Autoimmune Encephalopathies: PANDAS/PANS and Antineuronal Antibody Testing

Academy of Nutritional Medicine (AONM) March 26, 2019

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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

4

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 +55% depressed at age 18 years Higher IL-6 baseline levels increased the risks of psychotic +81% experiences and psychotic disorder at age 18 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 +62% disorders (bipolar affective disorder or depression) Hospitalization for autoimmune disease increased the risk of a mood +45% disorder diagnosis The two risk factors together increased the risk of subsequent mood +135% disorders



- 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

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)

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

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 3Abnormalities in biomarkers of immune dysregula-tion or inflammation in ASD

Abnormality	Number of studies	
Cytokine abnormalities Autoantibodies to brain tissue Abnormal brain or CSF biomarkers Abnormal number of CD4 or CD8 cells Alterations in MHC Antibodies to foods Abnormalities in immunoglobulins Abnormalities in certain growth factors Genetic mutations affecting immune function Maternal antibodies to fetal brain tissue or lymphocytes Decreased Bcl-2 expression Alterations in BDNF Microglial activation Abnormalities in natural killer cells	studies 30 23 20 16 15 12 11 9 7 7 6 6 6 3 3 4	As of 2012 there were <u>127 published</u> <u>studies</u> demonstrating immune dysregulation in autism patients
Abnormal leptin levels	2	

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

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





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 Streptococcustriggered (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



Molecular Mimicry is a Well-Established Mechanism of Autoimmune Dysfunction

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

Neurologic or CNS Co	onditions
Guillain-Barré Syndrome	Sydenham Chorea
Multiple Sclerosis	Myasthenia Gravis
Anti-NMDA Receptor Encephalitis	Schizophrenia and Portions of Autism
Axon ##	// _ / ////



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



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 diseases¹



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

<u>Pediatric Autoimmune Neuropsychiatric Disorder</u> <u>Associated with Streptococcal infection</u>



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 Evolution of PANS Nomenclature and Hierarchy

Infection-Triggered 1. PANDAS Pediatric Autoimmune Bacterial, Viral, • Neuropsychiatric Disorder Associated with Parasitic, Fungal or Streptococcal Infection **PITANDS** possibly Pediatric Infection environmental? **Triggered Autoimmune** Neuropsychiatric Autoimmune 2. Disorders PANS **Other Microbes** Pediatric Acute-Immune dysfunction (Lyme, Mycoplasma, • onset others?) or Immune-mediated Neuropsychiatric Syndrome Non 3. Neuropsychiatric Syndrome Infectious or Symptoms **Triggers Environmental factors Metabolic disorders** Multiple symptoms ٠ Others Directed against portions of 4. **JCAP** the brain Journal of **Child and Adolescent** JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY **Consensus Statement** Volume 25, Number 1, 2015 Psychopharmacology Mary Ann Liebert, Inc. **Basal** ganglia Pp. 3-13 DOI: 10.1089/cap.2014.0084 ental Psychopathology and Therapeutic Clinical Evaluation of Youth with Pediatric 5. Acute-Onset Acute-Onset Neuropsychiatric Syndrome (PANS): Celebraring 25 Years Recommendations from the 2013 PANS **Consensus Conference** (Criteria for • Kiki Chang, MD^{1,*} Jennifer Frankovich, MD^{2,*} Michael Cooperstock, MD, MPH³ PANDAS/PANS but not 2015 Chang, K. et al. J Child Adolesc 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 Psychopharmacol 25(1): 3-13. and Susan E. Swedo, MD11; From the PANS Collaborative Consortiun 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 fears50%



- 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





The Cunningham Panel[™] Biomarker Components

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

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

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

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: obsessivecompulsive 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.

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







Autoantibodies can act as:

Agonist: a substance which <u>initiates a physiological</u> <u>response</u> 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



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%)

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



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

Pre-Treatment Results

Post-Treatment Results

ly ganglio-

side G_{M1}

of Positive Tests/Pt

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

	Num er Elevate	d Markers
СаМКІІ	Pretreatment	Post Treatment
110	1	0
117	1	0
93	1	0
83	1	0
98	1	0
83	1	0
123	1	0
112	1	0
113	1	0
134	1	1
112	2	0
111	2	0
113	2	0
131	2	2
92	2	0
111	2	0
122	2	0
116	2	0
128	2	1
138	2	2
83	2	0
132	2	1
122	2	1
148	2	1
108	3	0
118	3	0
89	3	0
124	3	0
119	3	0
120	3	3
119	4	1
110	4	1
134	4	1
165	4	1
100	4	0
100	4	1
150	4	1

Portion of data in submitted manuscript under review

Pre-Treatment Results

Post-Treatment Results

of Positive Tests/Pt

Case #		P	retreatmer	nt			Pc	ost treatme	nt		Number Elev	ated 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
20	2000	2000	2000	40	164	4000	16000	8000	160	150		
55	2000	8000	2000	320	160	4000	16000	8000	80	152		A
42	32000	4000	2000	80	112	4000	16000	2000	160	164		
39	8000	250	2000	160	159	2000	16000	4000	80	167	2	
26	4000	32000	8000	320	94	8000	16000	8000	1280	177		
14	8000	4000	2000	640	148	8000	16000	16000	40	07	3	
63	8000	32000	2000	320	142	22000	22000	8000	640	113	4	3
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

CaMKII Stimulation Assay Results



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

Sensitivity/Specificity Based Upon Positive Tests Compared to Symptoms

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









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

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







Portion of data in submitted manuscript under review

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 Connery¹, Marie Tippett¹, Leanna M. Delhey¹, Shannon Rose¹, John C. Slattery², Stephen G. Kahler¹, Juergen Hahn¹, ³⁴, Uwe Kruger³, Madeleine W. Cunningham⁵, Craig Shimasaki⁶ and Richard E. Frye³

Abstract

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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 MIG. 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

"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."

- 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

A Patent with Schizophrenia Diagnosis Responds to Immunomodulation Therapy

Hindawi Case Reports in Psychiatry Volume 2013, Article ID 3139067, 5 pages https://doi.org/10.1155/2013/8189067



Case Report

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

Drew H. Barzman ⁽⁵⁾,^{1,2} Hannah Jackson,^{2,3} Umesh Singh ⁽⁵⁾,⁴ Marcus Griffey,² Michael Sorter,^{2,5} and Jonathan A. Bernstein⁴

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Received 11 April 2018; Revised 1 June 2018; Accepted 6 June 2018; Published 28 June 2018

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

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY	Introduction		
Volume 27, Number 7, 2017	miroduction		
Pp. 1–4		JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY	Review-Article
DOI: 10.1089/cap.2017.0042		Volume 27, Number 7, 2017 Mary Ann Liebert, Inc.	Heren Article
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Overview of Treatment of Pediatric Acute-0	Onset		
Neuropsychiatric Syndrome		Oliniaal Management of Dedictric Acu	
Neuropsychiatric Syndrome		Clinical Management of Pediatric Acu	te-Onset
		Neuropsychiatric Syndrome:	
Susan E. Swedo, MD, Jennifer Frankovich, MD, MS, and Tanya K. Murphy,	MD, MS ⁴	Part I-Psychiatric and Behavioral Inte	rventions
		Margo Thienemann, MD ¹ Tanya Murphy, MD ² , James Leckman, MD ³ , Rich	hard Shaw, MD, PhD,
		Kyle Williams, MD, ⁴ Cynthia Kapphahn, MD, MPH, ¹ Jennifer Frankovich, MD, I	MPH ¹ Daniel Geller, MD ⁵
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Pp. 1–16 DOI: 10.1090/con.2016.0149			
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Part II—Use of Immunomodulatory Therapies	DOI: 10	0.1089/cap.2016.0151	
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Jennifer Frankovich, MD, MS ^{1,2} Susan Swedo, MD ³ Tanva Murphy, MD, MS ⁴ Russell C, D	ale, MD ⁵	Olinical Management of Dedictri	
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Gail Bernstein, MD,18 Reuven Bromberg, MD,19 Theresa Willett, MD, PhD,1 Kayla Brown,	BA, ^{1,2}	Part III—Treatment and Prevention of Ir	nfections
Bahare Farhadian, MSN, RN, FNP-C, ¹ Kiki Chang, MD, ^{1,20} Daniel Geller, MD, ²¹	or MD ²²		
James Leckman, MD, PhD, ²³ and Margo Thienemann, MD ^{1,20} ; PANS/PANDAS Consor	tium		
		Michael S. Cooperstock, MD, MPH, ¹ Susan E. Swedo, ME	D ²
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Developmental Psychology and Therapeutics 2. 2017 Frankovich et a	al. <u>J Child Adoles</u>	<u>c Psychopharmacol</u> 27(7): 574-593	
3 2017 Cooperstock e	t al. I Child Adol	esc 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"





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

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Patient Result		8,000	8,000	80	500	145	
Normal Ranges	54	0 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-1 0	6
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Ref: (1) Reported by Dr. Amirm Katz base upon his 112 patients studied and our patient responses

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

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
- More research and clinical studies to better identify the etiology and discover more efficacious and targeted treatments
- 4. Perseverance!



Neuroinflammation, Autoimmunity and the Brain

"This is an important book, a hopeful book, for anyone who wants to think about depression in a new way." Tom Insel, CEO and President, Mindstrong Health

THE INFLAMED MIND

A radical new approach to depression

EDWARD BULLMORE

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

This chiring accesses of a mother's determinations and a birt' attentiating bravery makes you want to stand up and chirr' Beth Alison Maloney Saving Saangy A Mother's Fight to Cure Her Son's OCD





BRAIN ON FIRE my month of madness

SUSANNAH CAHALAN



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



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Additional Information Sources



Pediatric Autoimmune Neuropsychiatric Disorders

pandasnetwork.org



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 <u>shimasakic@moleculera.com</u> <u>www.MoleculeraLabs.com</u> U.S. +1(405) 239-5250

Grace's Story – One of Thousands we Have Tested



Swedish Study of Cunningham Panel



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 <u>test-</u> <u>retest reliability of CaMKII may be insufficient,</u> <u>and that Cunningham Panel results are</u> commonly elevated in healthy controls.

Corrigendum



^a Center for Psychiatry Research, Department of Clinical Neuroscience, K ^b School of Medical Sciences, Orebro University, Orebro, 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)"... <u>The use of another blood collection tube than the</u> <u>one recommended by Moleculera could be viewed as a</u> <u>limitation in our study.</u>

Swedish Study of Cunningham Panel



Swedish Study Conclusions of Cunningham Panel

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



Red Col

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





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 <u>random intervals</u> over a period of <u>several months for 344</u> <u>individual tests</u>. We observed 62 readings at one dilution higher, 207 readings at the most commonly observed dilution, and 75 readings at one dilution lower

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)



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

Neurology[•] Neuroimmunology & Neuroinflammation

Antibody status of patients with AE

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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

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Figure 1

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

> Antibodies against synaptic receptor, ion channel, or other cell surface proteins

Antibodies against intracellular

neuronal or muscle antigens

Antibody negative

VGKCc
 LGI1
 Aquaporin 4

AChR
 Striational

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



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



A patient population unable to be identified by current autoantibodies

Thank you!



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 <u>shimasakic@moleculera.com</u> <u>www.MoleculeraLabs.com</u> 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

