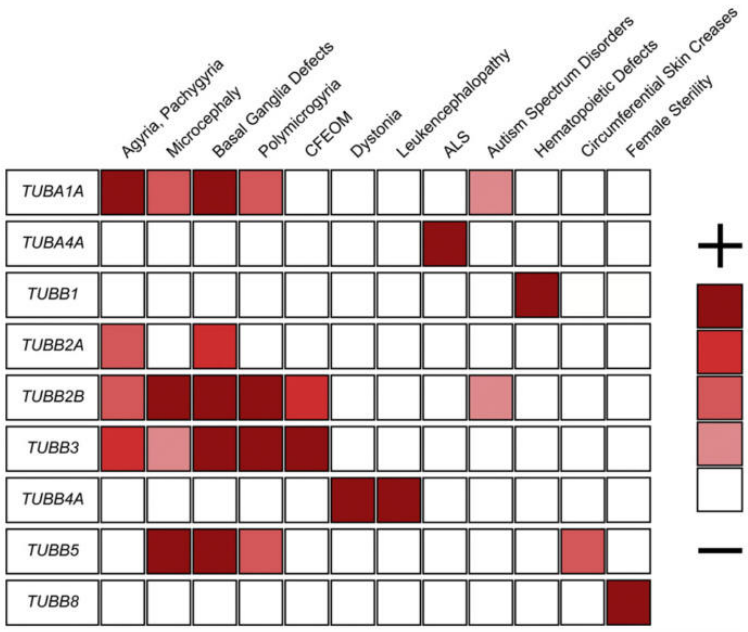
Test 3) Anti-Lysoganglioside GM1 Biological Functions

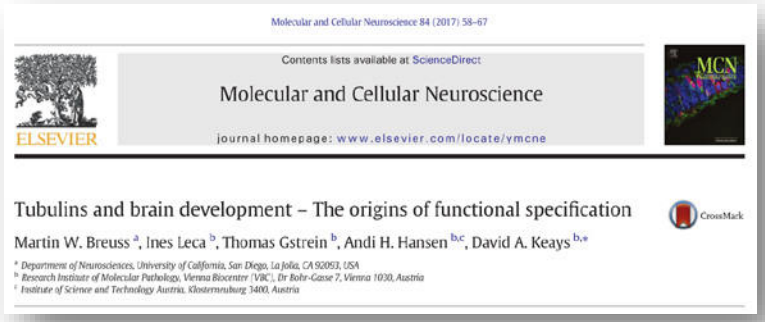
Gangliosides are lipid components of neuronal cell membranes and found in Myelin Sheath





Test 4) Anti-Tubulin Biological Functions and Interruption in Function

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journal homepage: www.elsevier.com/locate/ymcne

Tubulins and brain development – The origins of functional specification

Martin W. Breuss [a], Ines Leca [b], Thomas Gstrein [b], Andi H. Hansen [b,c], David A. Keays [b,*]

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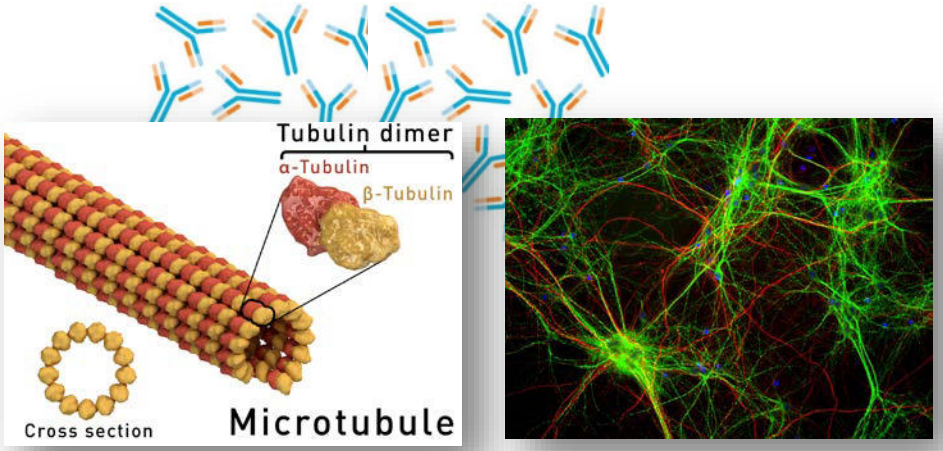
[b] Research Institute of Molecular Pathology, Vienna Biocenter (VBC), Dr Bohr-Gasse 7, Vienna 1030, Austria
[c] Institute of Science and Technology Austria, Klosterneuburg 3400, Austria

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



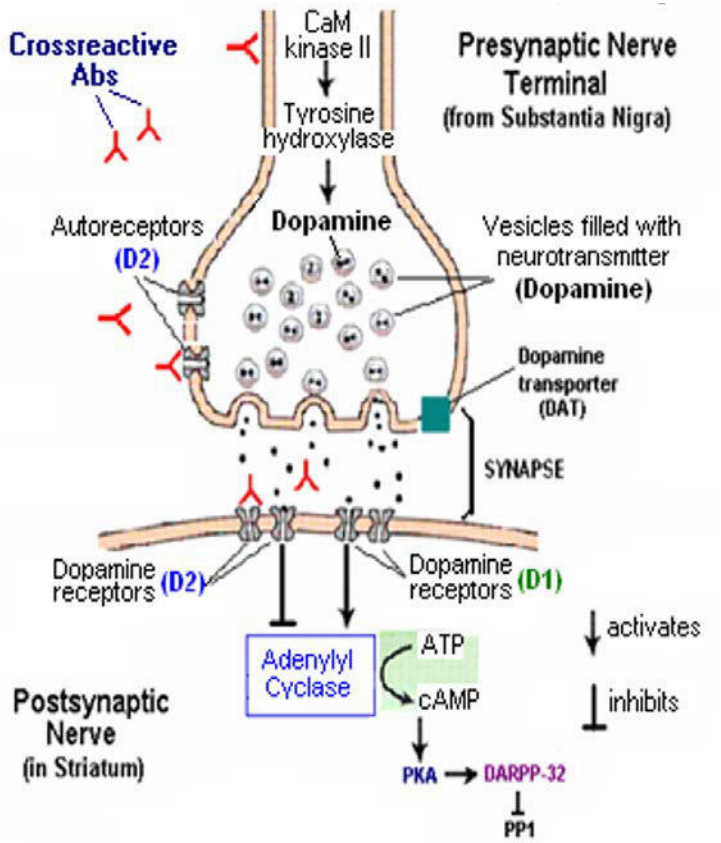
Autoantibodies against Tubulin

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

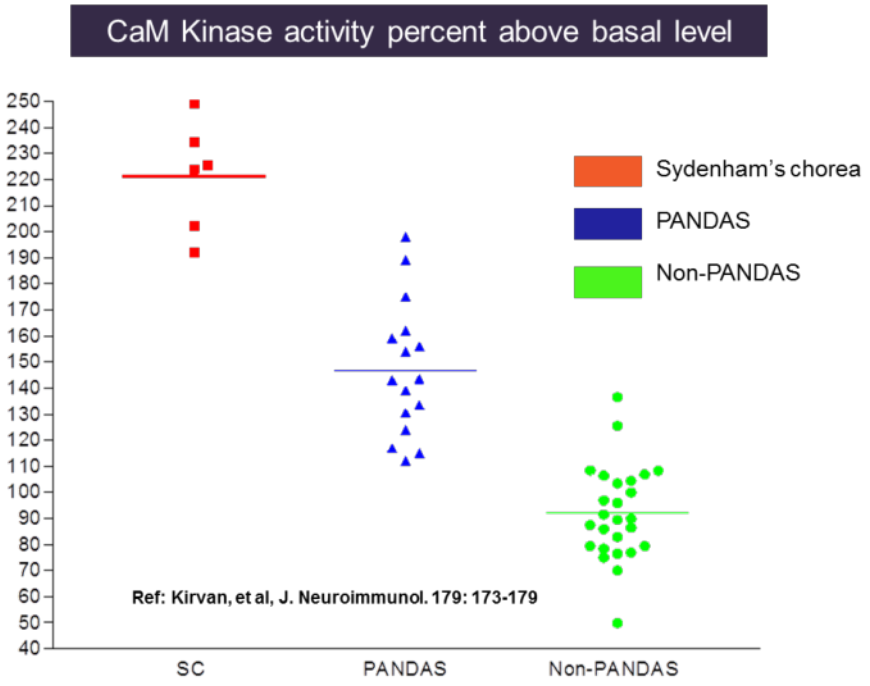
- ***OCD*** and ***cognitive impairment*** sometimes referred to as “brain fog” (82%).
- Symptoms inattentive, disengaged, “tuned out”, or they may struggle with concentration, memory and comprehension.
- Aggressive and/or rage behaviors have also been noted (50%), Patients also report sensory or motor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

Breuss, M. W. et al. (2017). *Mol Cell Neurosci, 84*, 58-67 *“Tubulins and brain development - The origins of functional specification.”*

Test 5) Autoantibodies that stimulate CAMKII in Children with neuropsychiatric syndromes

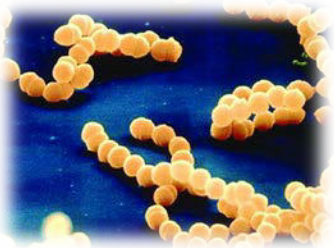
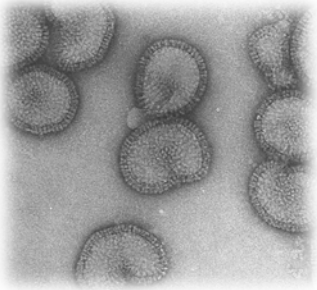
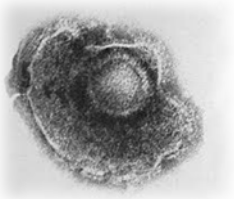
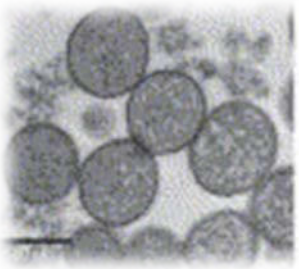
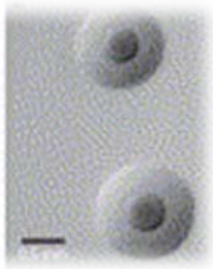
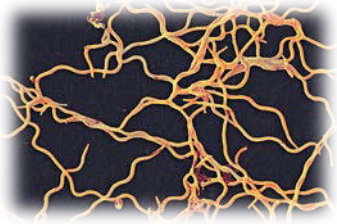
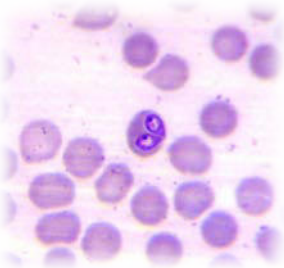
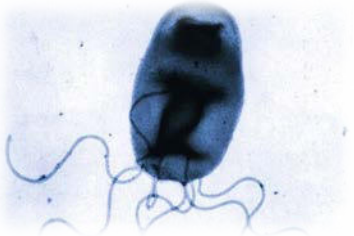
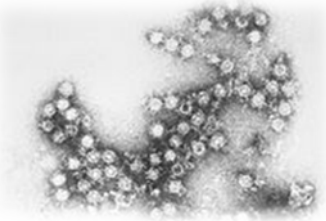


CaMKII Cell Stimulation Test



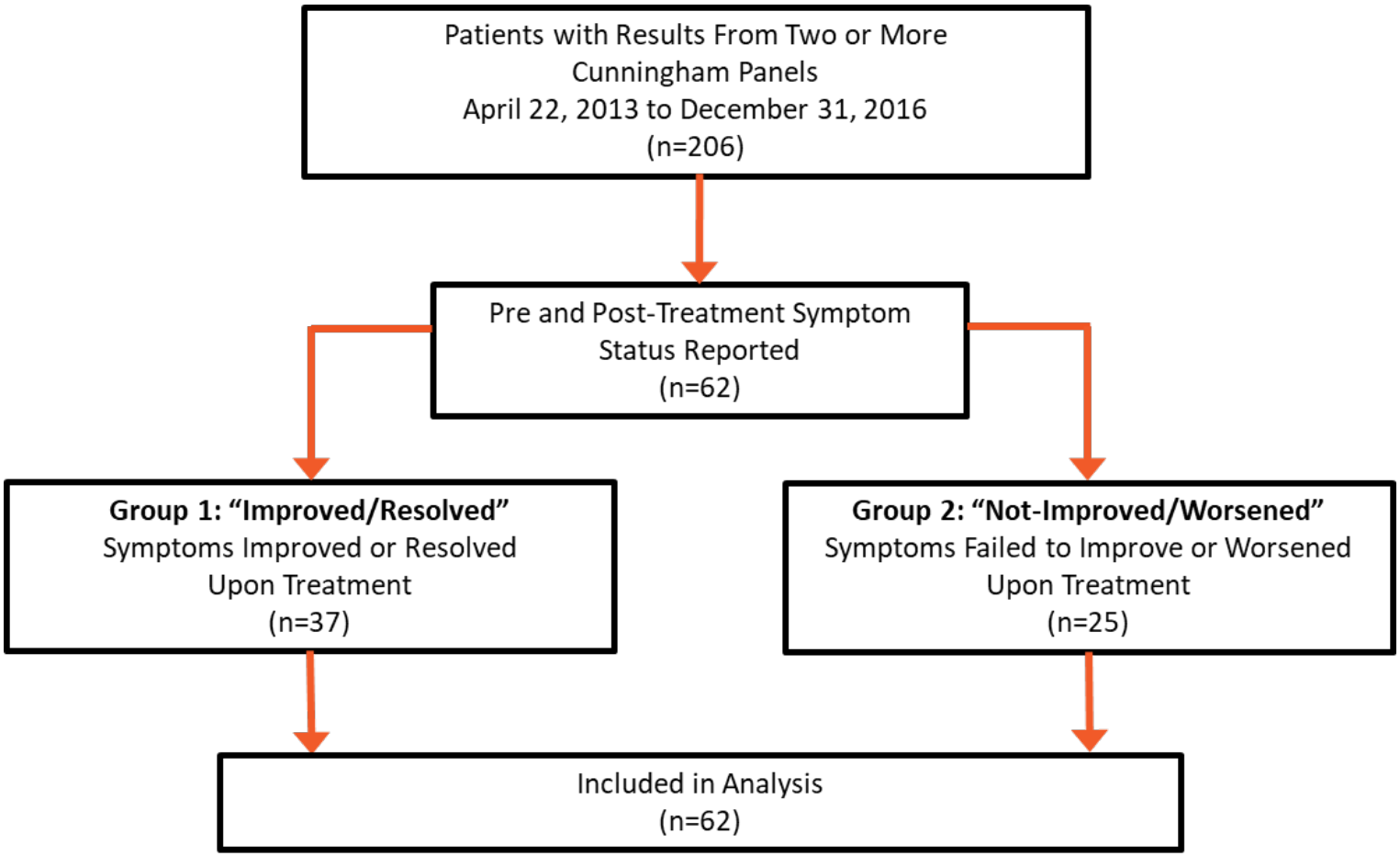
Some Infectious Triggers that are Associated with PANDAS or PANS

- 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



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Group 1: Patients who Improved/Resolved (n=37)

Pre-Treatment Results

Case #	Pretreatment				
	D1R	D2R	Tubulin	lysoganglio-side G_{M1}	CaMKII
6	4000	8000	1000	160	125
72	2000	2000	500	320	137
55	1000	2000	500	80	138
1	1000	2000	500	160	142
30	1000	4000	500	20	143
3	500	1000	250	40	157
42	2000	4000	1000	40	167
7	2000	4000	500	80	172
29	500	4000	1000	80	184
26	1000	1000	250	40	250
5	2000	2000	2000	640	95
56	1000	16000	500	80	144
12	2000	8000	4000	320	149
71	1000	4000	2000	20	179
37	4000	1000	1000	320	164
39	8000	500	1000	640	123
40	4000	4000	4000	320	122
74	2000	8000	4000	40	133
19	1000	2000	4000	20	151
66	8000	2000	2000	160	103
41	8000	500	1000	320	177
16	2000	2000	2000	320	237
69	2000	16000	8000	80	109
43	16000	2000	8000	160	71
4	8000	32000	4000	320	119
34	4000	16000	500	320	160
54	8000	4000	4000	160	156
70	4000	8000	2000	160	140
35	4000	2000	16000	320	192
2	2000	32000	4000	320	253
23	4000	16000	2000	320	139
79	4000	16000	2000	160	167
17	8000	2000	4000	640	139
60	8000	16000	2000	80	179
45	8000	8000	4000	1280	143
13	8000	8000	4000	640	176
9	32000	4000	8000	640	153

Post-Treatment Results

Post treatment				
D1R	D2R	Tubulin	lysoganglio-side G_{M1}	CaMKII
2000	4000	1000	80	110
500	1000	250	80	117
1000	1000	250	10	93
2000	4000	1000	320	83
1000	2000	1000	80	98
1000	2000	500	80	83
1000	4000	1000	80	123
500	4000	1000	80	112
2000	4000	1000	80	113
1000	1000	250	40	134
500	2000	250	40	112
1000	500	250	40	111
1000	8000	1000	20	113
1000	4000	2000	320	131
500	1000	250	40	92
1000	4000	1000	160	111
250	2000	500	20	122
1000	4000	500	160	116
2000	4000	2000	80	128
2000	8000	2000	320	138
2000	1000	250	20	83
2000	8000	1000	320	132
2000	4000	2000	80	122
1000	4000	1000	80	148
1000	8000	500	40	108
500	2000	500	40	118
500	2000	500	10	89
2000	8000	1000	160	124
2000	4000	1000	80	119
8000	16000	4000	320	120
4000	8000	1000	320	119
2000	16000	1000	160	110
500	2000	250	20	134
1000	4000	500	80	165
2000	2000	1000	80	100
1000	2000	2000	80	100
2000	4000	1000	80	150

of Positive Tests/Pt

Number Elevated Markers	
Pretreatment	Post Treatment
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	1
2	0
2	0
2	0
2	2
2	0
2	0
2	0
2	0
2	1
2	2
2	0
2	1
2	1
2	1
3	0
3	0
3	0
3	0
3	0
3	3
4	1
4	1
4	1
4	1
4	0
4	1
4	1

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Group 2: Patients Not Improved/Worsened (n=25)

Pre-Treatment Results | **Post-Treatment Results** | **# of Positive Tests/Pt**

Case #	Pretreatment					Post treatment					Number Elevated Markers	
	D1R	D2R	Tubulin	lysoganglio-side G_{M1}	CaMKII	D1R	D2R	Tubulin	lysoganglios ide G_{M1}	CaMKII	Pretreatment	Post Treatment
24	1000	8000	500	80	119	2000	8000	250	320	105	0	0
16	1000	4000	1000	20	124	2000	4000	1000	80	138	0	1
18	1000	2000	250	20	121	1000	1000	500	80	138	0	1
19	1000	250	250	160	115	2000	4000	2000	40	116	0	1
34	2000	2000	500	320	121	2000	8000	1000	20	145	0	1
77	500	2000	1000	20	126	1000	2000	2000	40	141	0	2
64	500	2000	250	320	134	1000	4000	2000	80	125	1	1
29	1000	2000	500	80	138	1000	2000	250	160	127	1	0
104	2000	4000	1000	40	149	2000	4000	1000	40	175	1	1
33	2000	4000	250	40	168	4000	16000	1000	40	126	1	2
38	1000	1000	1000	160	179	8000	8000	4000	1280	140	1	4
62	2000	4000	1000	80	216	2000	2000	500	80	123	1	0
45	2000	4000	500	80	217	4000	4000	2000	80	158	1	3
8	1000	8000	1000	40	219	4000	16000	1000	320	139	1	3
48	1000	2000	2000	80	156	2000	8000	1000	160	145	2	1
122	500	8000	1000	640	136	2000	4000	4000	320	143	2	2
36	2000	16000	1000	160	164	8000	8000	4000	160	123	2	2
20	2000	2000	2000	40	164	4000	16000	8000	160	150	2	4
55	2000	8000	2000	320	160	4000	16000	8000	80	152	2	4
42	32000	4000	2000	80	112	4000	16000	2000	160	164	2	4
39	8000	250	2000	160	159	2000	16000	4000	80	162	3	3
26	4000	32000	8000	320	94	8000	16000	8000	1280	177	3	5
14	8000	4000	2000	640	148	8000	16000	16000	40	92	4	3
63	8000	32000	2000	320	142	32000	32000	8000	640	113	4	4
35	4000	32000	4000	160	130	8000	32000	4000	1280	149	4	5

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

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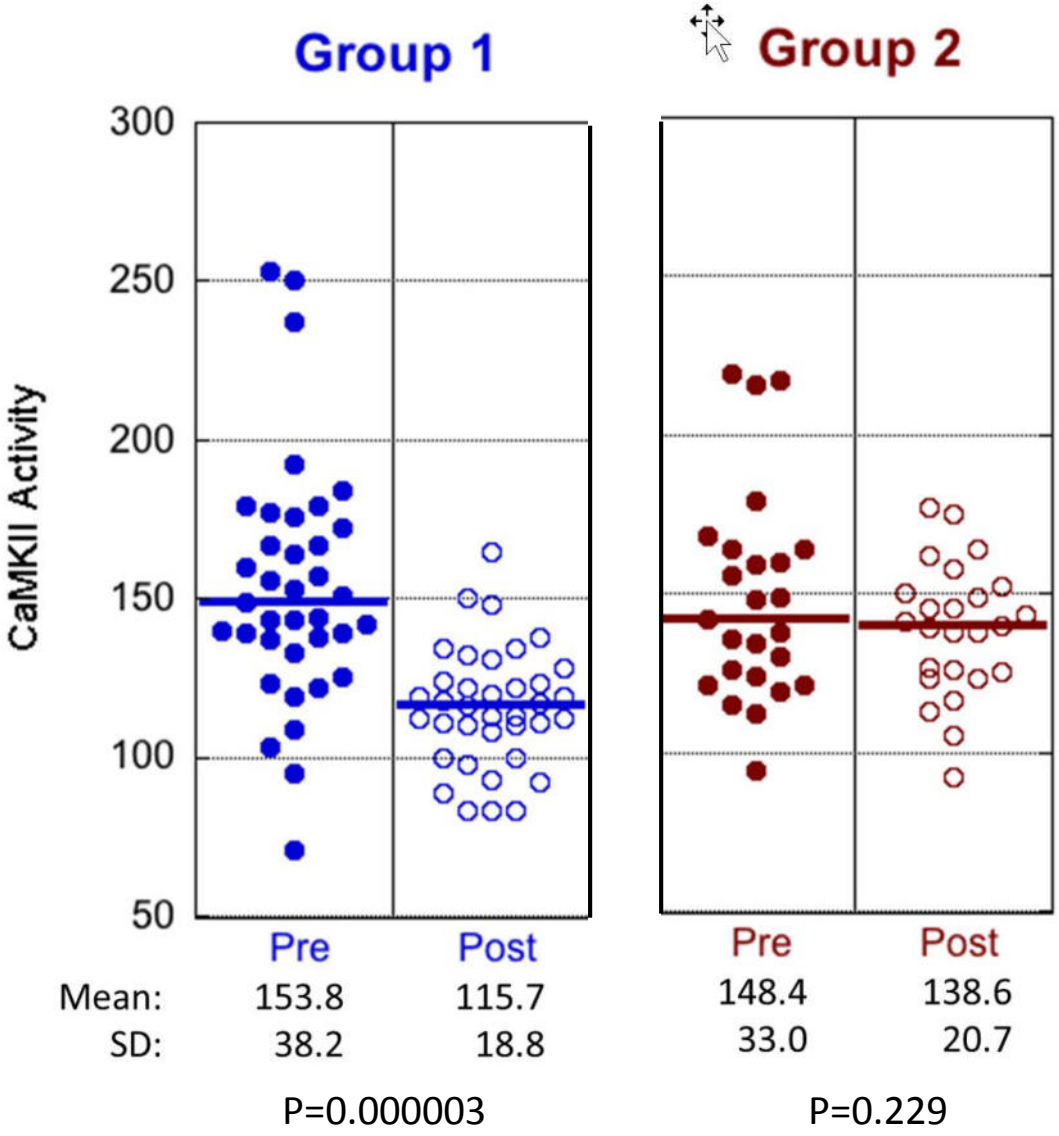
CaMKII Stimulation Assay Results



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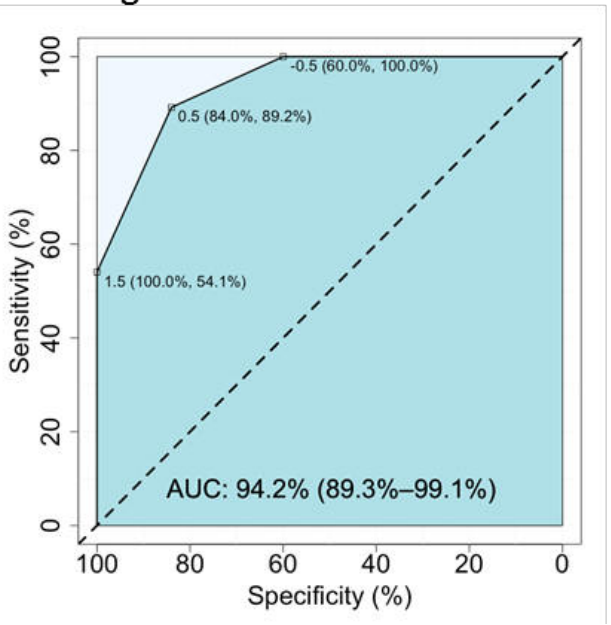
Sensitivity & Specificity of the Cunningham Panel: Symptom Correlation to Positive Test Results

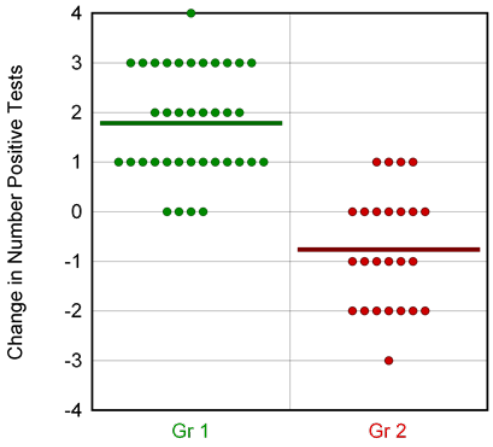
Sensitivity/Specificity Based Upon Positive Tests Compared to Symptoms

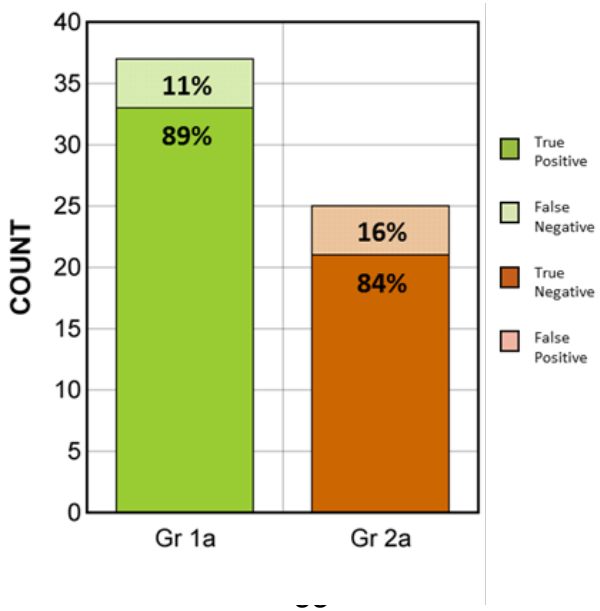
		Symptoms Improved			
		Yes	No	**Sensitivity**	89%
				Specificity	84%
Panel Prediction	Yes	33	4	**PPV**	89%
	No	4	20	**NPV**	84%
				Accuracy	87%

Receiver Operator Curve (ROC) Change in Number Positive Tests



Change in Number Positive Tests





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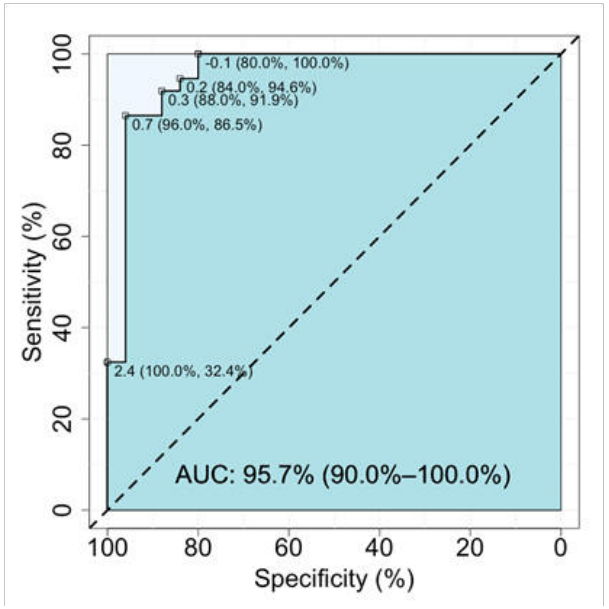
Sensitivity & Specificity of the Cunningham Panel: Symptom Correlation to Magnitude of Test Result Changes

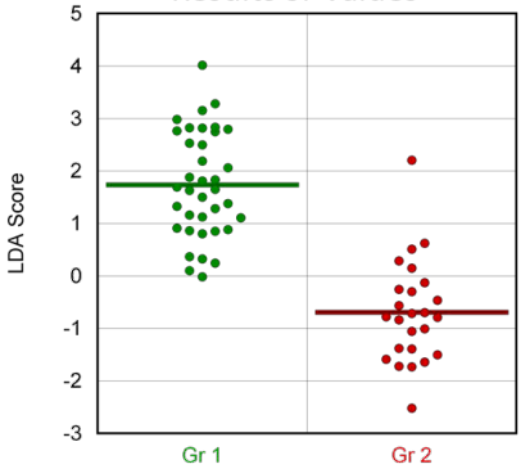
Sensitivity/Specificity Based Upon Magnitude Change in Individual Test Values (LDA)

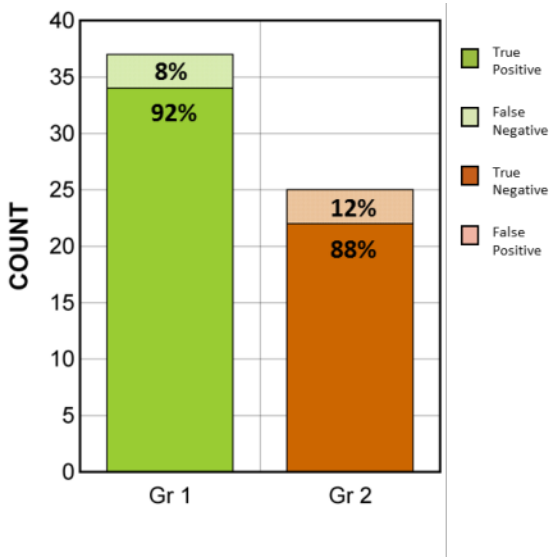
		Symptoms Improved			
		Yes	No	**Sensitivity**	92%
				Specificity	88%
Panel Prediction	Yes	34	3	**PPV**	92%
	No	3	22	**NPV**	88%
				Accuracy	90%

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



Change in Magnitude of Test Results or Values





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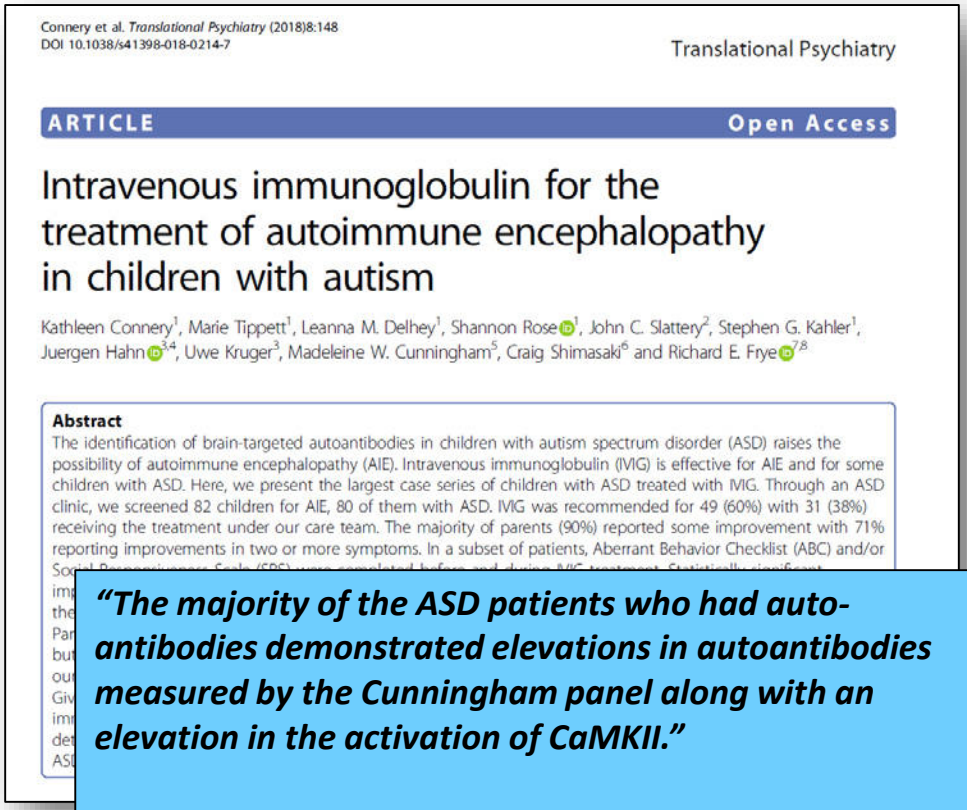
Autism Patients with Autoimmune Encephalopathy Respond to Immunotherapy



Connery et al. *Translational Psychiatry* (2018)8:148
DOI 10.1038/s41398-018-0214-7

Translational Psychiatry

ARTICLE Open Access

Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism

Kathleen Connery[1], Marie Tippett[1], Leanna M. Delhey[1], Shannon Rose[1], John C. Slattery[2], Stephen G. Kahler[1], Juergen Hahn[3,4], Uwe Kruger[3], Madeleine W. Cunningham[5], Craig Shimasaki[6] and Richard E. Frye[7,8]

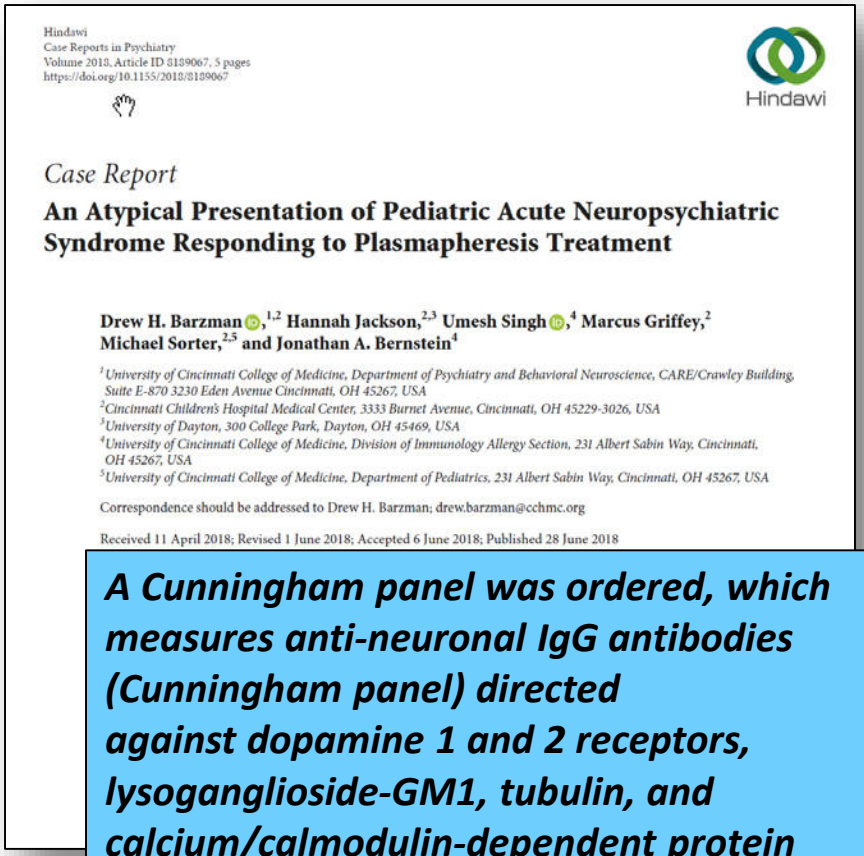
Abstract
The identification of brain-targeted autoantibodies in children with autism spectrum disorder (ASD) raises the possibility of autoimmune encephalopathy (AIE). Intravenous immunoglobulin (IVIG) is effective for AIE and for some children with ASD. Here, we present the largest case series of children with ASD treated with IVIG. Through an ASD clinic, we screened 82 children for AIE, 80 of them with ASD. IVIG was recommended for 49 (60%) with 31 (38%) receiving the treatment under our care team. The majority of parents (90%) reported some improvement with 71% reporting improvements in two or more symptoms. In a subset of patients, Aberrant Behavior Checklist (ABC) and/or

- **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 auto-antibodies 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 Patent with Schizophrenia Diagnosis Responds to Immunomodulation Therapy



Hindawi
Case Reports in Psychiatry
Volume 2018, Article ID 8139067, 5 pages
https://doi.org/10.1155/2018/8139067

Hindawi

Case Report

An Atypical Presentation of Pediatric Acute Neuropsychiatric Syndrome Responding to Plasmapheresis Treatment

Drew H. Barzman,[1,2] Hannah Jackson,[2,3] Umesh Singh,[4] Marcus Griffey,[2] Michael Sorter,[2,5] and Jonathan A. Bernstein[4]

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[2]Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3026, USA
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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

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Introduction

Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome

Susan E. Swedo, MD,[1] Jennifer Frankovich, MD, MS,[2,3] and Tanya K. Murphy, MD, MS[4]

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Review-Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I–Psychiatric and Behavioral Interventions

Margo Thienemann, MD,[1] Tanya Murphy, MD,[2] James Leckman, MD,[3] Richard Shaw, MD, PhD,[1] Kyle Williams, MD,[4] Cynthia Kapphahn, MD, MPH,[1] Jennifer Frankovich, MD, MPH,[1] Daniel Geller, MD,[5] Gail Bernstein, MD,[6] Kiki Chang, MD,[1] Josephine Elia, MD,[7] and Susan Swedo, MD[8]

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Pp. 1–16
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Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies

Jennifer Frankovich, MD, MS,[1,2] Susan Swedo, MD,[3] Tanya Murphy, MD, MS,[4] Russell C. Dale, MD,[5] Dritan Agalliu, PhD,[6] Kyle Williams, MD, PhD,[7] Michael Daines, MD,[8] Mady Hornig, MD, MA,[9] Harry Chugani, MD,[10] Terence Sanger, MD, PhD,[11] Eyal Muscal, MD, MS,[12] Mark Pasternack, MD,[13] Michael Cooperstock, MD, MPH,[14] Hayley Gans, MD,[15] Yujuan Zhang, MD,[16] Madeleine Cunningham, PhD,[17] Gail Bernstein, MD,[18] Reuven Bromberg, MD,[19] Theresa Willett, MD, PhD,[1] Kayla Brown, BA,[1,2] Bahare Farhadian, MSN, RN, FNP-C,[1] Kiki Chang, MD,[1,20] Daniel Geller, MD,[21] Joseph Hernandez, MD, PhD,[1,2] Janell Sherr, MD,[1,2] Richard Shaw, MD[20] Elizabeth Latimer, MD,[22] James Leckman, MD, PhD,[23] and Margo Thienemann, MD[1,20]; PANS/PANDAS Consortium

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Pp. 1–13
DOI: 10.1089/cap.2016.0151

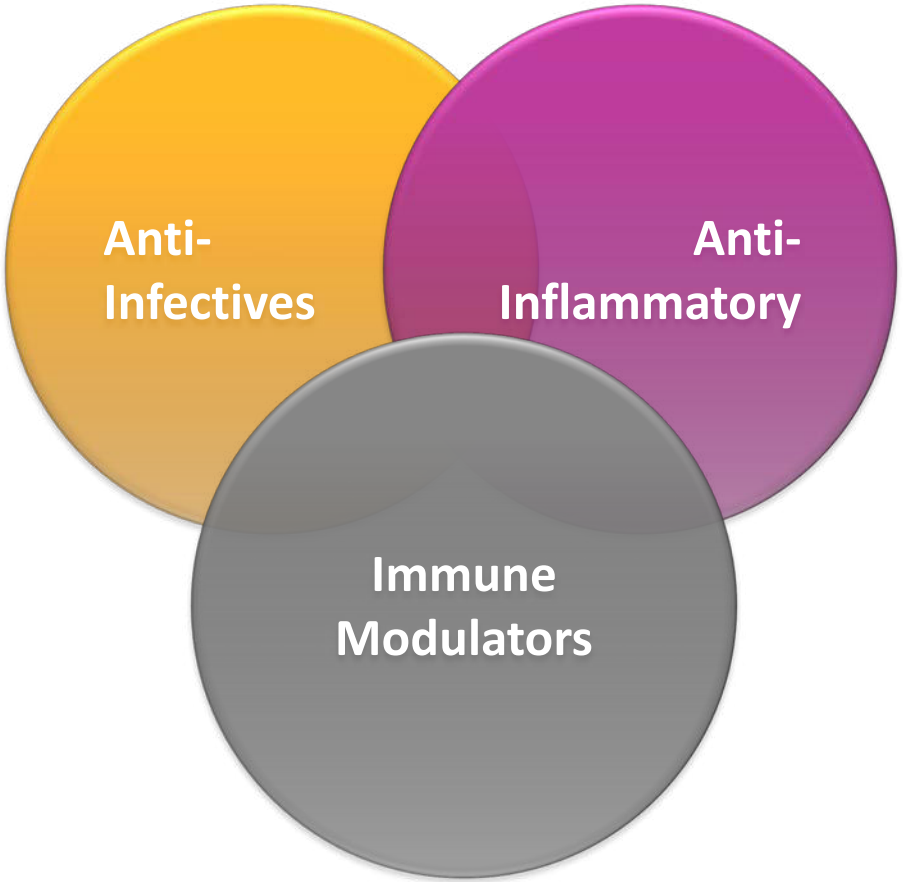
Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part III—Treatment and Prevention of Infections

Michael S. Cooperstock, MD, MPH,[1] Susan E. Swedo, MD,[2] Mark S. Pasternack, MD,[3] and Tanya K. Murphy, MD[4]; for the PANS PANDAS Consortium

1. 2017 Thienemann et al. J Child Adolesc Psychopharmacol **27**(7): 566-573
2. 2017 Frankovich et al. J Child Adolesc Psychopharmacol **27**(7): 574-593
3. 2017 Cooperstock et al. J Child Adolesc Psychopharmacol **27**(7): 594-606

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

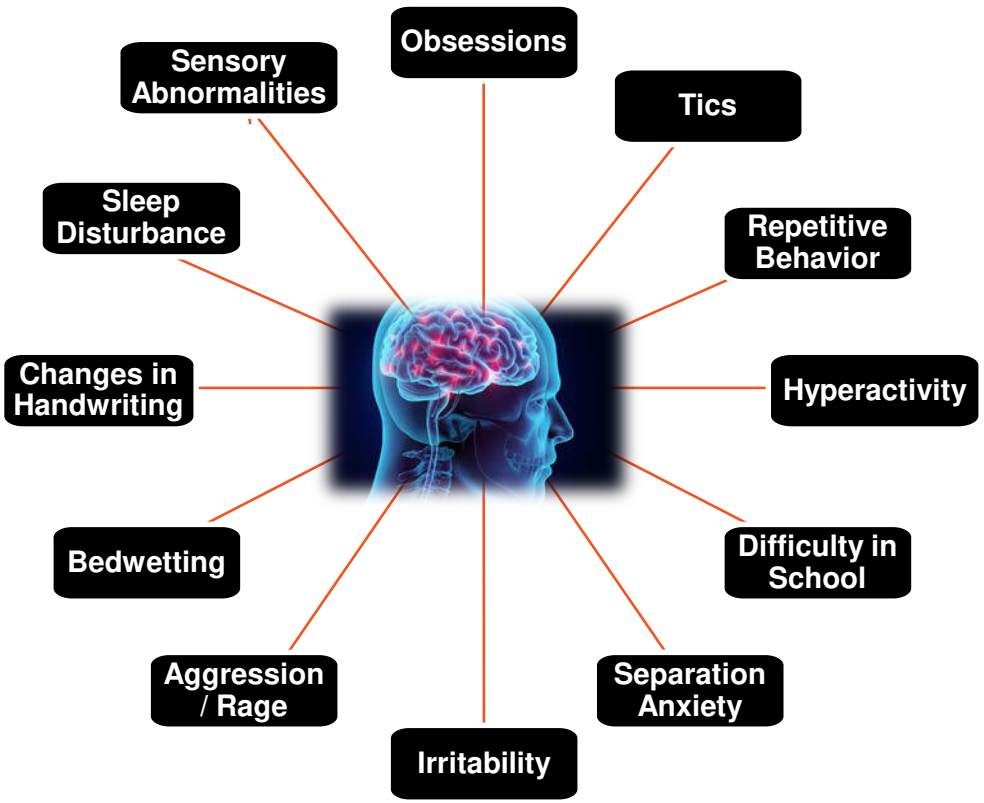
Tack Law #2

- 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

Problem: Patients May be Labeled into Symptom-Based Categories Typically Deemed "Incurable"

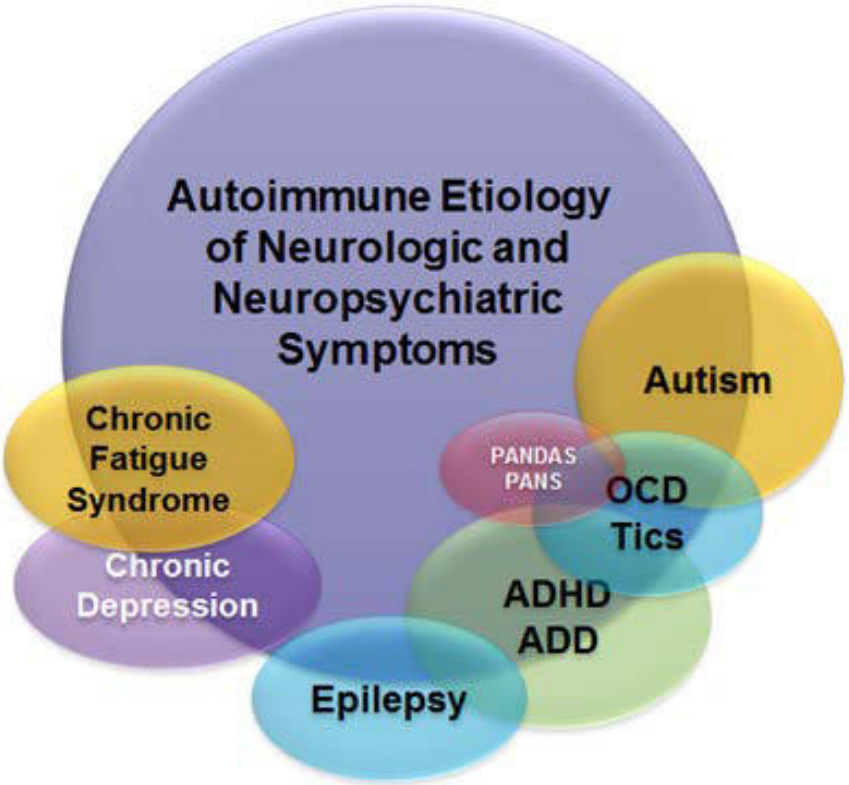
Common Symptoms



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)*

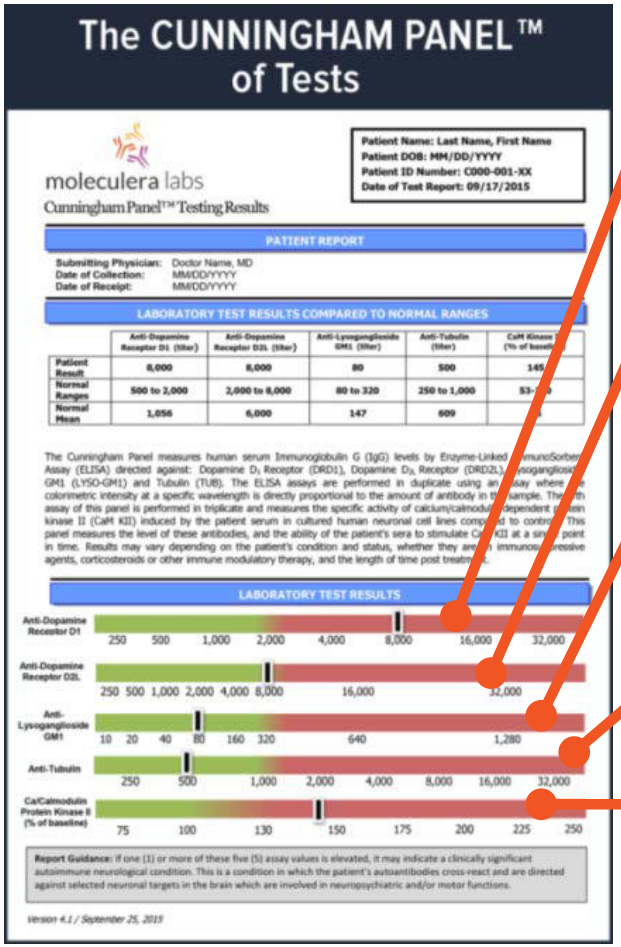
Many Chronic Disorders can have a Patient Segment whose Cause is an Autoimmune Etiology



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


The CUNNINGHAM PANEL™ of Tests

moleculera labs

Cunningham Panel™ Testing Results

Patient Name: Last Name, First Name
Patient DOB: MM/DD/YYYY
Patient ID Number: C000-001-XX
Date of Test Report: 09/17/2015

PATIENT REPORT

Submitting Physician: Doctor Name, MD
Date of Collection: MM/DD/YYYY
Date of Receipt: MM/DD/YYYY

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase (% of baseline)
Patient Result	8,000	8,000	80	500	145
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-[illegible]
Normal Mean	1,056	6,000	147	609	[illegible]

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked [illegible]Sorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), [illegible]lysoganglioside GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an [illegible] assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fourth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to control. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Report Guidance: If one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets in the brain which are involved in neuropsychiatric and/or motor functions.

Version 4.1 / September 25, 2015

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

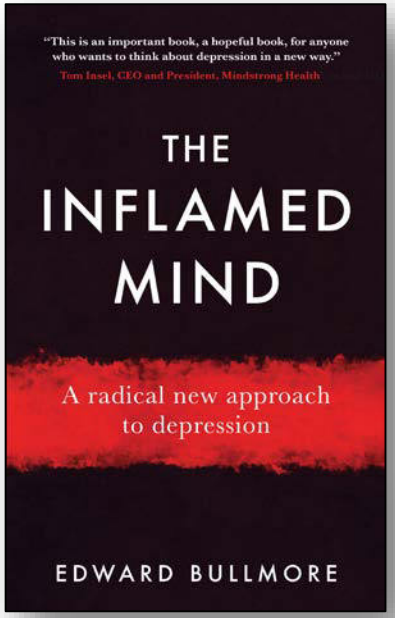
Locate a Doctor Who is Open to Working with Patients Having Autoimmune Neurologic Disorders

Can be prescribed through doctors who work with AONM

Keys to Change

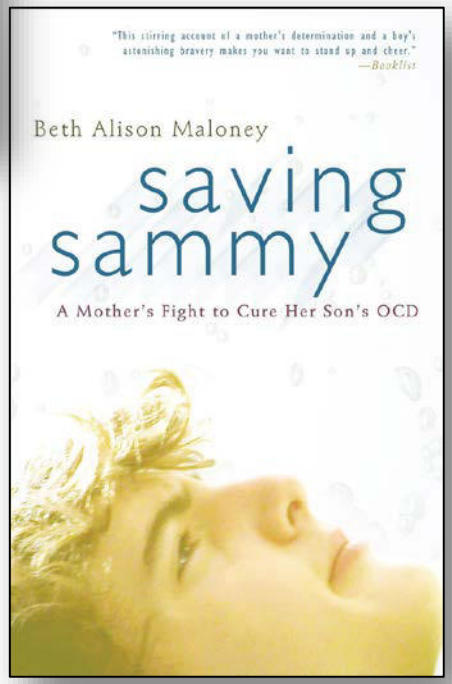
1. Increase awareness of autoimmune neurological disorders
2. More education about these biology of these conditions
3. More research and clinical studies to better identify the etiology and discover more efficacious and targeted treatments
4. **Perseverance!**

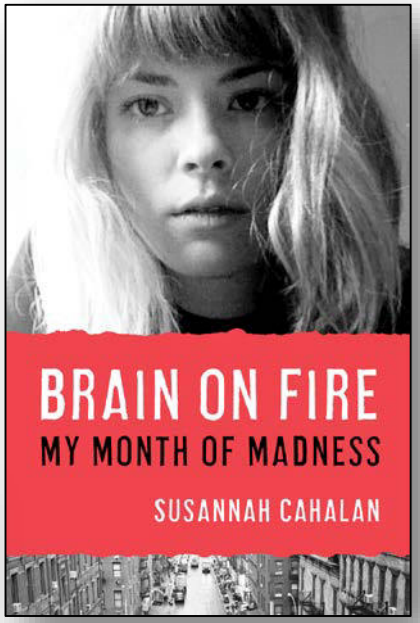
Neuroinflammation, Autoimmunity and the Brain



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

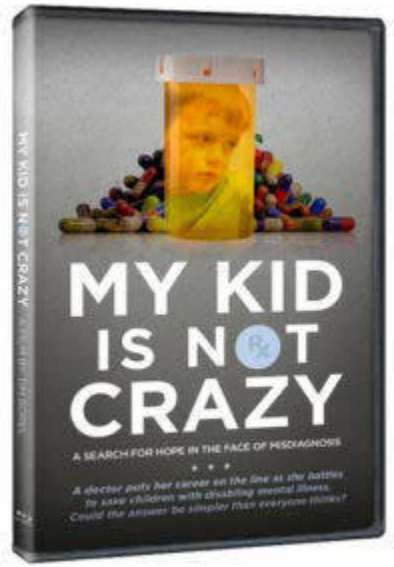
Linking infection to "mental" illness, as strep antibodies are linked to the neurological Tourette's syndrome, has been rejected by many doctors since the rise of psychoanalysis, but Maloney insisted Sammy be tested for strep titers when he became unable to attend school and to walk. He was diagnosed 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.

DVD: Documentary chronicling several families and their children suffering from PANDAS and what they went through to reach a diagnosis and begin recovery

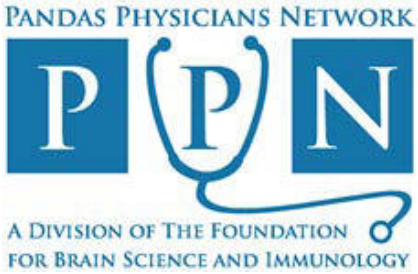


Additional Information Sources

moleculeralabs.com

aonm.org

panspandasuk.org



pandasppn.org

nimh.nih.gov

pandasnetwork.org

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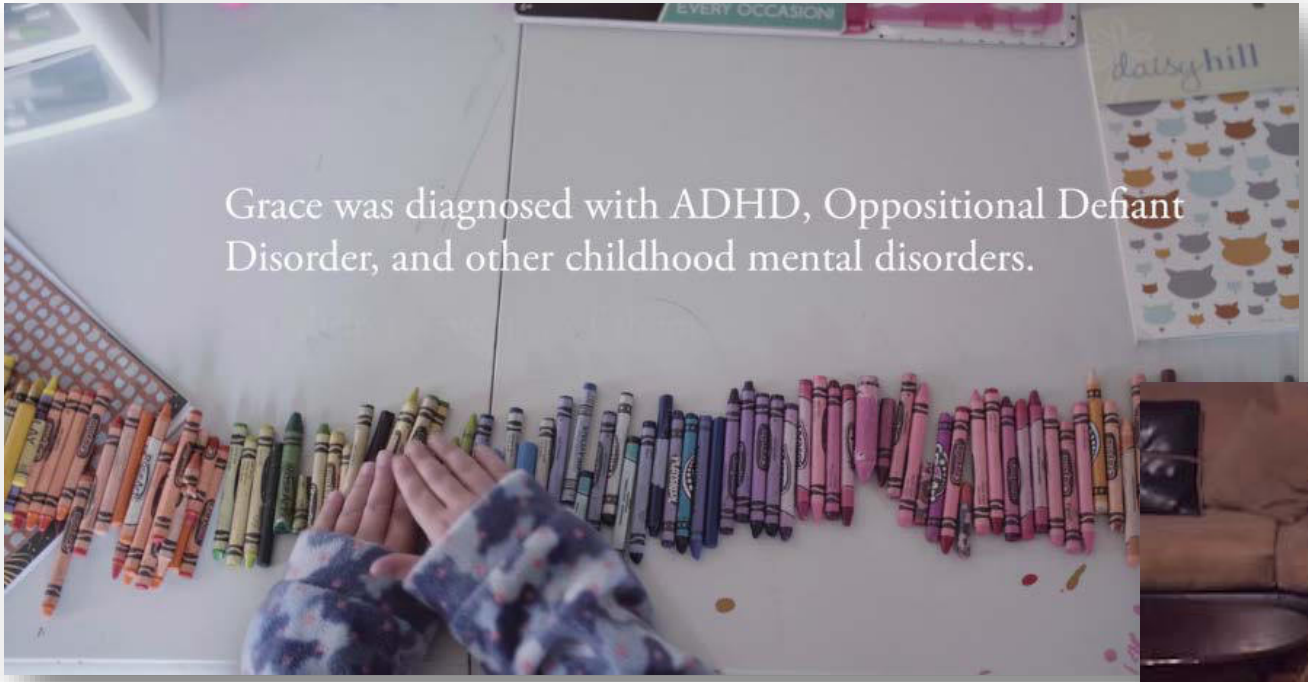
Our Mission is to Help Change How Medicine is Practiced for Neuropsychiatric Disorders

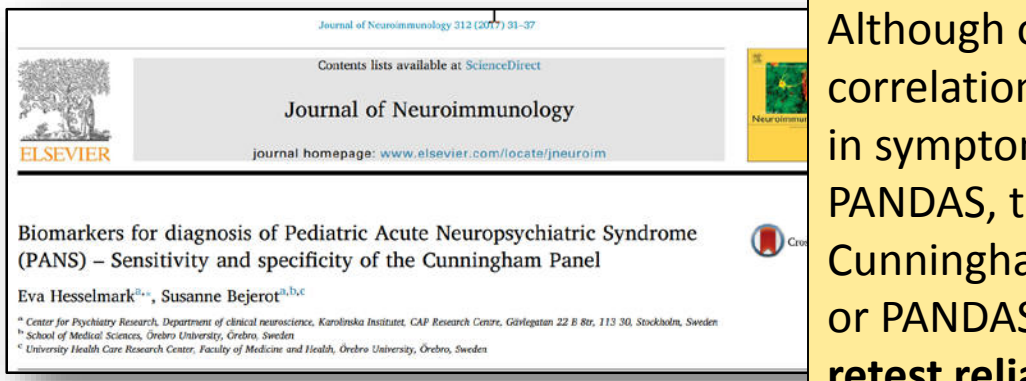
Thank you for helping those suffering with this disorder, to gain hope and get well!

For More Information Contact:
Craig Shimasaki, PhD, MBA
shimasakic@moleculera.com
www.MoleculeraLabs.com
U.S. +1(405) 239-5250

Grace's Story – One of Thousands we Have Tested



Swedish Study of Cunningham Panel



Journal of Neuroimmunology 312 (2017) 31–37

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

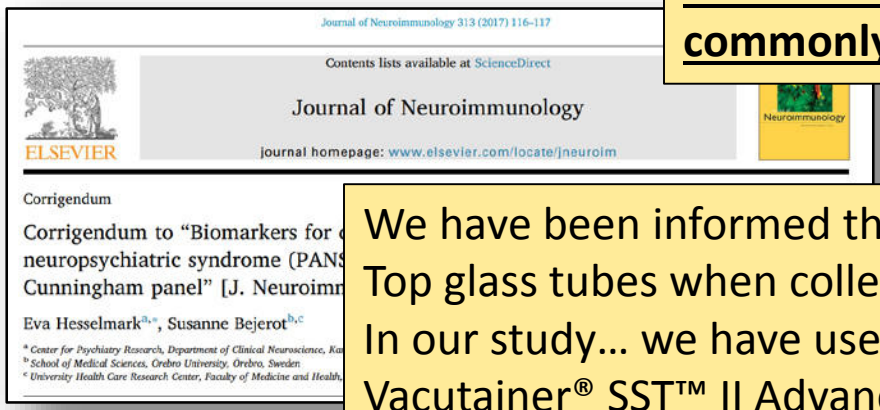
ELSEVIER

Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel

Eva Hesselmark[a,*], Susanne Bejerot[a,b,c]

[a] Center for Psychiatry Research, Department of clinical neuroscience, Karolinska Institutet, CAP Research Centre, Gävlegatan 22 B 8tr, 113 30, Stockholm, Sweden
[b] School of Medical Sciences, Örebro University, Örebro, Sweden
[c] University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

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.**



Journal of Neuroimmunology 313 (2017) 116–117

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ELSEVIER

Corrigendum

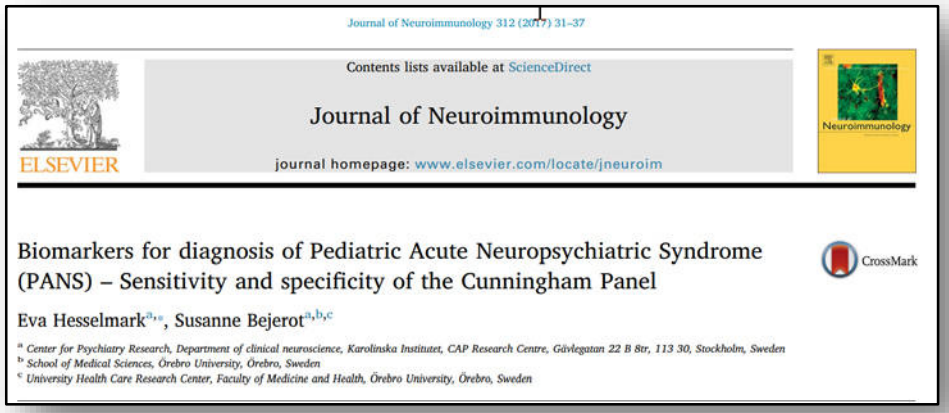
Corrigendum to "Biomarkers for
neuropsychiatric syndrome (PANS
Cunningham panel" [J. Neuroimm

Eva Hesselmark[a,*], Susanne Bejerot[b,c]

[a] Center for Psychiatry Research, Department of Clinical Neuroscience, Ka
[b] School of Medical Sciences, Örebro University, Örebro, Sweden
[c] University Health Care Research Center, Faculty of Medicine and Health,

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.**

Swedish Study of Cunningham Panel



Journal of Neuroimmunology 312 (2017) 31–37

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

ELSEVIER

Neuroimmunology

Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel

CrossMark

Eva Hesselmark[a,*], Susanne Bejerot[a,b,c]

[a] Center for Psychiatry Research, Department of clinical neuroscience, Karolinska Institutet, CAP Research Centre, Gävlegatan 22 B 8tr, 113 30, Stockholm, Sweden
[b] School of Medical Sciences, Örebro University, Örebro, Sweden
[c] University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Swedish Study Conclusions of Cunningham Panel

1. **"…test-retest reliability of CaMKII may be insufficient"**
2. **"…results are commonly elevated in healthy controls"**

SST Gold Top Blood Collection Tube

Red Top Glass Blood Collection Tube

Invalid Blood Collection Tube

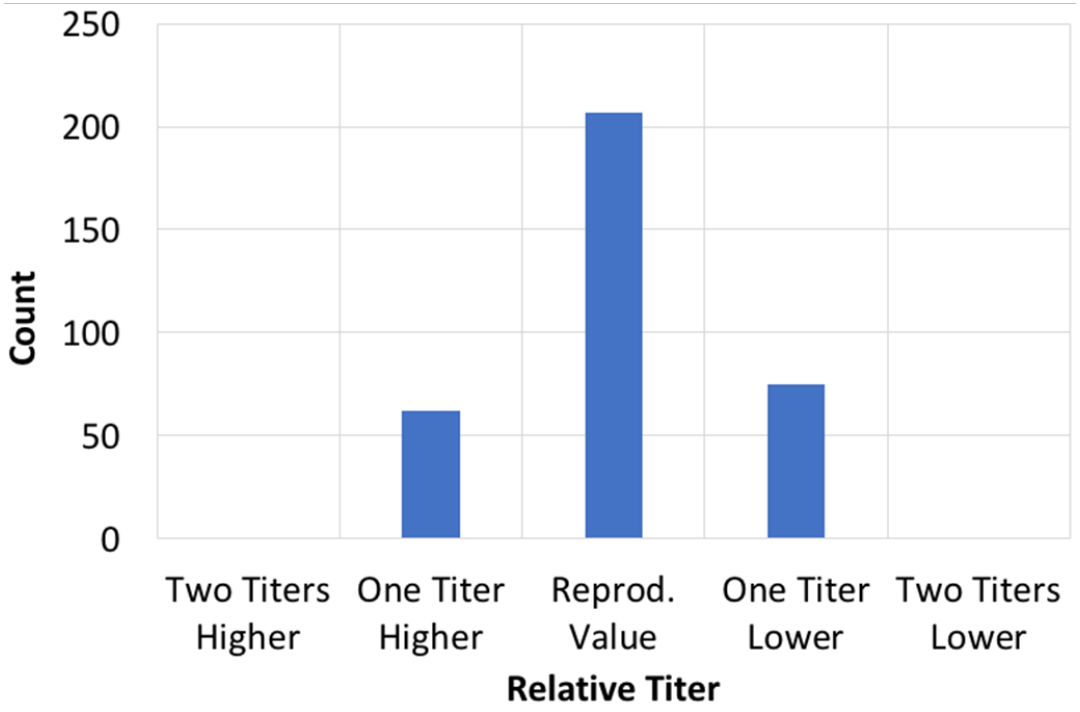
- Polymer Gel for serum separation
- **Interferes with assay results**

Only validated Blood Collection Tube

- No Polymer Gel

Test-Retest Reproducibility in Tubes w/o Additives

Figure 8. D1R ELISA Assay Reproducibility

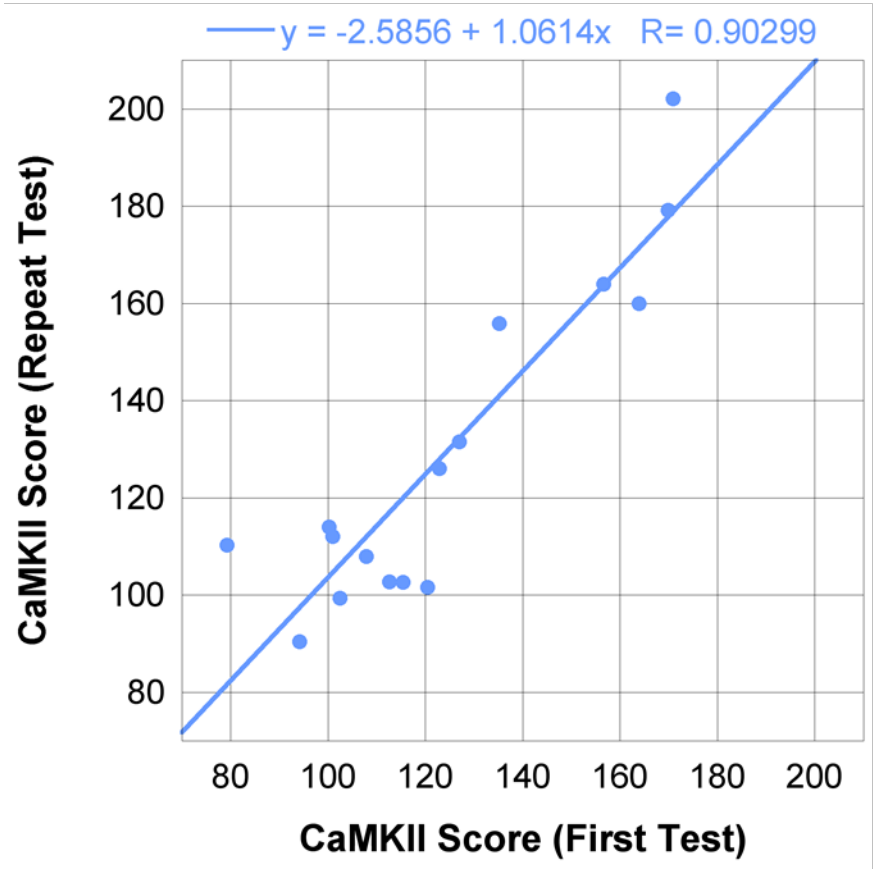


Results of 344 individual repeated tests on 7 individual patients over several months

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

CaMKII Test-Retest Reproducibility in Tubes w/o Additives

Figure 9. CaMKII Assay Reproducibility



Multiple Test-retesting of samples collected in Red Top Glass Tubes (No additives)

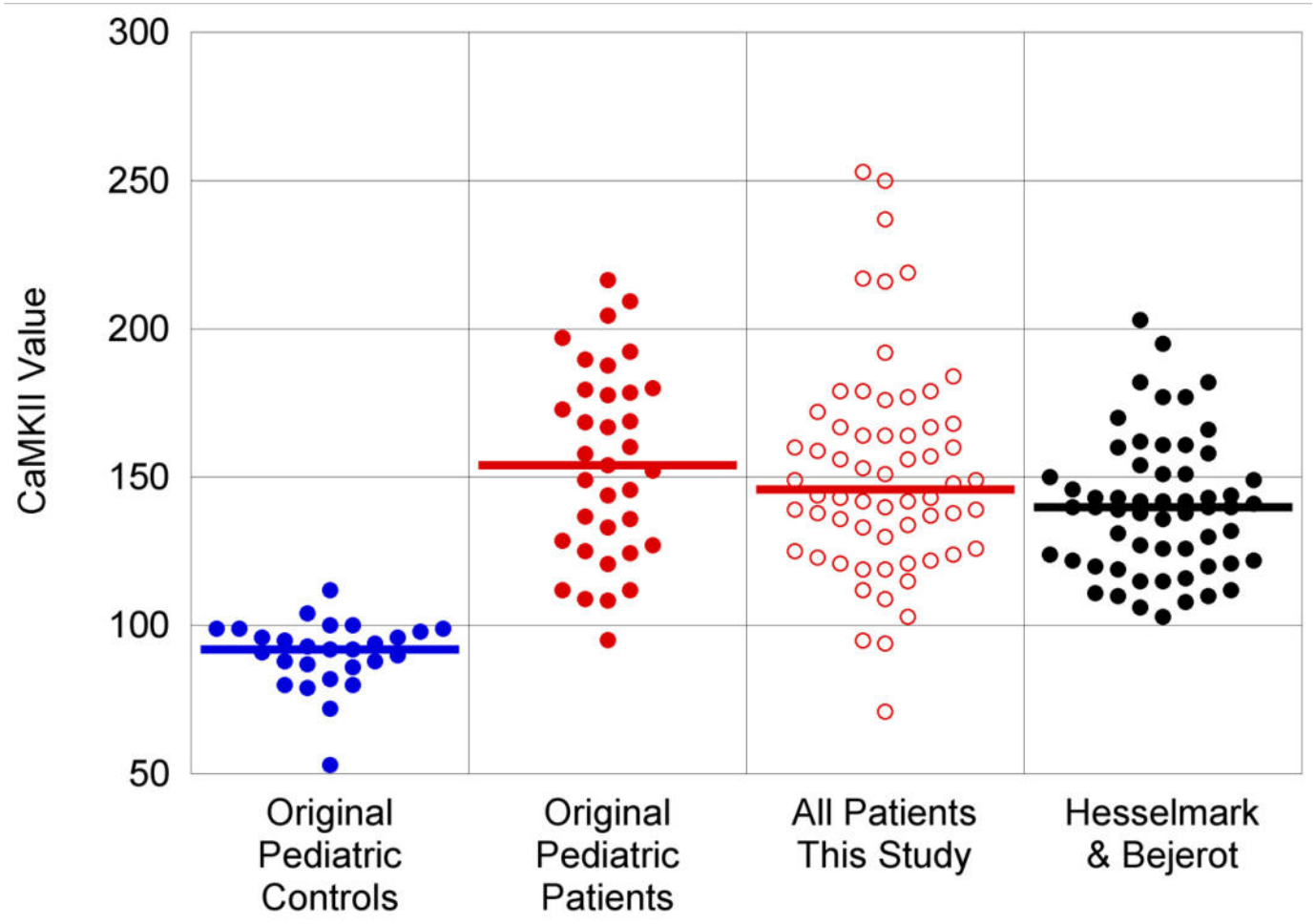
- **First test on the X axis**
- **Repeat test on the Y axis**
- **R=0.90299**

Impact of Control Population Selection
CaMKII Results in Study Populations of Diseased Children

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

Figure 10. Results of CaMKII assays in Various Populations



What is the Controversy?

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

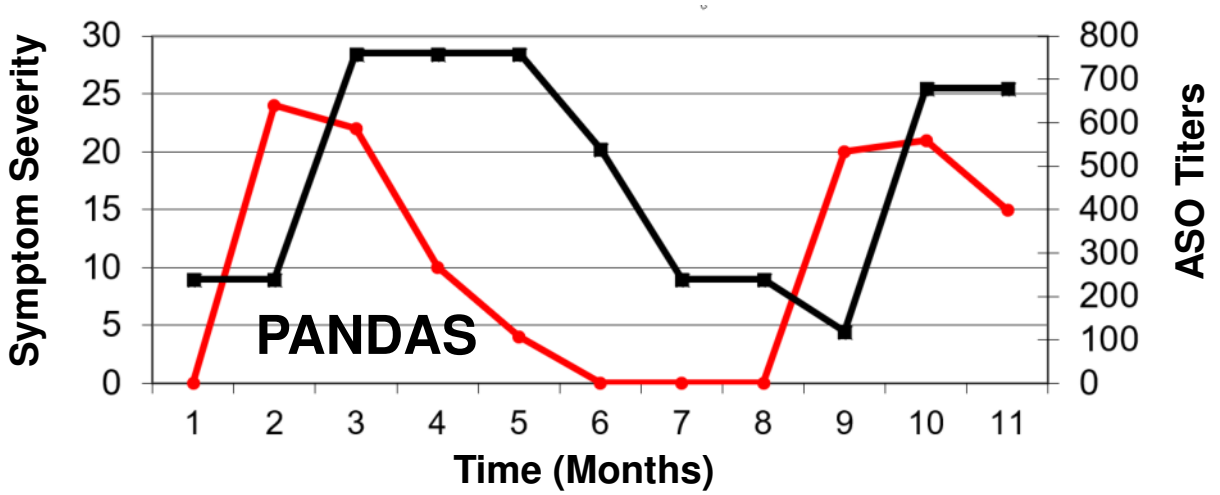
1. **PANDAS**
   - Association with Group A Streptococcus (GAS) but most all children get Strep

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

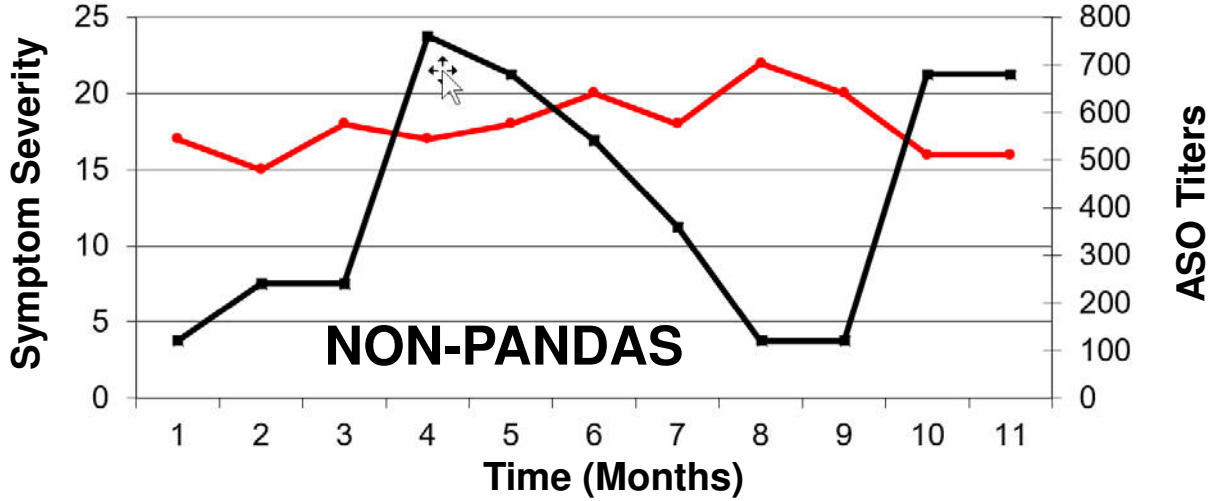
3. **Crosses multiple medical specialties**
   - Infectious Disease, Immunology/Rheumatology, Neurology, Psychiatry

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)



ASO TITER ---
Y-BOCS ---



ASO TITER ---
Y-BOCS ---

Credits: Dr. Susan Swedo

Other Recognized Anti-Neuronal Antibodies Account for a Portion of Autoimmune Encephalitis

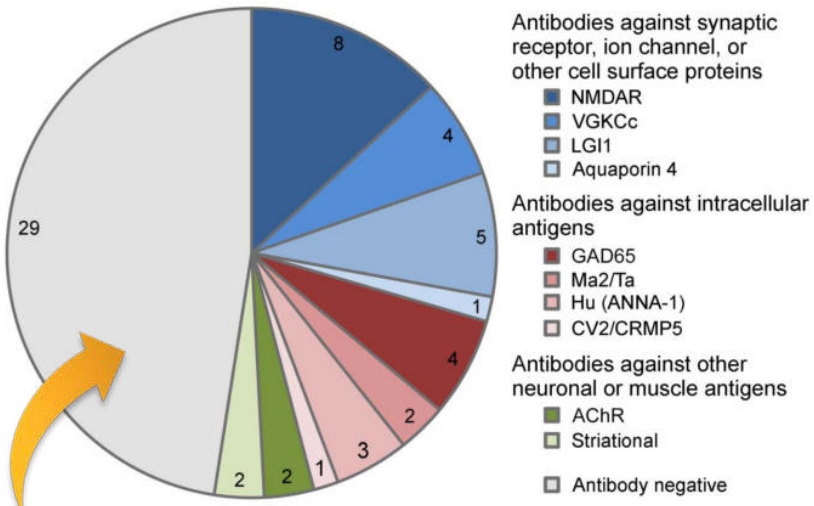
Neurology®
Neuroimmunology & Neuroinflammation
A peer-reviewed clinical and translational neurology open access journal

John C. Probasco, MD
Lilja Solnes, MD
Abhinav Nalluri, BS
Jesse Cohen, BA
Krystyna M. Jones, MD
Elcin Zan, MD
Mehrbod S. Javadi, MD
Arun Venkatesan, MD, PhD

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

OPEN

Figure 1 Antibody status of patients with AE



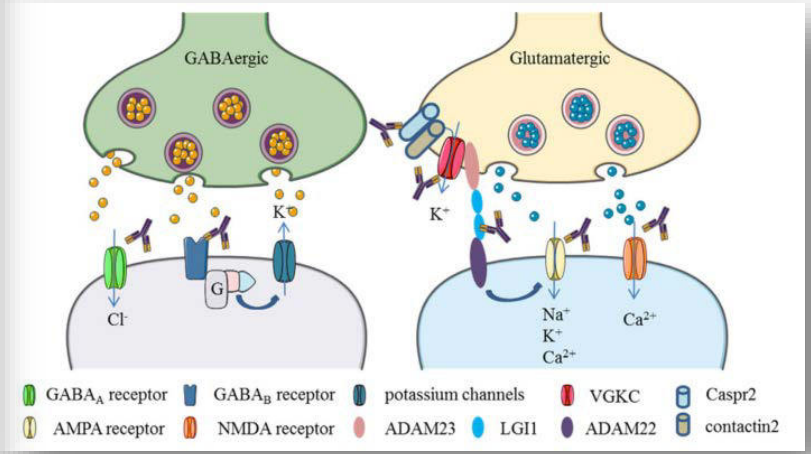
A patient population unable to be identified by current autoantibodies

frontiers in Immunology
REVIEW
published: 05 July 2017
doi: 10.3389/fimmu.2017.00752

Neuronal Surface Autoantibodies in Neuropsychiatric Disorders: Are There Implications for Depression?

*Shenghua Zong, Carolin Hoffmann, Marina Mané-Damas, Peter Molenaar, Mario Losen and Pilar Martinez-Martinez**

Division Neuroscience, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands



Thank you!

moleculera labs

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:

Craig Shimasaki, PhD, MBA

shimasakic@moleculera.com

www.MoleculeraLabs.com

U.S. +1(405) 239-5250

For orders outside the USA and Canada, please contact our partners:

The Academy of Nutritional Medicine – AONM

https://aonm.org/cunningham-panel-panspandas/

Email: cunninghampanel@aonm.org

Phone: 0044 3331 210 305

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