BRAIN ON FIRE:

Lessons learned from PANS/PANDAS

Elisa H. Song, MD

A4M 2020 – Module VI

February 27-29, 2019

LEARNING OBJECTIVES

- Discuss the diagnosis, pathophysiology and "conventional" treatment of PANS/PANDAS
- Describe the connection between infection ↔ autoimmunity ↔ psychiatric disorders
- Recall the relevance of infection-driven autoimmune encephalitis in adults with psychiatric disease, using PANS/PANDAS as a model
- Explain how to use a 6-step functional medicine approach to identify and address underlying biomedical imbalances in PANS/PANDAS
- Explain how to address biofilms and immune system-activated hypercoagulability to help patients when they're "stuck"
- Review cases

WHO I AM

The 2 things I'm most proud of:

- Mom to 2 awesome kids! ☺
- Integrative pediatrician in the SF Bay Area

WHO I AM

- Stanford undergrad in political science/public policy
- NYU School of Medicine
- UCSF Pediatric Residency
- Additional training in:
  - Functional Medicine
  - Homeopathy
  - Traditional Chinese Medicine (acupuncture and herbs)
  - Western herbs, homotoxicology, essential oils, acupressure, infant massage, clinical hypnosis (SDBP)
- Lecturer for: CEDH, Academy for Pain Research, Center for Advanced Acupuncture Pediatrics, IFM, Holistic Pediatric Association
- Started Whole Child Wellness, an integrative pediatric practice in December 2005, now Whole Family Wellness
- Started Healthy Kids Happy Kids in June 2016, an online holistic pediatric and pediatric functional medicine resource for parents!
- Host of Thriving Child Summit 2016 and 2017

whole family wellness

www.wholefamilywellness.org

healthy kids happy kids

www.healthykidshappykids.com

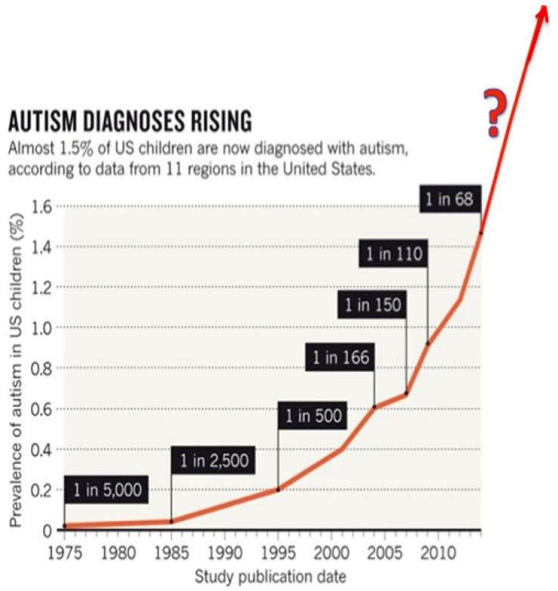
the thriving child summit

www.thrivingchildsummit.com

BRAINS ON FIRE…

EPIDEMIC OF CHILDHOOD NEURODEVELOPMENTAL & NEUROPSYCHIATRIC DISORDERS

- Autism rates are skyrocketing
  - 2017 CDC surveillance data: 1 in 59 children has autism spectrum disorder
    - 1 in 42 boys/1 in 189 girls
  - 1 in 41 in New Jersey
  - Higher in certain pockets of California
    - i.e., Silicon Valley



*2033
1 in 4

Assuming continued 13% annual growth rate.

*K. Weintraub, Nature 479, Nov. 3 2011, 22-24.

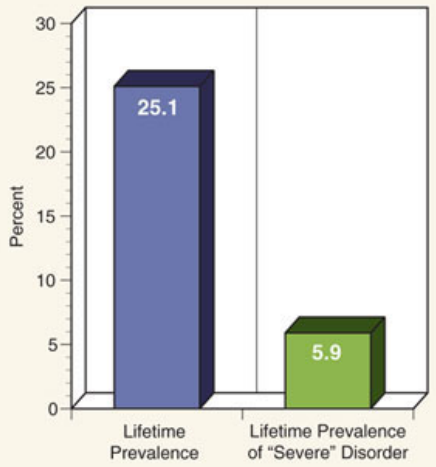
Estimates of 1 in 4 by 2033 are based on a projected annual growth rate of 13%; MIT Scientist Stephanie Seneff has estimated that 1 in 2 children will have autism by 2025

EPIDEMIC OF CHILDHOOD NEURODEVELOPMENTAL & NEUROPSYCHIATRIC DISORDERS

- Anxiety
  - 1 in 4 13-18 year-olds has an anxiety disorder
  - 1 in 15 has a "severe" anxiety disorder
- Depression
  - 1 in 10-15 teens has depression
- Any mental disorder13-18 years
  - 46% - ALMOST 1 IN 2!!!

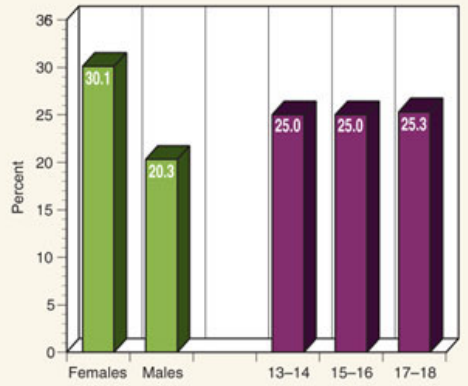
Lifetime Prevalence of 13 to 18 year olds

- **Lifetime Prevalence:** 25.1% of 13 to 18 year olds
- **Lifetime Prevalence of "Severe" Disorder:** 5.9% of 13 to 18 year olds have "severe" anxiety disorder



Demographics (for lifetime prevalence)

- **Sex:** Statistically different
- **Age:** Not statistically different



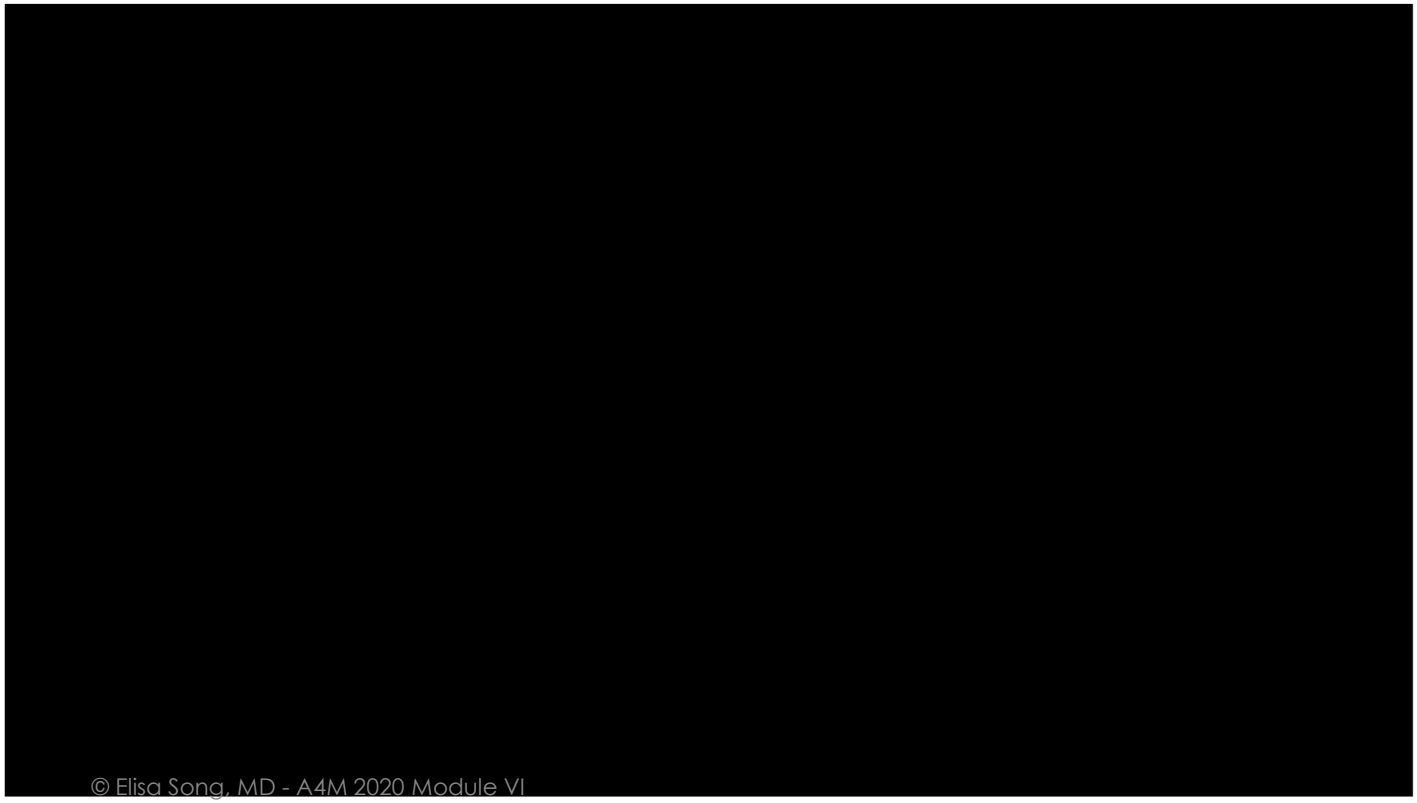
- **Race:** Statistically significant differences were found between non-Hispanic whites and other races

[1]Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J. *Lifetime prevalence of mental disorders in U.S. Adolescents.* Under review.

EPIDEMIC OF CHILDHOOD NEURODEVELOPMENTAL & NEUROPSYCHIATRIC DISORDERS

- PANS/PANDAS
  - As many as 1 in 200 US children may have PANS/PANDAS
  - As many as 1 in 4 kids with OCD and tic disorders (like Tourette syndrome) may have PANDAS
    - www.pandasnetwork.org
  - For more info, check out my 2-part interview for Fx Medicine Australia
    - https://www.fxmedicine.com.au/content/integrative-paediatrics-pandas-part-1-dr-elisa-song
    - https://www.fxmedicine.com.au/content/integrative-paediatrics-pandas-part-2-dr-elisa-song
  - And my interview with Dr. Kara Fitzgerald on New Frontiers in Functional Medicine
    - https://www.drkarafitzgerald.com/2019/07/13/functional-medicine-pediatrician-dr-elisa-song-pans-pandas-dx-treatment/

MY KIDS IS NOT CRAZY: A SEARCH FOR HOPE IN THE FACE OF MISDIAGNOSIS

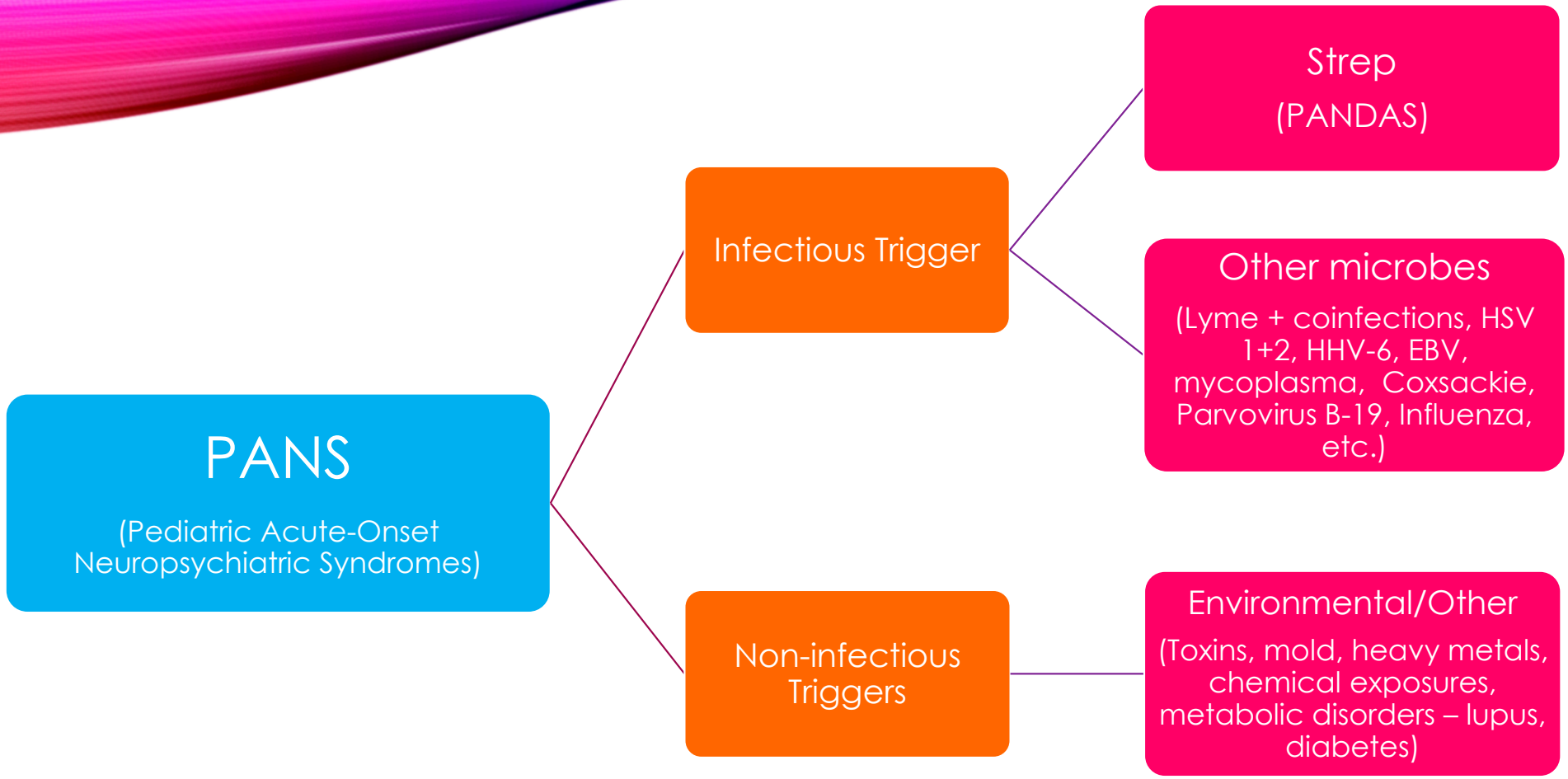


With permission, Tim Sorel, University of Florida, Journalism Professor

www.mykidisnotcrazy.com

WHAT IS PANS/PANDAS?

- Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS)
  - Infectious triggers
    - Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) is PANS triggered by strep
  - Non-infectious triggers



PANS IS AN AUTOIMMUNE ENCEPHALITIS

DIAGNOSTIC CRITERIA

PANS is defined by the following criteria:

Abrupt, dramatic onset of OCD or severely restricted food intake; symptoms are not better explained by a known neurologic or medical disorder; and the addition of at least 2 of the "accompanying" symptoms:

- Anxiety
- Emotional lability and/or depression
- Irritability, aggression and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration in school performance
- Sensory or motor abnormalities
- Somatic signs including sleep disturbances, enuresis or urinary frequency

The onset of PANS may start with infectious agents other than strep. It also includes onset from environmental triggers or immune dysfunction.

PANDAS is defined by the following criteria:

Clinical diagnosis of PANDAS includes 5 criteria:

- Presence of significant obsessions, compulsions and/or tics
- Abrupt onset of symptoms or a relapsing-remitting course of symptom severity
- Prepubertal onset
- Association with streptococcal infection
- Association with other neuropsychiatric symptoms (includes any of the PANS "accompanying" symptoms)

PANS/PANDAS remains a CLINICAL diagnosis

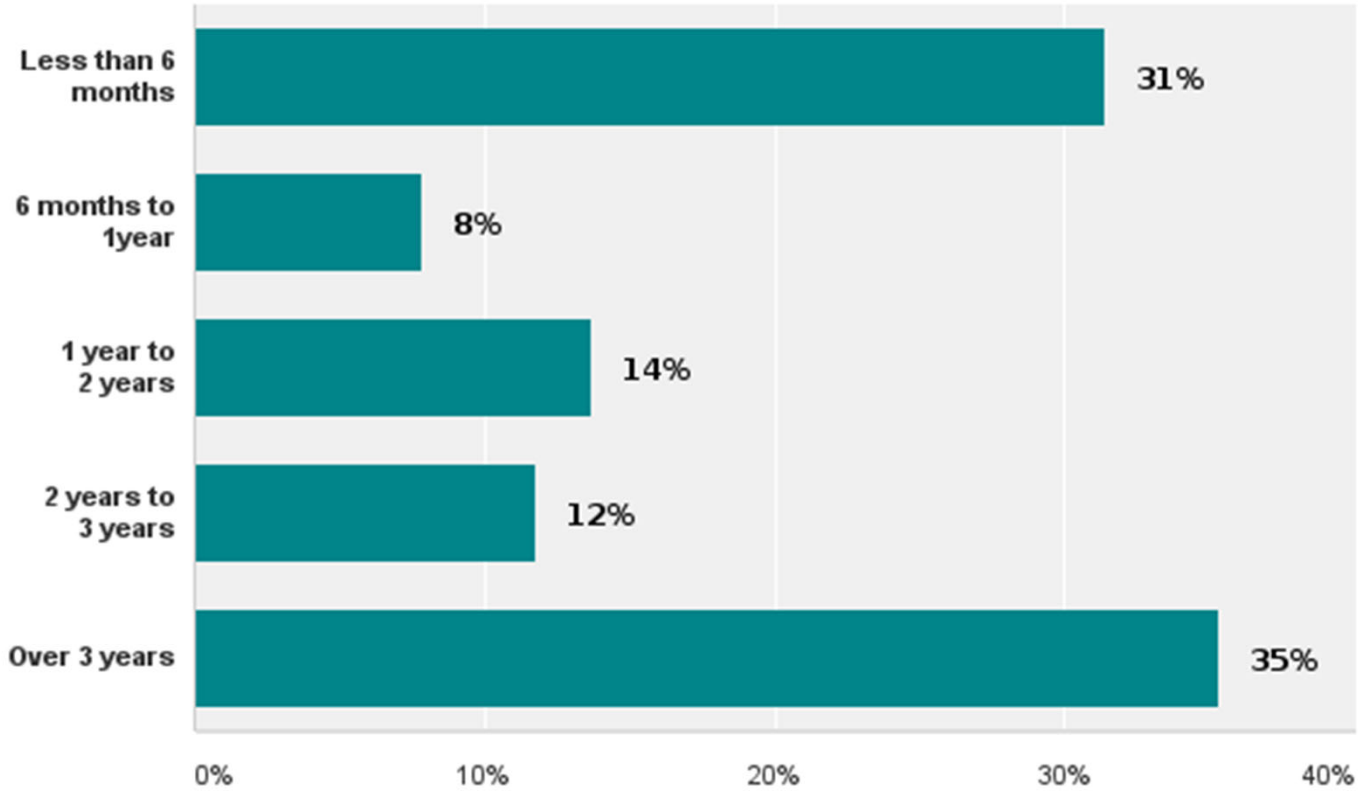
FREQUENT PANS SYMPTOMS I SEE

- Tics
- OCD
- Anxiety/Fears
- Separation anxiety
- Behavioral regression
  - Baby talk, loss of developmental milestones
- Personality changes
- Emotional lability
- Rages/Tantrums
- Oppositional behaviors
- Sleep disorders
- Hyper-alert flight-or-fight state
- Dilated pupils

- Decline in school performance
- **Handwriting decline**
- Inability to concentrate
- Slowed processing speed
- Short term memory loss
- Food restriction
  - Not necessarily dysmorphic
  - Fear based – choking, contamination, throwing up
  - Sensory – smells, taste, texture
- Hallucinations
- **Enuresis/Frequent urination**
- Choreiform movements (subtle)
- Dysphonia/Misophonia

PANS/PANDAS IS OFTEN MISDIAGNOSED AND LIKELY UNDERDIAGNOSED…

HOW LONG DID IT TAKE FOR DIAGNOSIS?



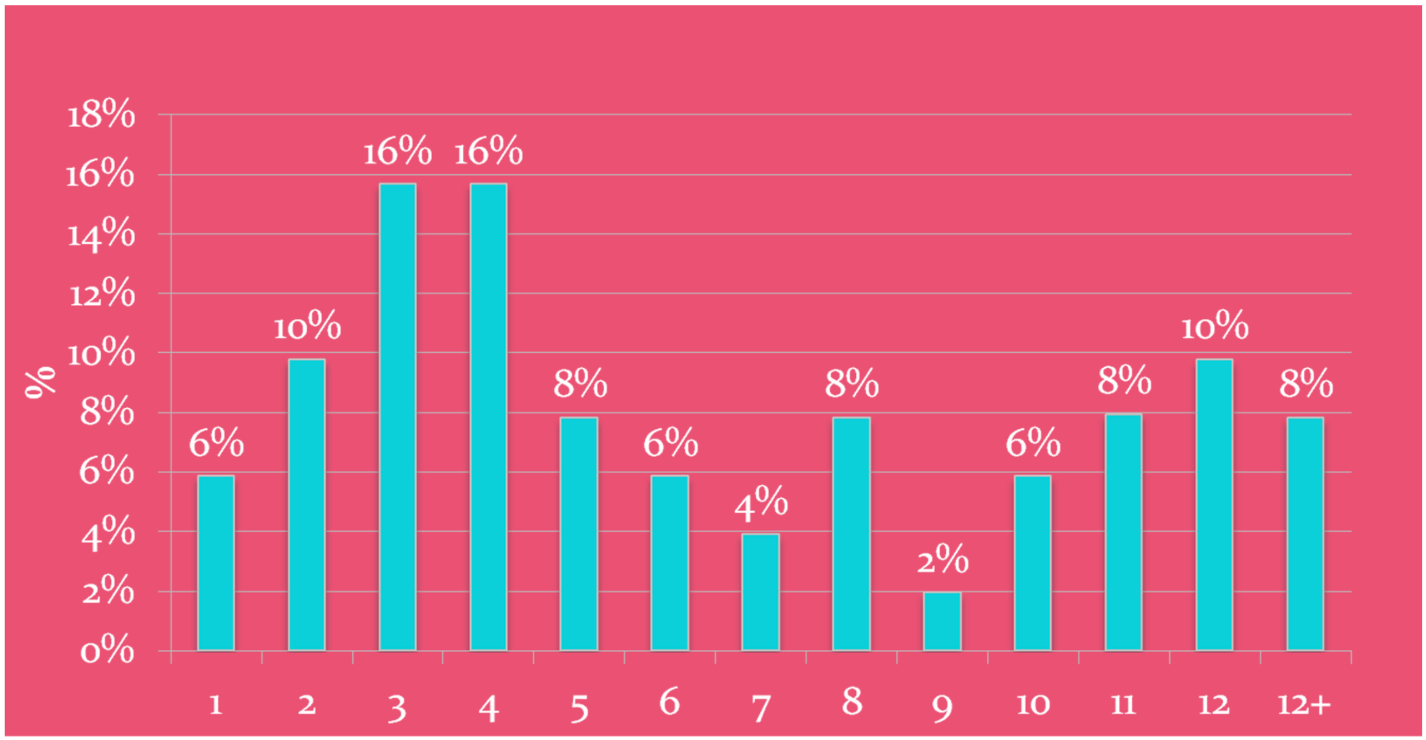
West Coast PANDAS/PANS Symposium

*PANDAS Parent Survey April 2014, San Francisco

Amy Fishman Smith, MS, Nurse Practitioner ©

HOW MANY DOCTORS DID WE SEE PRIOR TO PANDAS DIAGNOSIS?

- Almost 90% saw 3+ docs
- MORE THAN HALF (60%) saw 5+ doctors



# of Doctors Seen

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*PANDAS Parent Survey April 2014, San Francisco

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MOST COMMON INITIAL DIAGNOSES

Obsessive Compulsive Disorder (OCD) – 51%
Anxiety – 51%
Attention Deficit Disorder (ADHD) – 31%
Tourette's Syndrome/Tic Disorder – 18%
Asperger's Syndrome – 16%
Oppositional Defiant Disorder – 14%
Pervasive Development Disorder (NOS) – 4%
Conversion Disorder – 2%
Other – 24%

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*PANDAS Parent Survey April 2014, San Francisco

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CAN ADULTS HAVE PANS/PANDAS?

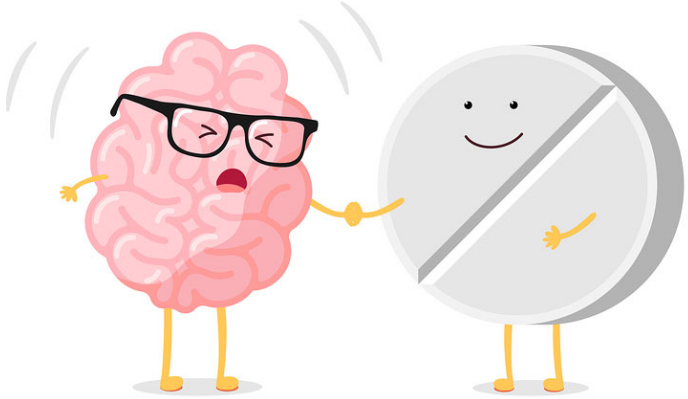
Probably…

INFLAMMATION & PSYCHIATRIC DISEASE

- Higher IL-6 and CRP in childhood associated with depression and psychosis in adulthood
  - Khandaker GM et al. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry.* (2014) 71:1121–8. doi: 10.1001/jamapsychiatry.2014.1332
  - Metcalf SA et al. Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: a prospective birth cohort study. *Brain Behav Immun.* (2017) 59:253–9. doi: 10.1016/j.bbi.2016.09.008
- Elevated cortisol and inflammatory markers associated with poor treatment response to typical anti-psychotic medications
  - Mondelli V et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophr Bull.* (2015) 41:1162–70. doi: 10.1093/schbul/sbv028
- Patients with severe depression have significantly higher levels of quinolinic acid (NMDA glutamate receptor agonist)
  - Quinolinic acid → marker for neuro-inflammation
    - Steiner, J. *et al.* Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: Evidence for an immune-modulated glutamatergic neurotransmission?. *J Neuroinflammation* **8,** 94 (2011). https://doi.org/10.1186/1742-2094-8-94

ANTI-INFLAMMATORY TREATMENT & MOOD DISORDER

- Anti-inflammatory therapy (aspirin) beneficial for treatment-resistant schizophrenia
    - Laan W et al. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders. *J Clin Psychiatry.* (2010) 71:520–7. doi: 10.4088/JCP.09m05117yel
- Concomitant use of SSRI with low-dose aspirin and ibuprofen associated with decreased risk of depression and psychiatric contact
    - Paracetamol increased mortality risk
        - Köhler et al. Inflammation and depression: combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes. *Brain Behav*. 2015;5(8):e00338. doi:10.1002/brb3.338



AUTOIMMUNE DISEASE & PSYCHIATRIC SYMPTOMS

- Anti-NMDA receptor (NMDA-R) encephalitis
  - Attack on the receptor for a single neurotransmitter, N-methyl-D-aspartate
  - Psychiatric and neurologic sx – anxiety, paranoia, hallucinations, cognitive impairment, movement disorders, seizures
    - Susannah Cahalan Brain on Fire
- Multiple studies show up to a 50% increased lifetime risk of autoimmune disorder with prior psychotic disorder and vice versa
  - Sometimes neuropsych concerns are the presenting symptoms of autoimmune disease…

AUTOIMMUNE DISORDERS ASSOCIATED WITH NEUROPSYCHIATRIC ISSUES

- Celiac disease
  - Study of over 3700 children → undiagnosed subclinical celiac disease (positive TTG Ab >= 7 U/mL WITHOUT any associated GI sx)
    - Significantly associated with emotional and behavioral problems (Anxiety, ODD, Aggression, Sleep disturbance)
    - Psychological sx may IMPROVE on gluten-free diet
      - Wahab RJ et al. Celiac disease autoimmunity and emotional and behavioral problems in childhood. Pediatrics October 2019, 144 (4) e20183933; DOI: https://doi.org/10.1542/peds.2018-3933
- Multiple studies showing increased risk of schizophrenia with celiac disease, and improvement of psychotic symptoms on GF diet

AUTOIMMUNE DISORDERS ASSOCIATED WITH NEUROPSYCHIATRIC ISSUES

- Multiple Sclerosis
- Systemic Lupus Erythematosus
  - Antibodies reacting to NR2 subunit of NMDA present in some cases of lupus
- Graves' disease
- Type 1 Diabetes?
  - Glutamic acid decarboxylase (GAD) antibodies can cross the BBB
    - Associated with some cases of limbic encephalitis
- Psoriasis
- Guillain-Barre syndrome
- Autoimmune hepatitis
- Crohn's disease
- Rheumatoid Arthritis may be PROTECTIVE against schizophrenia

Autoimmune disorders	Studies with positive association	Positive ass. only with concurrent infection	Studies with no significant association	Studies with negative association
Celiac disease	Chen et al (29), Cullen et al. (30), Benros et al. (26)		Benros et al. (25)	
Multiple sclerosis	Benros et al. (25), Benros et al. (26)		Wang et al. (27), Eaton et al. (28), Eaton et al. (24)	Johansson et al. (31)
Lupus	Wang et al. (27)	Benros et al. (26)	Cullen et al. (30), Benros et al. (25), Chen et al. (29), Eaton et al. (28), Eaton et al. (24)	
Graves/thyrotoxicosis	Chen et al. (29), Cullen et al. (30), Eaton et al. (28), Eaton et al. (24), Benros et al. (26)		Benros et al. (25)	
Autoimmune thyroiditis		Benros et al. (26)	Eaton et al. (28), Benros et al. (25)	
Diabetes type 1	Benros et al. (25), Eaton et al. (24), Benros et al. (26)		Chen et al. (29), Cullen et al. (30), Cremaschi et al. (32)	Juvonen et al. (33)
Rheumatoid arthritis	Wang et al. (27)	Benros et al. (26)	Eaton et al. (28), Eaton et al. (24)	Benros et al. (25), Chen et al. (29), Cullen et al. (30)
Psoriasis	Benros et al. (25), Chen et al. (29), Cullen et al. (30), Eaton et al. (24), Benros et al. (26)		Eaton et al. (28),	
Guillain-Barre	Benros et al. (25)	Benros et al. (26)	Eaton et al. (28),	
Crohns disease	Benros et al. (25)	Benros et al. (26)	Wang et al. (27), Cullen et al. (30), Eaton et al. (24)	
Autoimmune hepatitis	Benros et al. (25), Eaton et al. (28), Eaton et al. (24), Benros et al. (26)			
Pernicious anemia	Benros et al. (25), Cullen et al. (30), Chen et al. (29)			
Primary adrenocortical insufficiency	Benros et al. (25),			
Primary biliary cirrhosis	Benros et al. (25),			
Ankylosing spondylitis	Eaton et al. (24)	Benros et al. (26)	Benros et al. (25), Chen et al. (29), Eaton et al. (28)	Cullen et al. (30)
Sjögren syndrome	Eaton et al. (28)	Benros et al. (26)	Benros et al. (25), Chen et al. (29)	
Hypersensitivity vasculitis	Chen et al. (29)			
Haemolytic anemia	Eaton et al. (28)		Chen et al. (29)	
Pemphigoid	Cullen et al. (30)		Eaton et al. (28)	
Alopecia areata	Eaton et al. (28)		Benros et al. (25), Cullen et al. (30), Chen et al. (29)	
Polymylagia rheumatic	Eaton et al. (28)		Benros et al. (25), Chen et al. (29)	

Table 1. Associations found between autoimmune diseases and psychotic disorders.

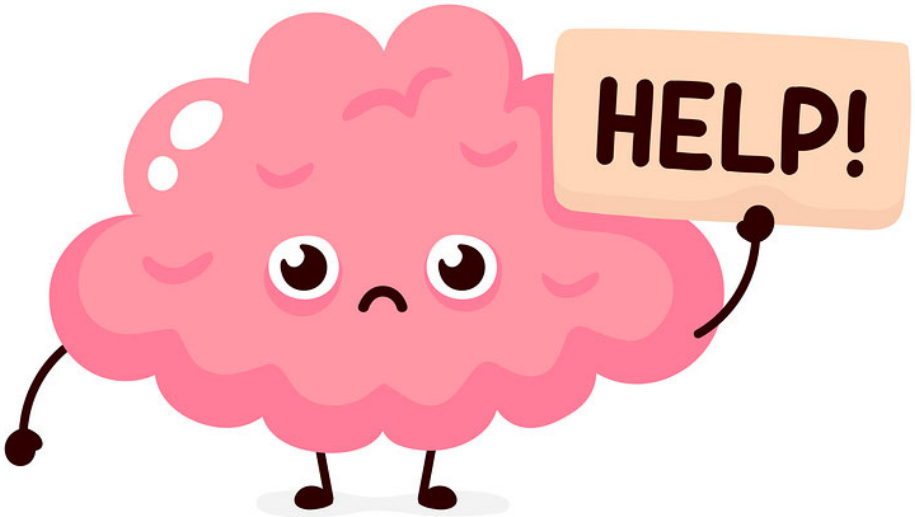
Jeppesen R and ME Benros. Autoimmune Diseases and Psychotic Disorders. Front. Psychiatry, 20 March 2019 | https://doi.org/10.3389/fpsyt.2019.00131

INFECTION & PSYCHIATRIC DISEASE

- Repeated low-grade infections significantly increases risk of developing major depressive disorder (MDD)
  - Patients with infection history and MDD had POORER response to antidepressants
  - Relative risk of MDD after repeated low-grade infections increased 37-91%
    - Jeng JS, Li CT, Chen MH, et al. Repeated low-grade infections predict antidepressant-resistant depression: a nationwide population-based cohort study. *The Journal of Clinical Psychiatry*. 2017 December 19. *https://doi.org/10.4088/JCP.17m11540*
- Infectious (HSV encephalitis) significant risk for subsequent NMDA-R encephalitis
    - Armangue T et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol.* (2018) 17:760–72. doi: 10.1016/S1474-4422(18)30244-8
- Prior infection significantly increases risk of schizophrenia – in DOSE-RESPONSE fashion (26), 72, 73)
    - Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry.* (2011) 168:1303–10. doi: 10.1176/appi.ajp.2011.11030516

INFECTIONS & THE BLOOD-BRAIN BARRIER

- Exposure to viral or bacterial infection → *increases* permeability of the BBB
  - Chaudhuri JD. Blood brain barrier and infection. *Med Sci Monit.* (2016) 6:1213–22.



INFECTIONS, AUTOIMMUNITY & PSYCHIATRIC DISEASE

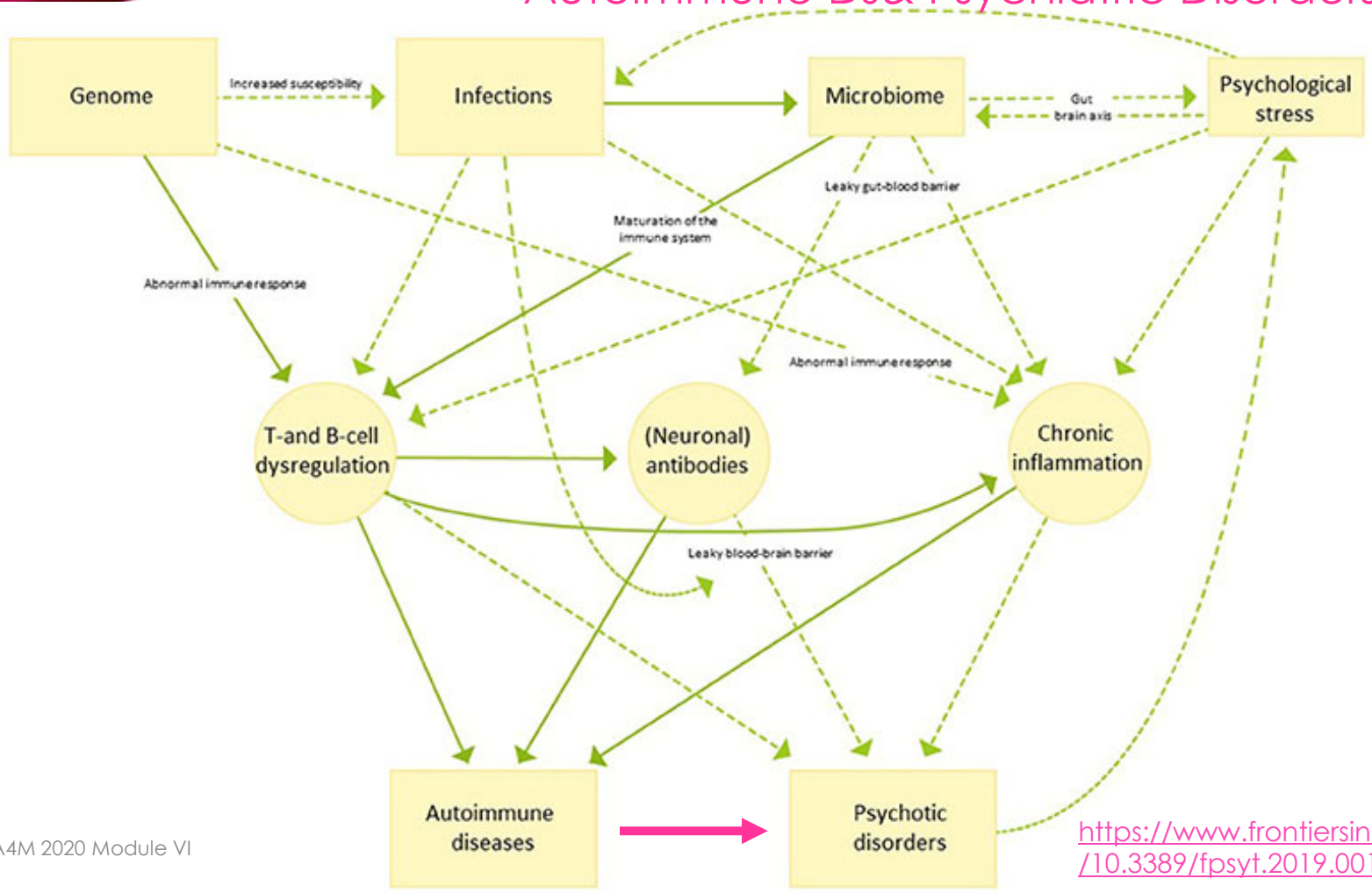
- Danish study of over 3.5 million people
  - ANY history of hospitalization for infection associated with 62% increased risk of later developing a mood disorder
    - Including depression and bipolar disorder
  - Past history of autoimmune disorder increased risk of future mood disorder by 45%
  - Having past infection AND autoimmune disorder associated with 2.35-fold increase in risk of future mood disorder
  - Dose-response relationship between number of infections and autoimmune diseases
    - Benros ME et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry.* 2013;70(8):812-820. doi:10.1001/jamapsychiatry.2013.1111

Infection + Autoimmune disorder → Mood disorder

(How common are infections & autoimmune ds???)

PANS AS A MODEL FOR INFECTION-DRIVEN AUTOIMMUNE ENCEPHALITIS

Possible Mechanisms Linking Infections, Autoimmune Ds& Psychiatric Disorders



https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00131/full

IMMUNE DYSREGULATION IN AUTOIMMUNE ENCEPHALITIS & PSYCHIATRIC DISORDERS

- Dysregulation between *decreased* regulatory T cells and *increased* Th17 cells implicated in many autoimmune disorders and psychiatric illnesses
  - Diller ML, Kudchadkar RR, Delman KA, Lawson DH, Ford ML. Balancing inflammation: the link between Th17 and regulatory T Cells. *Mediators Inflamm.* (2016) 2016:6309219. doi: 10.1155/2016/6309219
- Increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines (IL-10) found in patients with schizophrenia
  - IL-10 dysregulation linked with *abnormal response* to common infections and increased risk for autoimmune disease
    - Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol.* (2012) 32:23–63. doi: 10.1615/CritRevImmunol.v32.i1.30

JCI The Journal of Clinical Investigation

Group A *Streptococcus* intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells

Thamotharampillai Dileepan,[1] Erica D. Smith,[2] Daniel Knowland,[2] Martin Hsu,[2] Maryann Platt,[3] Peter Bittner-Eddy,[1] Brenda Cohen,[1] Peter Southern,[1] Elizabeth Latimer,[4] Earl Harley,[5] Dritan Agalliu,[2,3] and P. Patrick Cleary[1]

First published December 14, 2015

Abstract

Group A streptococcal (GAS) infection induces the production of Abs that cross-react with host
mechanisms that allow these Abs to cross the blood-brain barrier (BBB) and induce neuropatho
nasal-associated lymphoid tissue (NALT). Here, we identified GAS-specific Th17 cells in tonsils o
following i.n. infection. Intranasal challenge of repeatedly GAS-inoculated mice promoted mig
loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected
direct input from the OB. Together, these findings provide insight into the immunopathology of r
cellular immunity may be a general mechanism by which infectious agents exacerbate sympt

Introduction

Pharyngitis caused by Streptococcus pyogenes (group A Streptococcus [GAS]) is a common, t
rheumatic heart disease as well as motor and neuropsychiatric disorders, can produce chronic
20% to 30% of children with acute rheumatic fever (2, 3). An increasingly recognized neuropsyc
subset of individuals with abrupt onset of obsessive-compulsive disorder (OCD), anorexia nervo
infections or other undefined triggers. The time of onset and periodic exacerbation of symptom
mechanism; yet the role of T cells and the route of autoantibody entry into the CNS in SC and P

The connection between GAS infection, neuronal-specific autoantibodies, and SC is well estab
Indeed, very little is known about CNS immunopathology associated with bacterial infections, a
well characterized (12). Behavioral changes and IgG deposition in the brain have been reporte
GAS) or immunization with bacterial protein extracts. Yet, the mechanism by which Abs cross th
coadministration of either Bordetella pertussis toxin or LPS, two agents that disrupt the BBB (13, 1

GAS has a tropism for murine nasal–associated lymphoid tissue (NALT), which is functionally eq
dependent, protective Th17 cellular response in NALT. Repeated i.n. infections expand Th17 cel
through the generation of ROS in endothelial cells (19, 20). Moreover, IL-17A+ and IL-17A+IFN-γ
Peripheral blood contains few IL-17A+ T cells; however, tonsils are reported to contain large nu
us to examine whether tonsils contain streptococcus-specific Th17 cells. Here, we report that hu
plate, coupled with our discovery of significant numbers of GAS-specific T cells in human tonsils
Th17 cells to enter the brain in mice. Our results indicate the presence in the brain of GAS-speci
(microglia activation), and deficits in synaptic connectivity.

Major findings:

1. Repeated intranasal infections with Strep A in mice promoted Strep-induced Th17 cell differentiation and movement from the NALT (nasal tissue) into the brain, resulting in blood-brain barrier breakdown, serum IgG deposition, neuro-inflammation with loss of excitatory synaptic proteins, under conditions where **no viable bacteria** were detected in the brain.
2. T cells migrated from the nose into the brain along the olfactory sensory axons directly through the cribiform plate and NOT through the blood brain barrier.
3. Once in the brain, the Th17 cytokines broke down the blood-brain barrier, allowing circulating autoantibodies to cross the leaky blood-brain barrier, enter the brain and recognize / attack neuronal targets.
4. Th17 cytokines were present in the tonsils of children with PANDAS (and not control groups of 'normal' children or children with Tourette disorder.) This may be likened to the NALT in mice.

Amy Fishman Smith, MS, Nurse Practitioner ©

Summary adapted from pandasnetwork.org

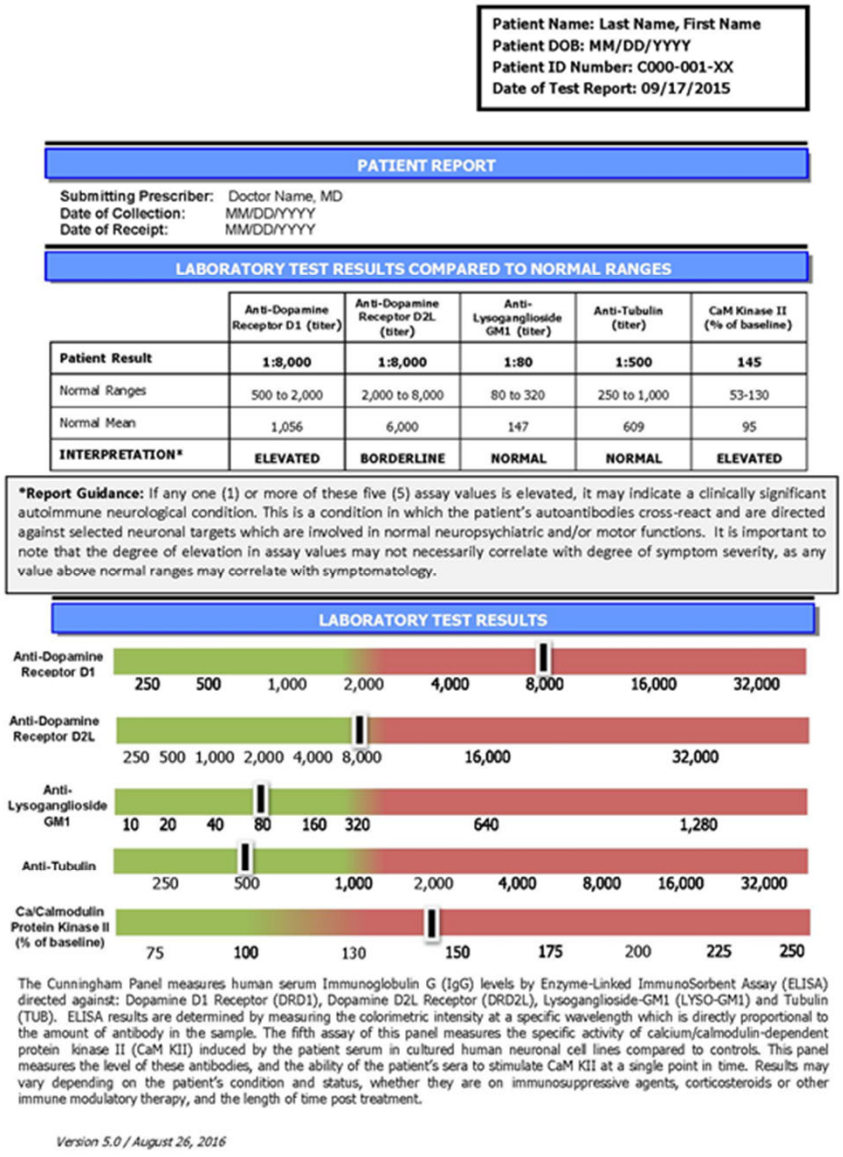
GROUP A STREP – A STEALTH PATHOGEN?

- Group A strep can evade and impair host defenses
- GAS has been found to:
  - Avoid phagocytic engagement
  - Inhibit complement and antibody functions required for opsonization
  - Impair phagocytic uptake mechanisms
  - Promote phagocytic lysis or apoptosis
  - Resist phagocytic killing mechanisms (antimicrobial peptides, ROS)
    - Kwin LA and V Nizet. **How group A Streptococcus circumvents host phagocyte defenses.** Future Microbiol. 2007 Feb;2(1):75-84.

THE "CUNNINGHAM PANEL"

Dr. Madeleine Cunningham, University of Oklahoma

- Four specific auto-antibodies against 4 brain antigen targets
- Signaling molecule called CAM-Kinase II reflective of blood-brain-barrier function
- Can help identify patients with PANS when other tests are inconclusive



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 Prescriber: 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 II (% of baseline)
Patient Result	**1:8,000**	**1:8,000**	**1:80**	**1:500**	**145**
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	**ELEVATED**	**BORDERLINE**	**NORMAL**	**NORMAL**	**ELEVATED**

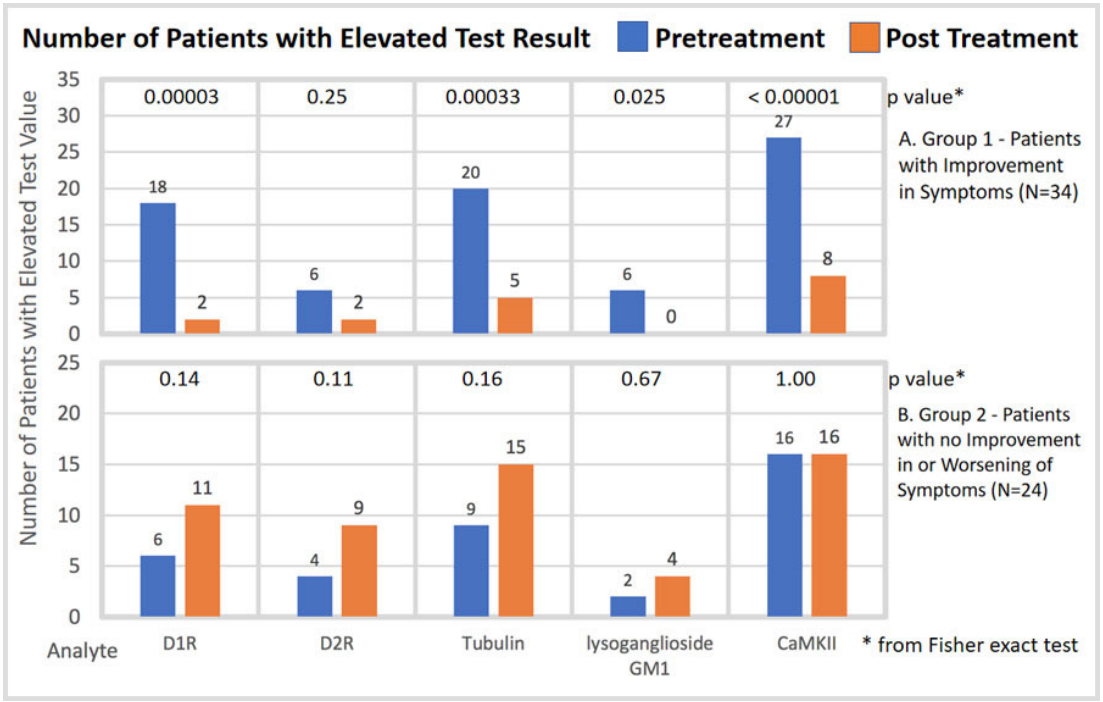
***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D1 Receptor (DRD1), Dopamine D2L Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). ELISA results are determined by measuring the colorimetric intensity at a specific wavelength which is directly proportional to the amount of antibody in the sample. The fifth assay of this panel 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 controls. 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.

Version 5.0 / August 26, 2016

CUNNINGHAM PANEL - A VALUABLE TOOL



- 58 pts tested with Cunningham panel
- Strong positive association between post-treatment changes in neuropsychiatric symptoms and changes in the level of antineuronal antibodies and antibody-mediated CaMKII human neuronal cell activation
- These study findings support clinical utility of the antineuronal and cell-stimulatory assays comprising the Cunningham Panel™ as an aid in diagnosis, and laboratory evidence supporting an underlying autoimmune etiology
  - https://doi.org/10.1016/j.jneuroim.2019.577138

EARLY DIAGNOSIS AND TREATMENT IS KEY FOR RECOVERY…

(PANS/PANDAS, like Lyme disease, remains a CLINICAL DIAGNOSIS)

DIAGNOSIS STARTS WITH CLINICAL SUSPICION…

- PANS is a "diagnosis of exclusion"
  - PANS remains a clinical diagnosis
  - No single confirmatory test
- Clues in the history…
  - A CHANGE in behaviors that steadily worsens and persists
    - Doesn't have to be sudden
    - Doesn't have to be in a previously totally neurotypical kid
    - Even if there's an "excuse" – baby sibling, new school, divorce, etc.
  - History of a prior illness (strep or non-strep) before behavioral change
  - Family history of tic disorder, neuropsychiatric disorder, autoimmune disorder, recurrent infections/immunodeficiency, CFIDS, fibromyalgia

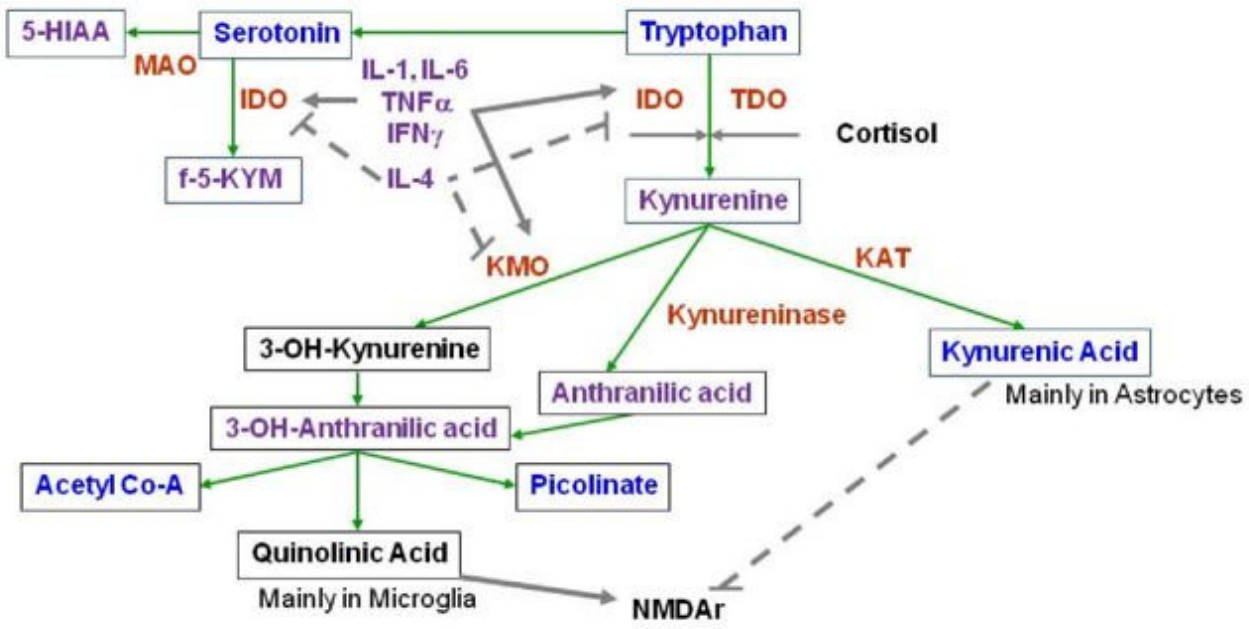
Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS):Recommendations from the 2013 PANS Consensus Conference , *Kiki Chang, Jennifer Frankovich, Michael Cooperstock, Madeleine W. Cunningham, M. Elizabeth Latimer, Tanya K. Murphy, Mark Pasternack, Margo Thienemann, Kyle Williams, Jolan Walter, Susan E. Swedo.*

INITIAL TESTING

- Look for the infectious trigger(s) – history may guide you
  - Cultures of throat, nose, anus, skin lesions for strep
  - ASO, Anti-DNAse B strep antibody
  - Quantitative IgG/IgM titers – Lyme + coinfections, EBV, Mycoplasma pneumonia, HSV 1+2, HHV-6, Coxsackievirus A+B, Parvovirus B-19, CMV, Influenza, Candida…
  - Stool analysis – strep in the gut, yeast, parasites

INITIAL TESTING

- Urine organic acid testing
  - Increased quinolinic acid or Quinolinic:Kynurenic



Tryptophan is an essential amino acid and a precursor for the synthesis of serotonin. Alternatively, tryptophan can be metabolized in glial cells via the kynurenine pathway to create kynurenic acid (synthesized by kynurenine aminotransferase, KAT) or quinolinic acid (QUIN). These substances are endogenous modulators of NMDA glutamate receptors. A key enzyme of the kynurenine pathway, indoleamine 2,3-dioxygenase (IDO), and the enzyme that catalyses the production of 3-OH-kynurenine, kynurenine monoxygenase (KMO), are activated by proinflammatory cytokines, including interleukin-1 and -6 (IL-1, IL-6), tumor necrosis factor a (TNFa), or interferon g (IFNg). These enzymes are inhibited by anti-inflammatory cytokines, including IL-4. Serotonin is normally broken down into 5-hydroxyindoleacetic acid (5-HIAA), but the indole ring of serotonin can also be cleaved by IDO to form formyl-5-hydroxykynurenamine (f-5-KYM). *Annotation:* grey arrows: activation; dotted grey lines with bar at the end: inhibition; black font: potentially neurotoxic; purple font: neutral or not known; bright blue: potentially neuroprotective. https://doi.org/10.1186/1742-2094-8-94

INITIAL TESTING

- Very elevated IgG titers may represent CHRONIC ACTIVE INFECTION
  - Even with negative IgM titers
  - Seen in severe chronic active EBV infection syndrome
    - Okano Motohiko, Matsumoto Shuzo, Osato Toyoro, Sakiyama Yukio, Thiele Geffrey M,. Purtilo David T. Clinical Microbiology Reviews, January 1991, 4(1): 129-135. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC358181/pdf/cmr00042-0145.pdf
- BE AWARE
  - Chronic infections lead to immune dysfunction and will lower IgG levels over time
  - Even low level of IgG titers may be significant
- Cunningham panel – when titers are "inconclusive"

INITIAL TESTING

- Autoimmune/inflammatory markers
  - Complete blood count
    - Often decreased WBC with neutropenia
  - Total IgG with subclasses, IgA, IgM
  - ANA and other autoantibodies
  - Celiac panel
  - Cunningham panel
- Consider non-infectious triggers
  - Heavy metals
    - Urine DMSA challenge (10mg/kg x 1 dose)
  - Mold
    - C4a level screening test
    - Urine mycotoxin testing, Shoemaker panel

LET HISTORY GUIDE YOUR TESTING

EVER SINCE WHEN…

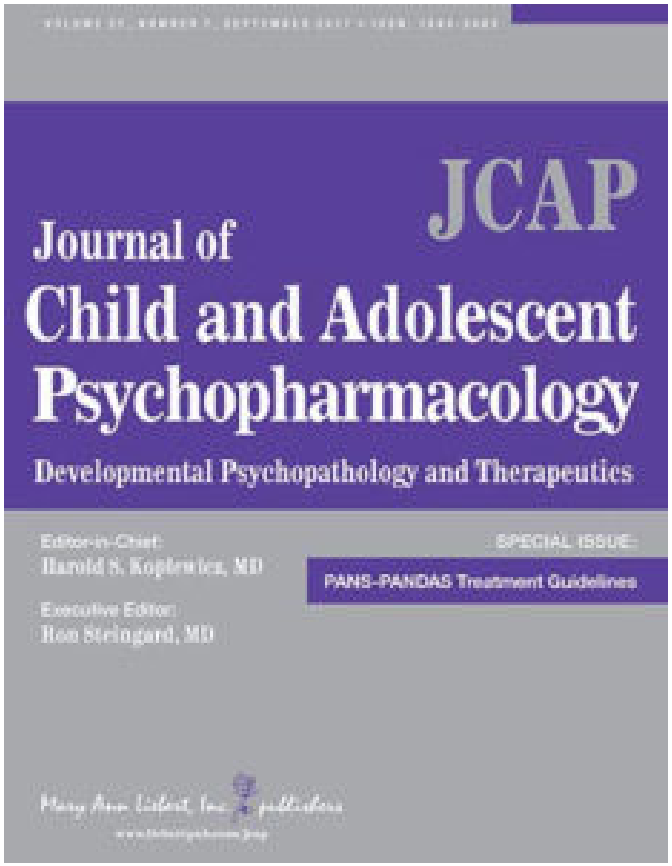
- Recurrent strep throat, perianal strep, impetigo
- Recurrent sinus infections (protected cavity for bacteria)
- Roseola (HSV-6), cold sores (HSV-1/2), slapped cheek (Parvo B-19)
- h/o tick bites, bug bites or tick endemic areas, or if family member especially a parent is known to have Lyme
- Symptoms suspicious for Lyme or coinfections – rashes, migratory joint pains or pain in the feet, dizziness, night sweats, air hunger, tingling sensations and do not get better with PANDAS treatment
- Recurrent antibiotics and thrush/signs of yeast overgrowth
- Heavy metal exposures
- Worse after moving, or better in different environment, water damage (?mold)

USE "TREATMENTS" AS DIAGNOSTIC TOOLS

- Trial of Ibuprofen 10mg/kg/dose TID x 1 week
- Trial of azithromycin or amoxicillin
- Trial of prednisone 2mg/kg/day x 5 days

"CONVENTIONAL" TREATMENT GUIDELINES BY THE PANS/PANDAS RESEARCH CONSORTIUM

1. Psychiatric/behavioral interventions – esp CBT
2. Therapeutic and/or prophylactic antimicrobials
3. Immunomodulatory and/or anti-inflammatory therapies
   - IVIG 2 gram/kg over 2 days
   - Oral corticosteroid bursts
   - Oral corticosteroid taper
   - IV methylprednisolone/oral dexamethasone pulse
   - Plasmapheresis, Plaquenil, Rituximab
4. Treatment may be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again given the ***relapsing-remitting nature of PANS symptoms***



MY 6-STEP FUNCTIONAL MEDICINE APPROACH TO PANS

STEP 1: IDENTIFY & TREAT THE ROOT CAUSE(S) - Treat the trigger(s)

STEP 2: PUT OUT THE FIRE – Lower the inflammation and protect the brain

STEP 3: KEEP THE FIRE DOWN – Modulate the immune response

STEP 4: ADDRESS CORE CLINICAL IMBALANCES

STEP 5: RESTORE THE BODY-MIND-SPIRIT CONNECTION

STEP 6: INTEGRATIVE CARE

STEP 1: TREAT THE ROOT CAUSE(S)

- There may be multiple triggers
- New triggers may arise with each "flare"

STEP 1: TREAT THE ROOT CAUSE(S)

- **Treat infection(s) with pathogen-specific antimicrobial(s)**
  - Strep – azithromycin, amoxicillin, amoxicillin-clavulanic acid, consider T&A
  - Viral infections – valacyclovir, olive leaf extract, lauricidin, vitamin A
  - Yeast – fluconazole, nystatin, GSE, lauricidin, MCT oil, uva ursi
  - Parasites – nitazoxanide, black walnut hulls, artemisinin, GSE
  - Mycoplasma – azithromycin, doxycycline
  - Lyme + coinfections → refer to Lyme-literate doctor

STEP 1: TREAT THE ROOT CAUSE(S)

- **Treat heavy metal exposure**
  - Glutathione
  - Minerals
  - Modified citrus pectin
  - Chlorella, Alginate
  - DMSA
- **Treat mycotoxin exposure**
  - Glutathione
  - Activated charcoal
  - Mold remediation
  - Refer to an environmental mold specialist

STEP 2: PUT OUT THE FIRE

- GOAL: Reduce inflammation and protect the brain
- You may need to do this repeatedly with each flare…

PHARMACEUTICAL ANTI-INFLAMMATORIES

- Ibuprofen bursts
- Steroid bursts or longer taper
- Long-term NSAID (naproxen)
  - Watch for GI side effects, gastritis, abdominal pain, GI bleed
  - Always give with food
  - Use with demulcent foods to help protect mucous layer
    - Slippery elm, DGL, aloe
    - Bone broth

HERBAL ANTI-INFLAMMATORIES

- Omega-3 essential fatty acids
- Curcumin
- Quercetin
- Anti-oxidants (Glutathione, Vitamin C, Vitamin A, Vitamin E, Resveratrol)

ADDITIONAL ANTI-INFLAMMATORY SUPPORTS

- Anti-inflammatory diet
  - Gluten-free
  - Organic, wild, free-range
  - Low in processed foods and refined sugars
  - No artificial dyes, flavors, preservatives
- Stress reduction
  - Cognitive-behavioral therapy
    - Dawn Huebner's Outsmarting Worry and What to do When You Worry Too Much
  - Mindfulness/meditation
    - Stop Breathe Think Kids, Insight Timer app, Breathe app, Calm app, Headspace app
    - Heartmath

STEP 3: KEEP THE FIRE DOWN

Goal: modulate the immune system to REDUCE frequency of flares and achieve permanent remission

- IVIG
- Low-dose naltrexone
- Specialized pro-resolving mediators (SPMs)
- CBD oil
- Chinese Skullcap (Baikal or Scutellaria baicalensis)

HIGH-DOSE IVIG

- IVIG 2 grams/kg over 1 days
  - KA Williams, SE Swedo, CA Farmer, et al. Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. Journal of the American Academy of Child & Adolescent Psychiatry, August 6, 2016. http://www.jaacap.com/article/S0890-8567(16)31158-3/pdf
  - Used as an immune "reboot"
  - NOT the same as IVIG replacement doses for immunodeficiency (500mg/kg qmo)
  - Can be a GAME-CHANGER

- "Conventional" options are invasive and not accessible to many
- Promising functional medicine/alternative options…

LOW-DOSE NALTREXONE

- In low doses, naltrexone (LDN) can have anti-inflammatory/ immunomodulatory on CNS via microglial cells
- Benefit for autism, fibromyalgia, Crohn's disease, MS, complex regional pain syndrome (CRPS), ?infertility
- Naltrexone has antagonist effects on opioid receptors AND non-opioid receptors (Toll-like receptor 4 or TLR4) found on macrophages like microglia
  - Activated microglia produce inflammatory factors → neuropsychiatric sx like pain sensitivity, fatigue, cognitive disorders, sleep disruption, mood disorders, general malaise
  - Chronic microglial activation → neurotoxicity
- LDN → neuroprotective and analgesic effects

- Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN(as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol (2014) 33:451–459. DOI 10.1007/s10067-014-2517-2

LOW-DOSE NALTREXONE

- Typical adult dosage – 4.5mg QHS
- ??? Pediatric dosage
  - Ranges anywhere from 0.5 – 3.5mg QHS

SPECIALIZED PRO-RESOLVING MEDIATORS

- Derived from EPA and DHA omega-3 essential fatty acids
- "SPMs are lipid mediators that are part of a larger family of pro-resolving molecules, which includes proteins and gases, that together restrain inflammation and resolve the infection"
- NOT immunosuppressants
- Act to modulate inflammatory response to KEEP INFLAMMATION DOWN

REMEMBER: ACUTE INFLAMMATION IS A NORMAL RESPONSE TO INFECTION. CHRONIC INFLAMMATION AND AUTOIMMUNITY OCCUR WHEN INFLAMMATION GOES UNCHECKED…

- Basil MC and Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. doi:10.1038/nri.2015.4

SPECIALIZED PRO-RESOLVING MEDIATORS

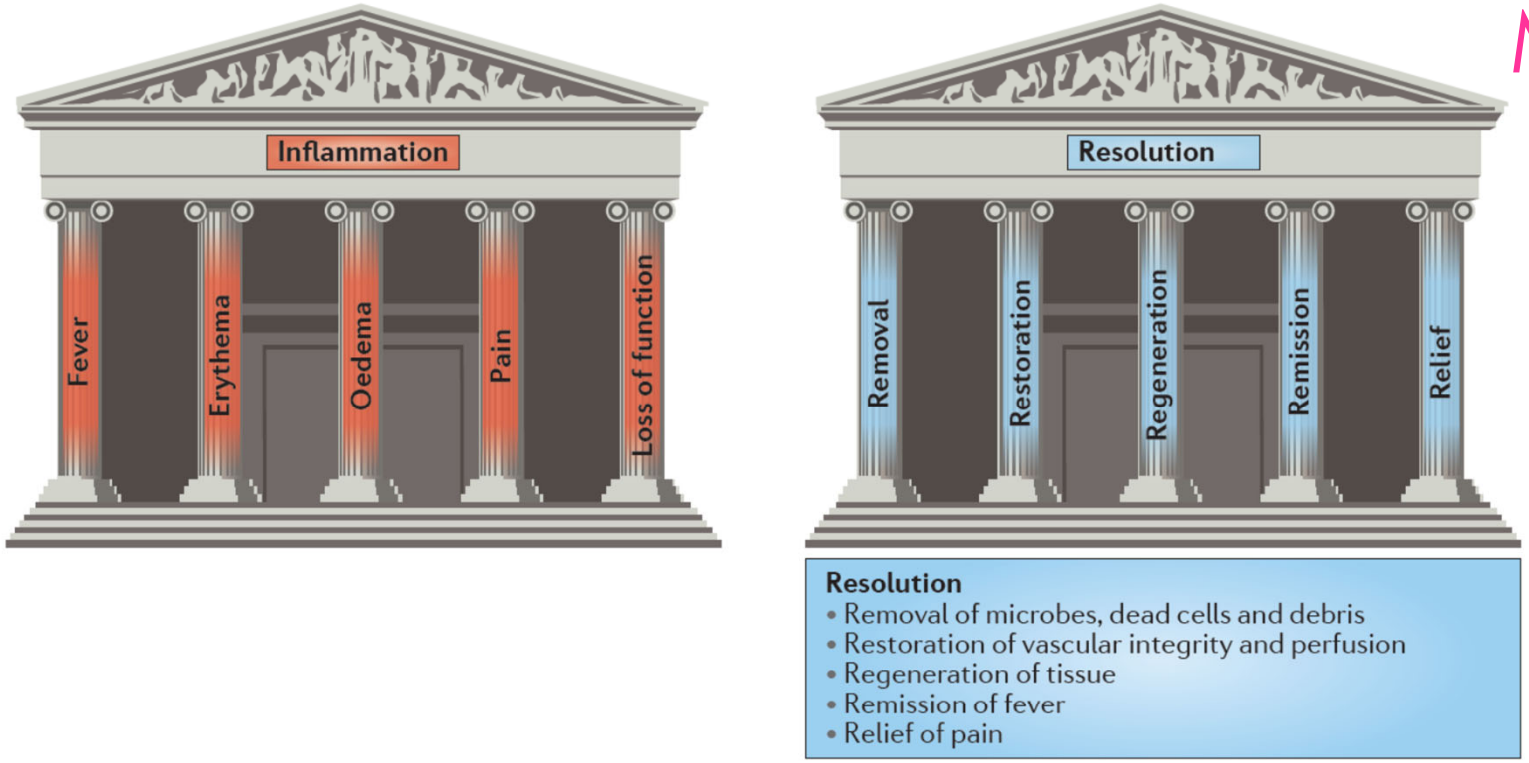


Figure 1 | **Cardinal signs of inflammation and its resolution.** Tissue- and organism-level responses to inflammation have been well recognized for centuries and can be summarized as the 'five pillars of inflammation'; namely, *calor* (fever), *rubor* (redness), *tumor* (swelling and oedema), *dolor* (pain) and *functio laesa* (loss of function). With the recognition that the resolution of inflammation is an active process, recent research has identified molecular and cellular processes that promote catabasis. These can be summarized as the 'five pillars of resolution'; that is, removal of microorganisms, dead cells and debris, restoration of vascular integrity and perfusion, tissue regeneration, remission of fever and relief from inflammatory pain.

TH17 MODULATION

- REMINDER: TH17 cytokines implicated in PANS/PANDAS
  - Once in the brain, the Th17 cytokines broke down the blood-brain barrier, allowing circulating autoantibodies to cross the leaky blood-brain barrier, enter the brain and recognize / attack neuronal targets.
  - TH17 cells mediate many autoimmune and infectious diseases
    - MS, Hashimoto's, Type 1 Diabetes, RA, SLE, IBD, Spondyloarthropathies, Psoriasis, Vitiligo, Glioma, Atherosclerosis, Cardiovascular disease, Hepatitis B, Hepatitis C, HIV (and PANDAS/PANS!)
      - Zambrano-Zaragoza, et al. Th17 Cells in Autoimmune and Infections Diseases. Intl J Inflamm. 2014. doi: 10.1155/2014/651503
- Are there ways to target and modulate the TH17 response?

TH17 MODULATION

- Potential ways to inhibit TH17 response
  - Stress reduction
  - Sunlight
  - Exercise
  - Broccoli sprouts/sulforaphane
  - Nutrients: Vitamin D, Vitamin A, Zinc
  - Supplements: Probiotics, fish oil, CBD Oil
  - Herbs: Chinese skullcap(aka Baical or Baikal Skullcap – also beneficial in Alzheimer's), Curcumin, Berberine, EGCG, Olive leaf extract, Fisetin

CBD OIL

- Cannabinoids (THC & CBD) reduce the TH17 phenotype found in many inflammatory autoimmune illnesses
  - Mouse model of EXPERIMENTAL AUTOIMMUNE ENCEPHALITIS showed that CBD and THC and significant dose-dependent suppression of production and secretion of IL-17
    - Kozela, E., Juknat, A., Kaushansky, N. et al. J Neuroimmune Pharmacol (2013) 8: 1265. https://doi.org/10.1007/s11481-013-9493-1

SCUTELLARIA BAICALENSIS (CHINESE SKULLCAP)

- Baicalin – bioactive flavonoid in Chinese Skullcap
  - ** DIFFERENT THAN AMERICAN SKULLCAP**
- Baicalin significantly improved outcomes in mouse-model of Experimental Autoimmune Encephalomyelitis)
  - Reduced infiltration of immune cells into CNS
  - Inhibited expression of pro-inflammatory molecules and chemokines
  - Prevented Th1 and TH17 cell differentiation via STAT/NFkB signaling pathways
    - Zhang et al. Therapeutic effects of baicalin on experimental autoimmune encephalomyelitis is mediated by SOCS3 regulatory pathway. Scientific Reports. 5:17407. DOI: 10.1038/srep17407.

STEP 4: ADDRESS CORE CLINICAL IMBALANCES

START WITH THE GUT!

- Optimize nutritional insufficiencies
- Address gut dysregulation
  - Gut dysbiosis
  - Increased intestinal permeability (aka "Leaky gut")
- Address the Cell Danger Response
  - Mitochondrial dysfunction
  - Mast cell activation

OPTIMIZE NUTRITIONAL INSUFFICIENCIES

OPTIMIZE NUTRITIONAL INSUFFICIENCIES

- Optimize Vitamin D levels
- Optimize Zinc levels
  - Check RBC zinc
  - Check plasma zinc, copper (ideal Copper:Zinc <1.5)
    - Some kids have concurrent Pyroluria
- Optimize Magnesium levels
  - Check RBC magnesium
  - Magnesium glycinate, Epsom salt baths
- Optimize methylation
  - Consider MB12 injections (64.5mcg/kg/injection q3days)
- Consider urine organic acid testing to further guide you

ADDRESS GUT DYSREGULATION

Gut Dysbiosis & Increased Intestinal Permeability ("Leaky Gut")

ADDRESS GUT DYSBIOSIS

ALWAYS OPTIMIZE THE GUT-BRAIN CONNECTION

- **Do a comprehensive stool analysis**
  - You don't know what's in there until you look!
- So many PANS kids have been on rounds and rounds of antibiotics – even before PANS
  - Yeast dysbiosis can be a trigger or exacerbating factor!
- Strep in the GUT can be a hidden PANDAS trigger…
- Klebsiella, Citrobacter, Proteus spp → autoimmune triggers
- Gut dysbiosis can trigger inflammation and neurotransmitter imbalance

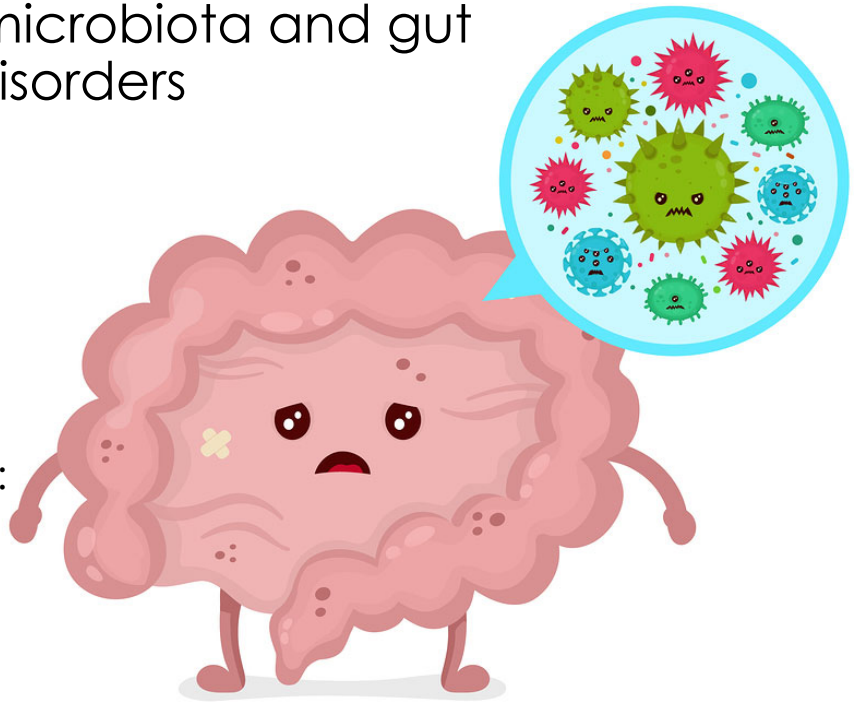
INFECTIONS & AUTOIMMUNE DISORDERS

- Infections are a risk factor for autoimmune disease, esp gut dysbiosis

Gut Microbe	Disorder
Klebsiella	Ankylosing spondylitis
Citrobacter, Klebsiella, Proteus, Porphyromonas	Rheumatoid arthritis
Yersinia	Graves', Hashimoto's
S. Pyogenes	Rheumatic fever
Campylobacter	Guillain-Barre syndrome
Chlamydia	Multiple sclerosis
E. coli, Proteus Strep species	Autoimmunity in general ?PANDAS

GUT-BRAIN CONNECTION – THE MICROBIOME & MENTAL HEALTH

- Several studies have shown altered gut microbiota and gut dysbiosis in patients with mental health disorders
  - Chen Z et al. Comparative metaproteomics analysis shows altered fecal microbiota signatures in patients with major depressive disorder. Neuroreport. 2018 Mar 21;29(5):417-425.
  - Aizawa E et al. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. J Affect Disord. 2016 Sep 15;202:254-7. doi: 10.1016/j.jad.2016.05.038.
  - Gareau MG et al. Bacterial infection causes stress-induced memory dysfunction in mice. Gut. 2011 Mar;60(3):307-17. doi: 10.1136/gut.2009.202515.
  - …



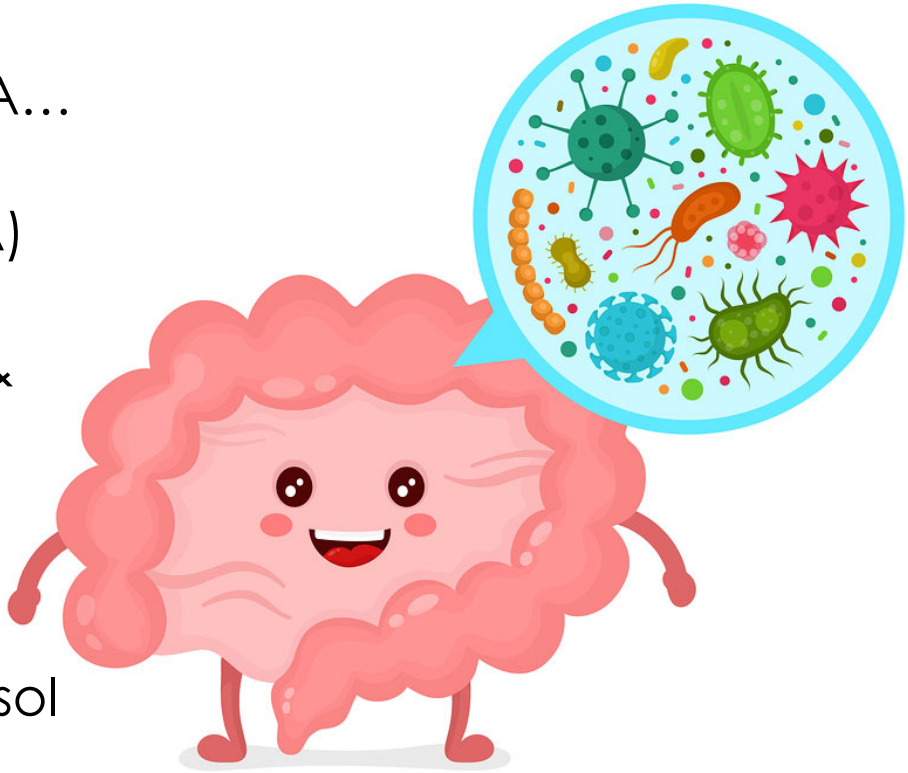
GUT MICROBIOME – NEUROTRANSMITTER CONNECTION

- Gut microbes produce hormones and neurotransmitters identical to those produced by humans.
  - *Lactobacillus* species produce acetylcholine and GABA
  - *Bifidobacterium* species produce GABA;
  - *Escherichia* produce norepinephrine, serotonin and dopamine;
  - *Streptococcus* and *Enterococcus* produce serotonin; and
  - *Bacillus* species produce norepinephrine and dopamine
- 90% of our serotonin is made in our gut

Galland Leo. The Gut Microbiome and the Brain. Journal of Medicinal Food. 2014;17(12):1261-1272. doi:10.1089/jmf.2014.7000.

PSYCHOBIOTICS – "HAPPY BUGS"

- Supports optimal neurotransmitter production – serotonin, dopamine, GABA…
- Regulates the body's stress response via the Hypothalamic-Pituitary-Adrenal (HPA) axis
- Reduces inflammation in the gut, body & brain
- Studies show psychobiotics can:
  - Treat depression, anxiety, & other psychological disorders
  - Help manage stress and reduce cortisol



PROBIOTIC SUPPLEMENTATION REDUCES ANXIETY & DEPRESSION

- Lactobacillus plantarum strain PS128 increases dopamine and serotonin
  - New research around AUTISM → daily administration improves 2 core sx of autism
    - Persistent deficits in social communication and social interaction
    - Restricted, repetitive patterns of behavior or activities
- Lactobacillus helveticus Rosell-52 ME and Bifidobacterium longum Rosell-175 ME reduces anxiety and depression
- Lactobacillus helveticus NS8 works better than citalopram in reducing stress-induced anxiety, depression, and cognitive dysfunction; lowers cortisol and restores serotonin to normal.

Mital et al. 2016. Neurotransmitters: The critical modulators regulating the gut-brain-axis. J Cell Physiol. Aug 11. doi: 10.1002/jcp.25518.

PROBIOTIC SUPPLEMENTATION REDUCES ANXIETY & DEPRESSION

- 2 meta-analyses of 17 randomized controlled human trials show psychological benefit from probiotic supplementation
  - Pirbaglou M et al. Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials. Nutr Res. 2016 Sep;36(9):889-898. doi: 10.1016/j.nutres.2016.06.009.
  - McKean J et al. Probiotics and Subclinical Psychological Symptoms in Healthy Participants: A Systematic Review and Meta-Analysis. J Altern Complement Med. 2017 Apr;23(4):249-258. doi: 10.1089/acm.2016.0023.

ENDOTOXEMIA & PANS/PANDAS

- Reminder: LPS is an endotoxin derived from the outer membrane of gram-negative bacteria. Circulating LPS binds to LBP and LPS-LBP complexes activated NKFb and increased inflammatory cytokines wherever they end up – brain, gut, joints, etc.
  - Metabolic endotoxemia occurs when serum endotoxins (LPS) are absorbed through permeable gut lining
  - Metabolic endotoxemia associated with increased risk for anxiety, depression, autoimmunity, diabetes, obesity and cardiovascular disease

CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline.
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function.
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions.
Anorexia Nervosa	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone.
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss.
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

Courtesy: Kiran Krishnan

LPS, ENDOTOXEMIA & STREP

- *Escherichia coli* LPS may trigger more invasive streptococcal disease
  - E. coli LPS injected intraperitoneally to mice whose muscles were inoculated with *S. pyogenes* → increased bacterial growth, muscular necrosis and death
  - Modulated by systemic TNF-a
    - Diao H et al. Lipopolysaccharide triggers invasive streptococcal disease in mice through a tumour necrosis factor-a-dependent mechanism. Immunology. 2002 Mar; 105(3): 344–349.

LPS, ENDOTOXEMIA & STREP

- Group A strep intracellular toxin elicits similar host response as Gram-negative endotoxin (LPS)
  - GAS produces 2 distinct pyrogenic toxins – intracellular and extracellular
    - Similar non-specific host factors involved in detoxification of streptococcal intracellular pyrogenic toxin and gram-negative bacterial endotoxin
      - Cremer N and DW Watson. **Host-parasite factors in group A streptococcal infections. A comparative study of streptococcal pyrogenic toxins and gram-negative bacterial endotoxin.** J Exp Med. 1960 Dec 1;112:1037-53.

GLUTATHIONE, STREP & ENDOTOXEMIA

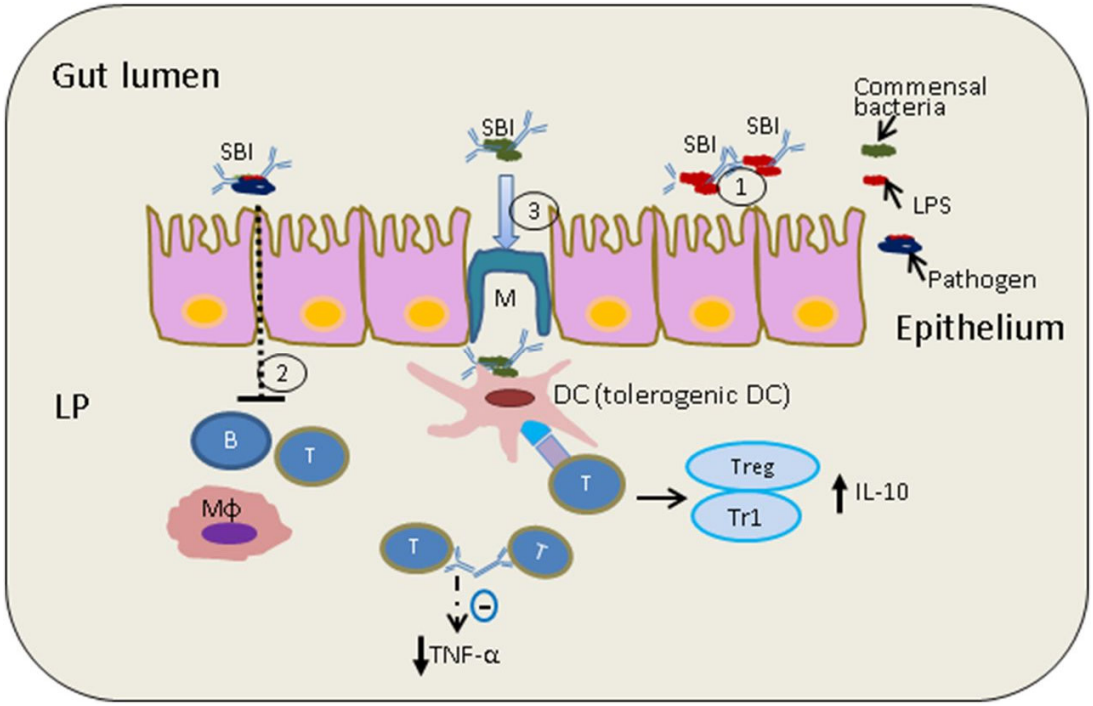
- Glutathione is ESSENTIAL for effective innate immune response against gram-positive Strep and gram-negative E. coli LPS
  - Glutathione reductase (Gsr) catalyzes reduction of glutathione disulfide to glutathione (one of our most important cellular antioxidants)
  - Gsr-deficient mice had much higher morbidity and mortality with greater bacterial burden from E. coli and Group B Streptococcus
    - → Increased oxidative stress
    - → Impaired neutrophil phagocytic activity
      - Yan J et al. **Glutathione reductase is essential for host defense against bacterial infection.** Free Radic Biol Med. 2013 Aug;61:320-32.

LPS, ENDOTOXEMIA & NEURO-INFLAMMATION

- Preventing leaky gut reduced endotoxemia and resulting neuro-inflammation
  - Lactobacillus farciminis suppresses stress-induced gut hyperpermeability
  - L. farciminis given BEFORE stressful event to rats
    - Suppressed leaky gut → reduced endotoxemia (decreased LPS blood concentration) → prevented HPA axis stress response (decreased plasma ACTH and corticosterone) and prevented neuroinflammation (decreased hypothalamic CRF and pro-inflammatory cytokine mRNA expression)
      - Ait-Belgnaoui, A et al. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. Psychoneuroendocrinology 37, 1885–1895. doi:10.1016/j.psyneuen.2012.03.024.

SERUM-DERIVED IMMUNOGLOBULIN (SBI)

FIGURE 1 PROPOSED MECHANISMS OF ACTION OF ORAL IG SBI....



(1) SBI binds luminal bacteria and their endotoxins (LPS), providing a level of immune exclusion. **(2)** Reduced transepithelial antigen absorption across the small and/or large intestine has been linked to reduced immune activation, including effects on B cells, T cells, and macrophages. **(3)** SBI may interact with healthy commensals to induce tolerogenic DCs. Shown is a tolerogenic DC signaling to $CD4^+$ helper T cells, which are known to communicate with Treg/Tr1 cells to produce anti-inflammatory cytokine IL-10. Immune homeostasis may reduce production of pro-inflammatory cytokines such as TNF-a and would increase production of IL-10. $CD4^+$, cluster of differentiation 4; DC, dendritic cell; LP, lamina propria; SBI, serum-derived bovine Ig; Treg, $Foxp3^+$ regulatory T cell; Tr1, $Foxp3^-$ IL10-producing regulatory T cell.

LEAKY GUT/INFLAMMATORY TRIGGERS

- Identify and remove allergenic/inflammatory foods
  - Gluten
  - Other foods found on testing or elimination diet
  - Refined sugar
  - Artificial dyes, flavors, preservatives
  - Histamine

GLUTEN AS A HIDDEN TRIGGER

- Gluten is a hidden TRIGGER for PANS
  - Gluten autoimmunity directly triggers TH-17 reactions and opens the BBB
    - Fasano A., and Shea-Donohue T.: Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. Nat Clin Pract Gastroenterol Hepatol 2005; 2: pp. 416-422

ARTIFICIAL FLAVORS, PRESERVATIVES & DYES – OH MY!

- Artificial dyes and preservatives can be huge triggers for some
  - Harmful behavior effects in kids in general, not just kids with ADHD
  - Since 2010, the European Union has required manufacturers to put a warning label on foods containing artificial food dyes that they "may have an adverse effect on activity and attention in children."

Arnold LE, Lofthouse N, Hurt E. "Artificial Food Colors and Attention-Deficit/Hyperactivity Symptoms: Conclusions to Dye for." Neurotherapeutics, 2012; 9: 599-609.

THE 5R PROGRAM TO HEAL YOUR CHILD'S GUT

- **Remove – anything toxic/inflammatory to the gut**
  - Food allergies/sensitivities/intolerances, food additives, medications, pathogens, glyphosate, heavy metals, medications, mold, environmental toxins, EMFs, STRESS!
  - Endotoxins → serum-derived bovine IgG
- **Reinoculate – with the good bugs**
  - Probiotics, including psychobiotics
  - Prebiotics
  - Fermented foods (if histamine is not an issue)
- **Repair – the gut lining**
  - Gut Mucosal Integrity Nutrients – glutamine, fish oil, zinc, quercetin

THE 5R PROGRAM TO HEAL YOUR CHILD'S GUT

- **Replace – whatever the gut is missing**
  - Digestive enzymes, +/- HCl, CHEW!
- **Rebalance – Restore the gut-mind-body-spirit connection**
  - Sleep, exercise, stress reduction/mindfulness, time in nature

Free infographic on the 5 R's to Healing Your Child's Gut for patient reference: http://healthykidshappykids.com/leaky-gut-guide/

ADDRESS THE CELL DANGER RESPONSE

Mitochondrial Dysfunction & Mast Cell Activation

THE HEALING CYCLE & THE CELL DANGER RESPONSE

- Described by Dr. Robert Naviaux at UC San Diego
- The 4 discrete stages of the HEALING CYCLE
  - The Health Cycle → wakeful activity, restorative sleep, seasonally-appropriate diet from local ecosystems
  - 3 stages of the Cell Danger Response initiated by a cellular injury
- CDR is an ADAPTIVE primitive protective response to chemical, physical, microbial, or psychological threats

- RK Naviaux. Metabolic features of the cell danger response. Mitochondrion 16(2014); 7-1. https://www.sciencedirect.com/science/article/pii/S1567724913002390
- RK Naviaux Metabolic features and regulation of the healing cycle – A new model for chronic disease pathogenesis and treatment. Mitochondrion 2018.

THE HEALING CYCLE & THE CELL DANGER RESPONSE

- Once threat neutralized, choreographed sequence of anti-inflammatory and regenerative pathways is activated to reverse CDR
  - Replace lost cells
  - Restore normal organ function
  - Achieve homeostasis and HEAL
- Metabolic MEMORY of the exposure that led to the CDR is stored
  - MITOCELLULAR HORMESIS → cellular *memory* of how to deal with physiological and psychological threat the next time…

"CELLULAR RESILIENCE"

PERSISTENT CELL DANGER RESPONSE

- Abnormal persistence of CDR even once the threat has been neutralized underlies many pediatric and adult chronic conditions
  - Autism, ADHD, PANS/PANDAS, asthma, atopy, autoimmune disease (lupus, MS, rheumatoid arthritis, Alzheimer and Parkinson disease, bipolar, schizophrenia, PTSD, traumatic brain injury

Persistent maladaptive metabolic changes

↓

Persistent MITOCHONDRIAL DYSFUNCTION and MAST CELL ACTIVATION

↓

CHRONIC DISEASE

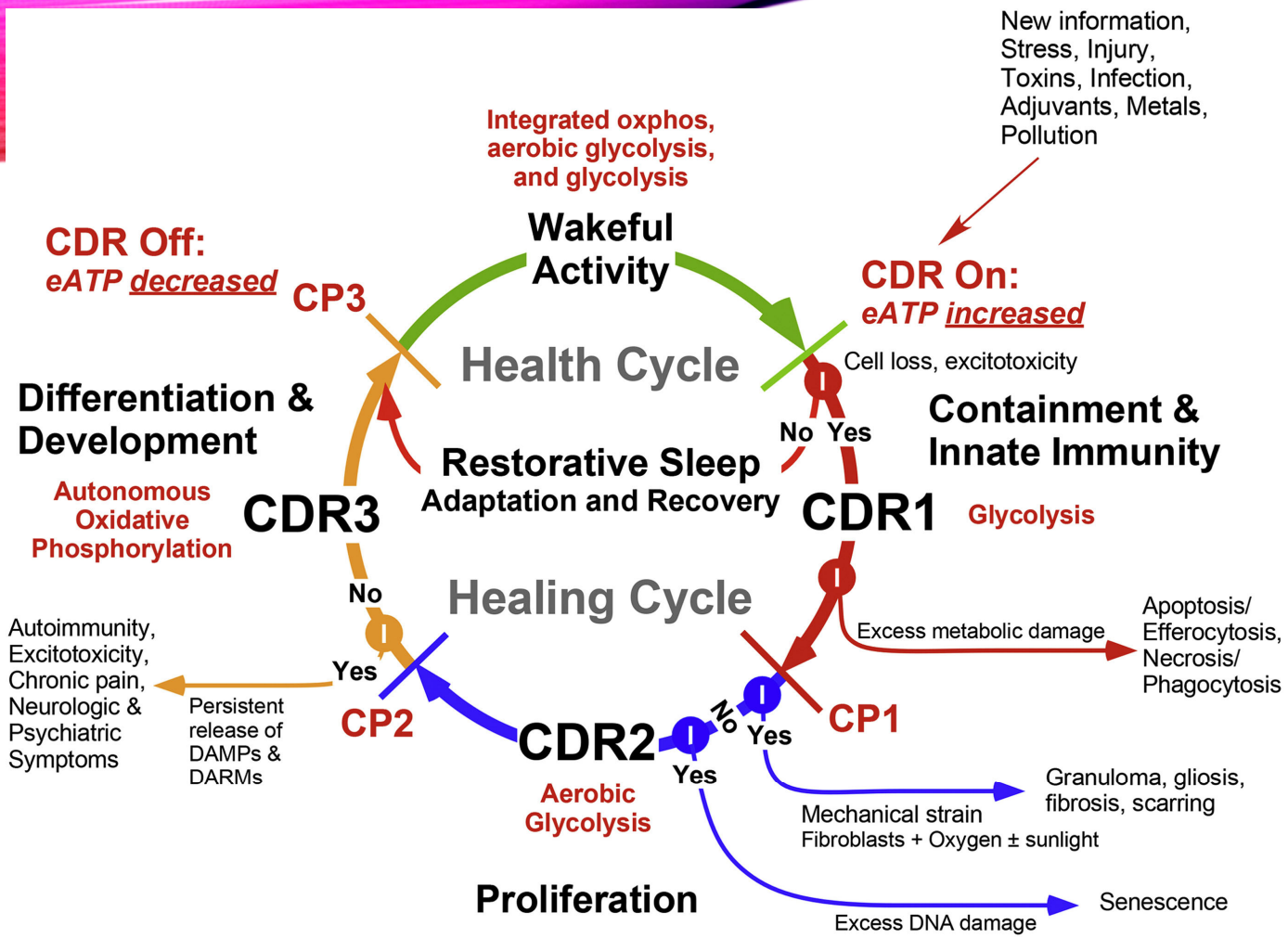


Fig. 1. A metabolic model of the health and healing cycles. Health is a dynamic process that requires regular cycling of wakeful activity and restorative sleep. The healing or damage cycle is activated when the cellular stress exceeds the capacity of restorative sleep to repair damage and restore normal cell-cell communication. CDR1 is devoted to damage control, innate immunity, inflammation, and clean up. CDR2 supports cell proliferation for biomass replacement, and blastema formation in tissues with augmented regeneration capacity. CDR3 begins when cell proliferation and migration have stopped, and recently mitotic cells can begin to differentiate and take on organ-specific functions. **Abbreviations**: eATP; extracellular ATP; CP1–3: checkpoints 1–3; DAMPs: damage-associated molecular patterns; DARMs: damage-associated reactive metabolites.

THE CELL DANGER RESPONSE – PHASE 1

- Goal: Activate innate immunity, detect and remove threats, control and contain damage, repair the cell
  - Cells become autonomous, to contain the threat and repair the cell while protecting the host
- Exposure to a threat triggers mitochondria to release ATP from the cell
- Extra-cellular ATP binds to purinergic receptors on cell plasma membranes
  - → INITIATES THE CELL DANGER RESPONSE

THE CELL DANGER RESPONSE – PHASE 1

- Purinergic receptors
  - Implicated in learning and memory, locomotor and feeding behavior and sleep
  - Found on almost every cell in our body – including MAST CELLS
- ATP causes mast cells to degranulate
  - Mast cells release histamine and ATP
    - ↳ Histamine vasodilates to recruit 02 and immune cells to site of inflammation
      - ↳ ATP triggers further mast cell degranulation

↓

Mitochondrial & Mast Cell Activation

THE CELL DANGER RESPONSE – PHASE 2

- Goal: Stem cell recruitment to replace cells lost during CDR1, "wall off" any damaged areas or persistent infections with scar tissue not completely cleared by CDR1
  - The "clean-up" and repair phase

THE CELL DANGER RESPONSE – PHASE 2

- Functional medicine approaches to support normalization of these persistent cascades are important in this stage:
  1. MAKE SURE THE THREAT IS ELIMINATED
  2. Mitochondrial dysfunction – coQ10, carnitine, ribose, antioxidants, phospholipids
  3. Mast cell activation/histamine intolerance – luteolin, quercetin, PEA, DAO, cromolyn sodium, ketotifen, homeopathic Histaminum
  4. Methylation dysfunction – MTHF, mB12, SAMe
  5. Sulfur metabolism dysregulation – glutathione
  6. Vitamin D inactivation – Vitamin D3
  7. Vitamin B6 reduction – P-5-P
  8. Gut dysbiosis, leaky gut & gluten sensitivity – 5R program, gluten elimination

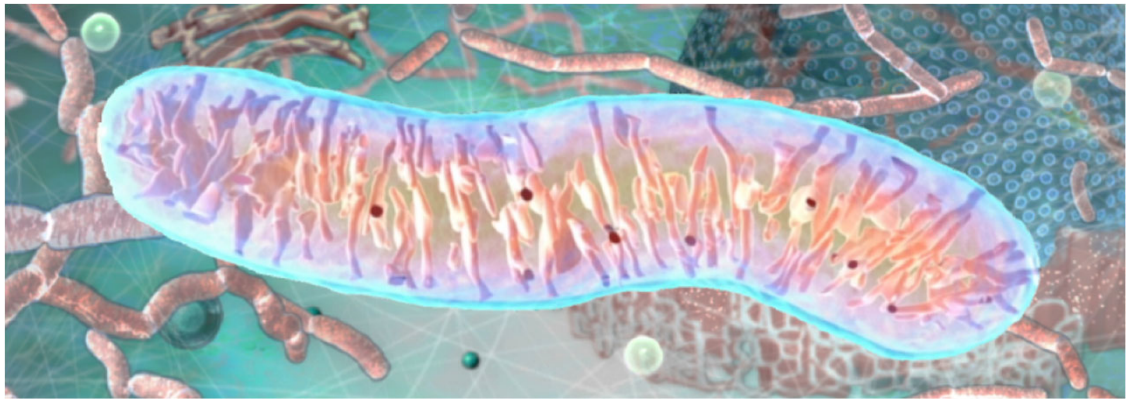
THE CELL DANGER RESPONSE – PHASE 3

- GOAL: Cellular differentiation of new cells regenerated in CDR2, restore cell-cell communication, metabolic memory, adaptive immunity, detoxification
- Cells that were autonomous in CDR1 and CDR2 must now re-establish communication with the brain via the **VAGUS NERVE**
  - Purinergic signaling and decrease in extracellular ATP is the major signal to cells that they are ready to reenter the HEALTH CYCLE
- Movement of CDR3 → Health Cycle often results in IMPROVED baseline physiologic performance than before the injury/stress
  - Mitocellular hormesis and metabolic memory → more RESILIENT cells

Stress can be ADAPTIVE if cells are able to complete the HEALING CYCLE

GETTING STUCK IN THE CELL DANGER RESPONSE

- Chronic disease occurs when cells get "stuck" in various stages of the cell danger response → even after the initial threat has resolved
  - Unable to complete the Healing Cycle & reenter the Health Cycle
- Mitochondrial dysfunction becomes more evident
  - Mitochondrial supports are very important



http://www.mrc-mbu.cam.ac.uk/what-are-mitochondria

PERSISTENCE OF CDR STAGES & CHRONIC DISEASE

Table 1
Provisional classification of stage-specific healing cycle disorders.*

CDR1 Disorders	CDR2 Disorders	CDR3 Disorders
Innate Immune Disorders	**Proliferative Disorders**	**Differentiation Disorders**
–HPA Axis, ATP, Lipids, mtDNA	–mTOR, p21, HIF, PHDs	–DARMs, Mito Polarization
Systemic Inflammatory Response Syndromes (SIRS)	Dyslipidemia	Autism spectrum disorder
	Hyperuricemia	Chronic Fatigue Syndrome
Multiple Organ Dysfunction Syndrome (MODS),	Diabetes	Post-traumatic stress disorder
	Diabetic retinopathy	Fibromyalgia, Chronic pain syndromes,
Septic shock	Hypertension	Allodynia
Acute Respiratory Distress Syndrome (ARDS)	Heart disease	Neuropathic pain syndromes
	Peripheral vascular disease	Complex regional pain syndromes
Allergies, asthma, atopy	Cerebral vascular disease	Obsessive Compulsive Disorder
Chronic infections (fungal, bacteria, viral, parasitic)	Inflammatory bowel disease (Crohn's, Ulcerative colitis)	Generalized Anxiety Disorder
		Major depressive disorder
Gulf War Illness (GWI)		Bipolar disorder
Tinea pedis, Tinea versicolor, Tinea corporis, Tinea barbae	Non-alcoholic steatohepatitis (NASH), Cirrhosis	Migraine headaches
		New daily persistent headaches
Histoplasmosis, Coccidiomycosis		POTS, PANS, PANDAS
Aspergillosis, Chronic mucocutaneous Candidiasis, Sporotrichosis, Cryptococcosis, Sarcoidosis, Chronic granulomatous disease, Chlamydia, Listeriosis, Toxoplasmosis, Bartonellosis, Syphilis, Helicobacter, Neisseria, Vibrio cholerae, Tuberculosis, Non-tuberculous mycobacteria infections, Leprosy, Lyme, Typhoid, Malaria, Leishmaniasis, Onchocerciasis, Schistosomiasis Trypanosomiasis, Filariasis	Idiopathic pulmonary fibrosis	Schizophrenia, acute psychosis
	Benign prostatic hyperplasia	Parkinson, Alzheimer
	Keloid formation	Multiple sclerosis, Tourette's
	Subacute spinal cord injury	Dystonia syndromes, Lupus Selected epilepsies, Behcet's
	Dermal vasculitis, Temporal arteritis, Kawasaki coronary arteritis	Scleroderma, Sjögren's, Polymyalgia rheumatica
	Cancers and Leukemias	Ankylosing spondylitis
		Amyotrophic lateral sclerosis
		Chronic traumatic encephalopathy
		Traumatic brain injury
		Selected post-stroke syndromes
		Wakeful delta wave activity (EEG)
		Hashimoto's thyroiditis
		Psoriasis, eczema
Ecosystem disorders		Alopecia areata, vitiligo
Coral reef fungal infections (*Aspergillus*),		Autoantibodies to intrinsic factor
Coral bleaching disorder (*Vibrio*),		Rheumatoid arthritis
Shrimp black gill disease (*Hyalophysa*),		Osteoarthritis
Microsporidial gill disease in fish,		Macular degeneration
Colony collapse disorder in honey bees,		Presbyopia, presbycusis
White nose disease in bats (*Geomycosis*),		Diabetic neuropathy
Chytridiomycosis in frogs and salamanders,		Diabetic nephropathy
Potato plague (*Phytophthera*),		Irritable bowel syndrome
Sudden Oak Death (*Phytophthera*),		**Adaptive Energy Conservation and Survival States**
Tea leaf blister,		Dauer, diapause, torpor, estivation
Coffee rust,		Hibernation, Persister cells
Cacao tree witch's broom fungus,		Plant seed embryo formation
White pine blister rust (*Cronartium*),		Caloric restriction metabolism
Sudden Aspen Decline (*Cytospora*)		Longevity metabolism

* Subdivisions occur within each of the 3 main stages of the CDR.

MITOCHONDRIAL DYSFUNCTION IN PANS/PANDAS – HISTORY

- Hypotonia
  - Weak pencil grasp, low core strength (can't get up from lying supine to sitting), difficulty pumping swing, sits in "W" position
- Multiple regressions
- Regressions especially after illness, vaccines, anesthesia
- Low energy
- Easy fatigue and poor endurance
  - Physical and mental
- Clumsiness
- Constipation
- Speech or articulation issues
- Worsening in altitude
- Commonly found if also underlying autism

LAB EVIDENCE OF MITOCHONDRIAL DYSFUNCTION

- Elevated AST, ALT
- Elevated creatine kinase (CK)
- Elevated lactate (performed STAT)
- Elevated pyruvate (performed STAT)
- Elevated fasting ammonia (performed fasting and STAT)
- Decreased free and total carnitine
- Abnormal acylcarnitine profile
- Decreased or suboptimal coenzyme Q10
- Fasting plasma amino acids: high alanine or Alanine:Lysine > 2.5-3
- Abnormal urine organic acid mitochondrial markers

MITOTOXIC INSULTS - MEDICATIONS

- Nitrous oxide
- Valproate (Depakote)
- Fluoxetine (Prozac)
- Risperidone (Risperdal)
- Alprazolam (Xanax)
- Diazepam (Valium)
- Acetaminophen (Tylenol)
- Naproxen (Aleve)
- Tetracycline/minocycline
- Metformin
- MSG
- Statins
- Rifampin
- Vaccines? (Hannah Poling case)

MITOTOXIC INSULTS

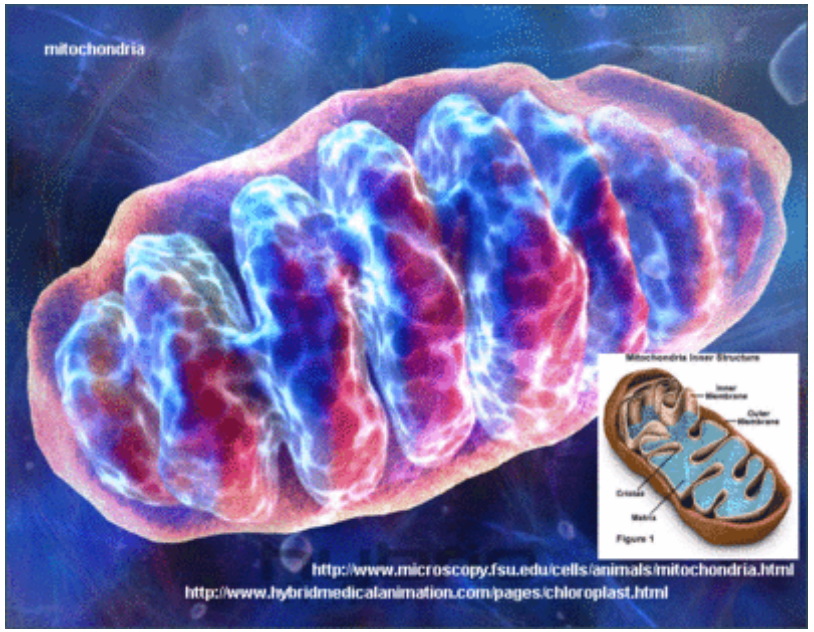
- Infections
  - Strep, EBV, HSV, Influenza A virus, CMV, Hep B, Lyme and coinfections, HIV, etc.
- Heavy metals
  - Mercury, lead, arsenic, aluminum, cadmium
- Pesticides (Glyphosate)
- Hypoxia
- Poor nutrition
- Propionic acid from clostridia
- Psychological trauma
- Sleep deprivation
- Alcohol/cigarette smoke
- Dehydration

STREP IS MITOTOXIC

- GAS pyrogenic exotoxin B causes mitochondrial damage to PMNs
  - Prevents phagocytosis of GAS
    - Chiang-Ni, et al. Streptococcal pyrogenic exotoxin B causes mitochondria damage to polymorphonuclear cells preventing phagocytosis of Group A streptococcus. Med Microbiol Immunol (2006) 195: 55.
    - Tsatsaronis JA et al. (2014) Host Responses to Group A Streptococcus: Cell Death and Inflammation. PLoS Pathog 10(8): e1004266. ttps://doi.org/10.1371/journal.ppat.1004266
    - Tstasaronis JA et al. **Group A Streptococcus Modulates Host Inflammation by Manipulating Polymorphonuclear Leukocyte Cell Death Responses.** J Innate Immun. 2015;7(6):612-22.
- GBS impairs brain mitochondrial function
  - B-hemolysin decreased mito fxn, increases oxidative stress, blocks ATP synthesis
    - (blocks proper function of the Cell Danger Response)
  - Phosphatidyl choline REDUCED this mitotoxic effect
    - Macchioni L et al. **Impairment of brain mitochondrial functions by β-hemolytic Group B Streptococcus. Effect of cardiolipin and phosphatidylcholine.** J Bioenerg Biomembr. 2013 Dec;45(6):519-29.

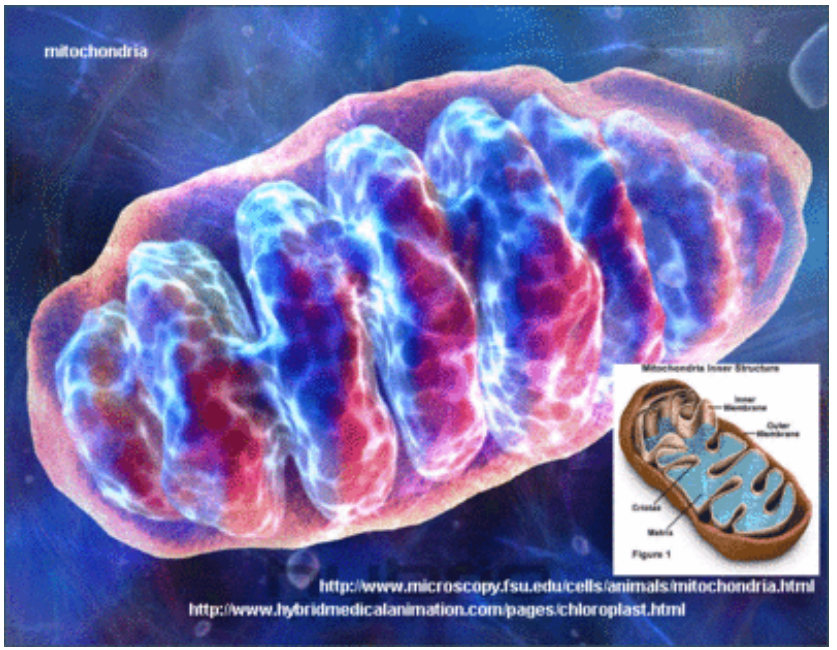
MITOCHONDRIAL SUPPORTS

- Supplement with cofactors of Mitochondrial respiratory chain complex
  - Coq10 as ubiquinol (up to 30 mg/kg/day)
  - L-carnitine (up to 100 mg/kg/day)
  - D-Ribose
  - B-vitamins
  - Phospholipids (PS, PC)

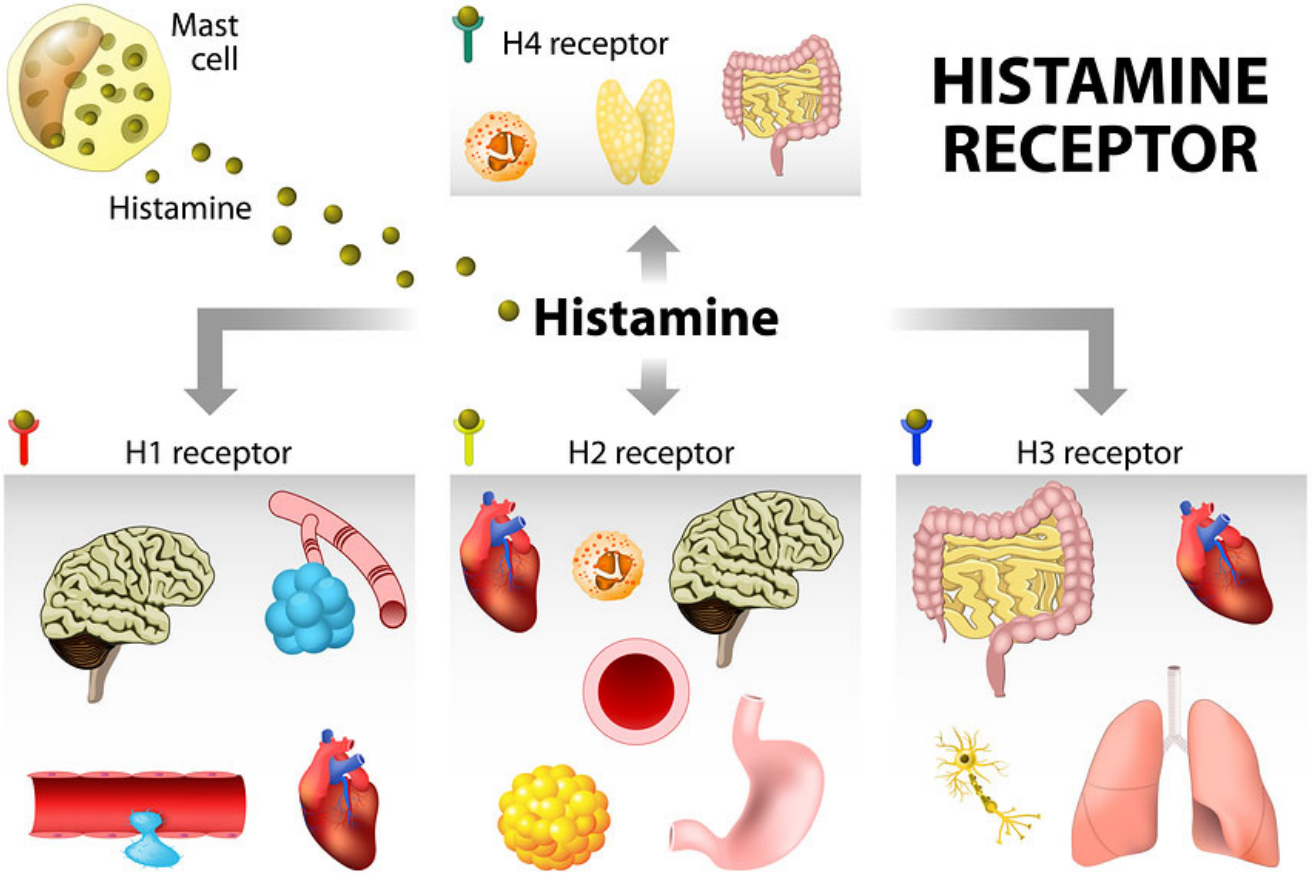


MITOCHONDRIAL SUPPORTS

- Reduce mitochondrial stressors
  - Excessive exercise
  - Fasting and dehydration
  - Extreme temperatures
  - Altitude
  - Heavy metals, vaccines, certain medications, and other mito-toxins
- "Strength" training exercise to build more mitochondria
- Antioxidants to counter increased oxidative stress
  - Eat a rainbow
  - Vitamin A, Vitamin C, vitamin E, GSH, ALA
- Sleep!!!



HISTAMINE – WHY IS IT SUCH A BIG DEAL?



Because histamine receptors are found on every single cell in our body…

HISTAMINE/MAST CELL ACTIVATION IN PANS/PANDAS – CLUES

- Dermatographism
- Anxiety
- Kids do worse on fermented foods
- Facial flushing
- Heat intolerance
- Tachycardia
- Eczema, hives, asthma, allergies other signs of histamine overload
- Reflux, nausea, vomiting, diarrhea
- Abdominal pain
- Headaches, dizziness
- Fatigue, sleep disturbance
- Changing reactivity to foods
- Sensitivity to NSAIDs

HISTAMINE/MAST CELL ACTIVATION – LAB WORKUP

- Suggestive lab findings
  - Total IgE
  - Eosinophil count
  - Plasma histamine
  - Serum tryptase
    - >20 ng/ml for MCAD
    - OR 20% above basal serum tryptase + 2ng/ml
  - Eosinophil cationic protein
  - Stool eosinophil protein X

HISTAMINE/MAST CELL ACTIVATION – TREATMENT

- Reduce high histamine foods and histamine-releasing foods
  - SUGAR
  - Artificial flavors, colors, preservatives
  - Chocolate, wine, strawberries, avocados, bananas, dairy, eggs, oranges, peaches, pineapples, raspberries, spinach, and tomatoes.
  - ?Fermented foods
  - Dr. Janice Jonega: Histamine and Tyramine Restricted Diet
    - https://www.jillcarnahan.com/downloads/HistamineRestrictedDiet.pdf
- Increase foods high in quercetin
  - Raw onion, apples (skin), red grapes, kale, spinach, capers, watercress, cherries, green tea, bee pollen, chili peppers
- Stabilize blood sugar/insulin response

HISTAMINE/MAST CELL ACTIVATION – TREATMENT

- DAO and/or cromolyn sodium before meals
- Luteolin, quercetin, PEA, ketotifen
- Chinese skullcap (Scutellaria baicalensis or Baikal skullcap)
- Vitamin C
- Zinc
- Low-dose naltrexone
- CBD oil
- H1-histamine blocker
  - Cetirizine not anticholinergic like loratadine and diphenhydramine
    - Anticholinergic medications linked to increased dementia risk
- H2-histamine blocker
  - Address resulting gut dysbiosis

STEP 5: RESTORE THE BODY-MIND-SPIRIT CONNECTION

RECONNECT VIA THE VAGUS NERVE

CLINICAL SIGNS OF VAGUS NERVE DYSFUNCTION

- Typically sympathetic overdrive
  - Dilated pupils
  - Elevated heartrate
  - Elevated blood pressure
  - Decreased heartrate variability (Sinus Respiratory Arrythmia)
    - HRV > 15 bpm is NORMAL
    - <10 bpm in patients < 40 years or <5 bpm at any age is ABNORMAL
  - Tremors
  - High blood sugar
  - Emotional lability, agitation
  - Constipation

CLINICAL SIGNS OF VAGUS NERVE DYSFUNCTION

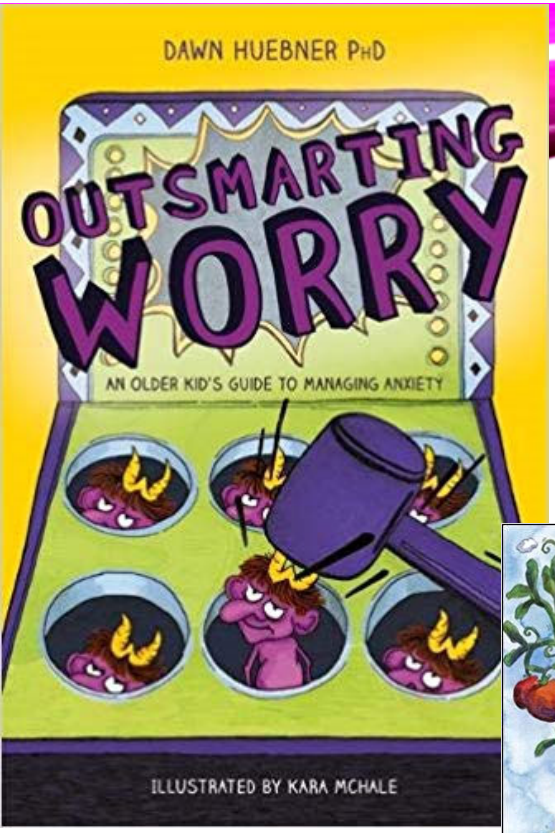
- Sometimes adrenal fatigue (even in toddlers!)
  - Fatigue
  - Muscle weakness and pain
  - Dizziness
  - Orthostatic hypotension
  - Low core tone
  - Abdominal weight gain
  - Confusion/Brain fog
  - Abdominal pain
  - Cold intolerance
  - Salt craving
  - Low blood sugar

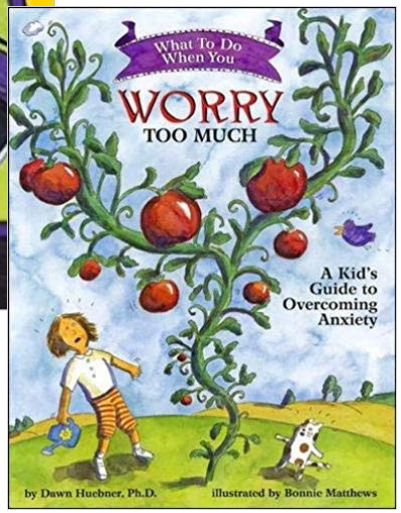
OPTIMIZE ADRENAL FUNCTION

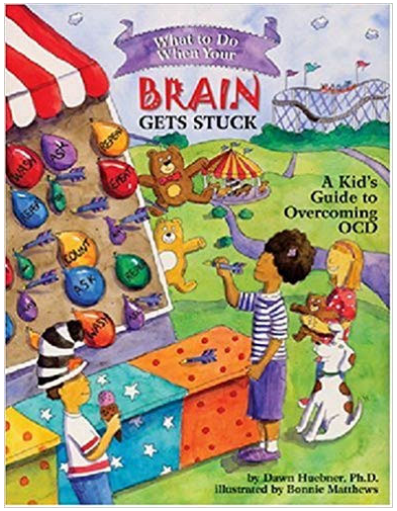
- Address "fight-or-flight" sympathetic overdrive
  - Phosphatidyl serine
  - Magnesium
  - Epsom salt baths
  - Theanine
  - Mindfulness/meditation
  - Diaphragmatic breathing
- Address adrenal fatigue
  - Adaptogens – Ashwagandha, Rhodiola
  - Avoid Panax (Korean/Chinese/Asian) ginseng in kids (increases testosterone)
  - Sleep

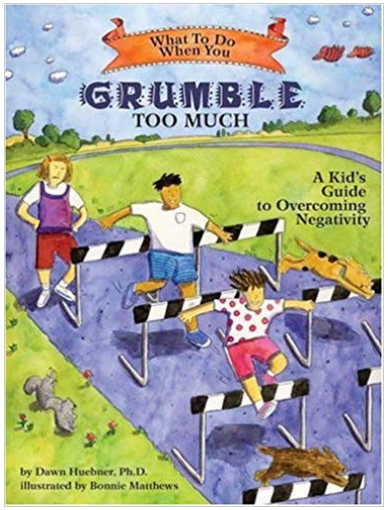
OPTIMIZE THE MIND-BODY CONNECTION – COGNITIVE-BEHAVIORAL THERAPY

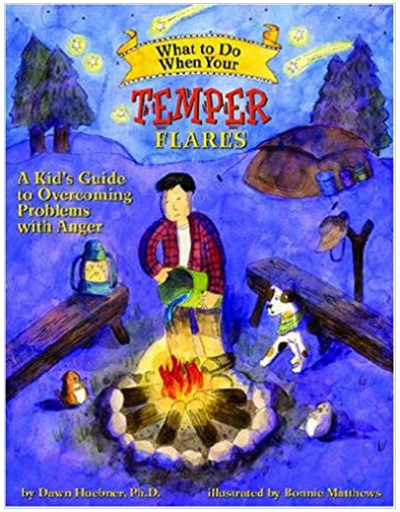
- Cognitive behavioral therapy
  - Individual therapy
  - Group therapy
- Dawn Huebner, PhD's kids' "self-help" books











OPTIMIZE THE MIND-BODY CONNECTION – MINDFULNESS/MEDITATION

- Mindfulness/meditation apps
  - Insight Timer
  - Stop, Breathe, Think Kids
  - Calm app
  - Headspace app
- Inner Balance Heartmath heartrate variability app

BREATHE…

- Diaphragmatic "belly breathing" to activate of the vagus nerve
  - Get out of fight-flight-freeze
  - Get into rest-digest-heal…

- Diaphragmatic breathing benefits:
  - Lower cortisol
  - Increased HRV
  - Increased energy, alertness, relaxation, mood
  - Decreased anxiety, depression, anger, confusion

Zaccar A et al. How Breath-Control Can Change Your Life: A Systematic Review on Psycho-Physiological Correlates of Slow Breathing. Front Hum Neurosci. 2018 Sep 7;12:353. doi: 10.3389/fnhum.2018.00353

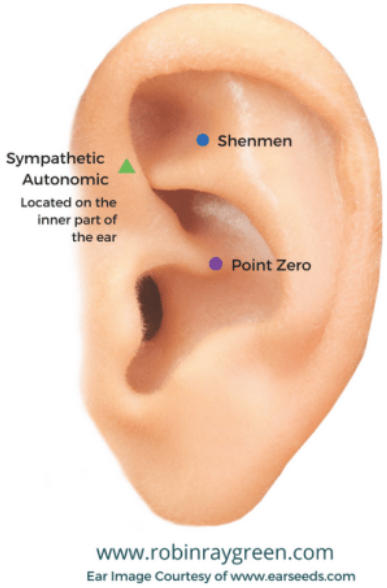
TEACH YOUR CHILD TO BELLY BREATHE

- Sit or lie comfortably
- Place one hand on chest
- Place the other hand on belly
- Pretend there's a balloon in their belly that they need to inflate every time you take a deep inhale, and deflate fully with every exhale
- Breathe in through their nose and fill that balloon, noticing the hand on their belly rise, and the hand on their chest staying still
- Breathe out through their mouth, feeling the hand on their belly sink all the way down, while the hand on their chest remains still

Sesame Street: Common and Colbie Caillat – "Belly Breathe" with Elmo
https://www.youtube.com/watch?v=_mZbzDOpyIA

ACUPUNCTURE & THE VAGUS NERVE

- Auricular acupuncture at Shenmen and Point Zero increases HRV during the post-op period in patients underdoing hemicolectomy for colon cancer
    - Young-Chang PA et al. Auricular Acupuncture at the "Shenmen" and "Point Zero" Points Induced Parasympathetic Activation. Evid Based Complement Alternat Med. 2013; 2013: 945063. Published online 2013 Jun 4. doi: 10.1155/2013/945063



ACUPUNCTURE & THE VAGUS NERVE

- Acupuncture works similarly to vagus nerve stimulation (VNS)
  - Vagus nerve plays a critical role in maintaining homeostasis of the innate immune response
- Acupuncture at ST36 , DU26, GB34 found to decrease LPS-induced pro-inflammatory cytokines TNF-a, IL-1B and IL-6 via the cholinergic anti-inflammatory pathway (animal studies)
  - Torres-Rosas et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. Nat Med, 20(3), 291-295.
  - Song J et al. Electroacupuncturing at ST26 attenuates pro-inflammatory cytokine release. African Journal of Traditional, Complement and Alt Med, 2014.11(2), 469.
  - Zhang L et al. Inhibiting effect of electroacupuncture at zusanli on early inflammatory facor levels formed by postoperative abdominal adhesions. Evid Based Complement Alt Med, 2014, 950326.

SLEEP AS THE MOST IMPORTANT RESTORATIVE SUPPORT

- Sleep!
- Melatonin is neuroprotective
- The glymphatic system
  - Waste clearance pathway for CNS runs along the veins in the brain
  - Activated DURING SLEEP
    - During sleep, glymphatic system 10x more active than during wakefulness
    - At same time, brain cells shrink ~ 60% for more efficient waste removal

** Brain HEALING & DETOX occurs during SLEEP**

NIH/National Institute of Neurological Disorders and Stroke. "Brain may flush out toxins during sleep; Sleep clears brain of molecules associated with neurodegeneration: Study." www.sciencedaily.com/releases/2013/10/131017144636.htm

SUPPORT & PROTECT SLEEP

- Reduce nighttime blue-light exposure
  - Turn OFF screens at least 1-2 hours before bedtime!!!
  - Amber blue-light blocking glasses if computer work necessary
  - F.lux app for computer
  - Night Shift mode on Iphones or Ipad
- Sleep supports
  - Phospatidyl serine to reduce cortisol excess
  - Melatonin to help fall asleep
  - Inositol to help stay asleep
  - Homeopathic remedies
    - Coffea cruda for "wired" mind and body
    - Ignatia for worries and grief

SUPPORT FOR CHILD AND FAMILY

- Behavior/psychiatric intervention is key → Cognitive Behavioral Therapy
  - ** Must find a therapist who is familiar with PANS
- Work with the schools on medical/behavioral plan
  - Children with PANS twice as likely to be unschooled (unplanned)
- Family counseling for parents and siblings
- Support systems/community for family → PANS is ISOLATING
  - Facebook groups
  - PANDAS Network

STEP 6: INTEGRATIVE CARE

- Be OPEN to and EXPLORE "alternative" treatments
  - Homeopathy
  - Essential oils
  - Acupuncture
  - Cranial osteopathy
  - Chiropractic
  - Reiki
  - Prayer
  - …

ACUPUNCTURE & ANXIETY

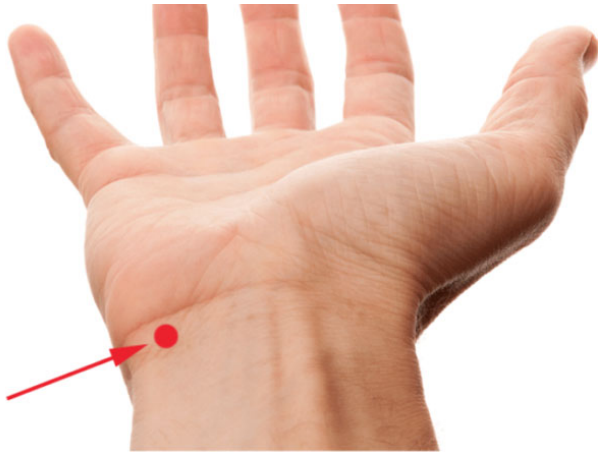
- Meta-analyses find positive and statistically significant benefits of acupuncture for treating anxiety with fewer side effects than conventional tx
  - Amorim D et al. **Acupuncture and electroacupuncture for anxiety disorders: A systematic review of the clinical research.** Complement Ther Clin Pract. 2018 May;31:31-37. doi: 10.1016/j.ctcp.2018.01.008.
  - Goyata SL et al. **Effects from acupuncture in treating anxiety: integrative review.** Rev Bras Enferm. 2016 Jun;69(3):602-9. doi: 10.1590/0034-7167.2016690325i.
- Acupuncture at ST41 reduced LPS-induced anxiety in rats
  - Yang TY et al. **Effect of acupuncture on Lipopolysaccharide-induced anxiety-like behavioral changes: involvement of serotonin system in dorsal Raphe nucleus.** BMC Complement Altern Med. 2017 Dec 11;17(1):528. doi: 10.1186/s12906-017-2039-y.
- Auricular acupuncture in patients with anxiety disorder found to decrease tension, anxiety, anger/aggression
  - Similar to Progressive Muscle Relaxation (accepted relaxation method)
    - De Lorent L et al. **Auricular Acupuncture Versus Progressive Muscle Relaxation in Patients with Anxiety Disorders or Major Depressive Disorder: A Prospective Parallel Group Clinical Trial.** J Acupunct Meridian Stud. 2016 Aug;9(4):191-9. doi: 10.1016/j.jams.2016.03.008.

ACUPRESSURE FOR ANXIETY

Heart 7 ("Shen Men" or "Spirit Gate")

- In depression at pinky side of wrist crease
- Relieves anxiety, insomnia, mania, panic, heart palpitation

- Use firm yet gentle pressure
- Circular motions, or steady pressure
- 30-60 seconds
- Apply essential oils to acupressure points for added therapeutic benefit!



Source: https://gettherightdiagnosis.com/home-remedies/acupressure-for-anxiety/

ESSENTIAL OILS & ANXIETY

- Essential oils that have been proven to have anxiolytic effects
  - Lavandula angustifolia
  - Citrus aurantium (bitter orange)
  - Citrus sinensis (sweet orange)
  - Bergamot
  - Achillea wilhelmsii (Iran)
  - Alpinia zerumbet (shell ginger)
  - Spiranthera odoratissima (Persia)

- De souse DP et al. A Systematic Review of the Anxiolytic-Like Effects of Essential Oils in Animal Models. Molecules. 2015 Oct 14;20(10):18620-60. doi: 10.3390/molecules201018620.
- Malcom BJ and K Tallian. Essential oil of lavender in anxiety disorders: Ready for prime time? Ment Health Clin. 2018 Mar 26;7(4):147-155. doi: 10.9740/mhc.2017.07.147.
- Zhang N and L Yao. **Anxiolytic Effect of Essential Oils and Their Constituents: A Review.** J Agric Food Chem. 2019 Jun 13. doi: 10.1021/acs.jafc.9b00433.

SILEXAN FOR ANXIETY

- Silexan – lavender oil in 80mg capsules
- Review of 7 trials using Silexan for generalized anxiety disorder
- Dosage 80mg-160mg daily
- Anxiolytic effect of Silexan was evident after 2 weeks
  - Comparable to results found with lorazepam and paroxetine
- Benefits also on impaired sleep, somatic complaints, comorbid depression, and quality of life
- NO serious adverse effects, drug interactions, sedation or withdrawal symptoms, except mild GI sx

"Silexan is a safe and effective treatment in anxiety disorders"

Kasper S and WE Muller et al. **Silexan in anxiety disorders: Clinical data and pharmacological background.** World J Biol Psychiatry. 2018 Sep;19(6):412-420. doi: 10.1080/15622975.2017.1331046.

HOMEOPATHY & ANXIETY

- Gelsemium 5C, 9C and 30C showed significant anxiolytic effect in rats with increased % time in open-field light compartment (marker for reduced anxiety)
  - Comparable to effects seen with buspirone

- Magnani P et al. **Dose-effect study of Gelsemium sempervirens in high dilutions on anxiety-related responses in mice.** Psychopharmacology (Berl). 2010 Jul;210(4):533-45. doi: 10.1007/s00213-010-1855-2.

WHAT TO DO WHEN YOU'RE STUCK…

WHEN YOUR PATIENT IS "STUCK"…

- Keep digging for additional infectious/non-infectious triggers
- Test close contacts, including pets, for colonization
- Consider biofilms
- Consider immune system activation of the coagulation cascade
- Consider emotional stress as a perpetuating factor
  - Patients, parents, siblings

BIOFILMS

- Biofilms can occur anywhere
  - Gut, sinuses, tonsils, eustachian tube, blood vessels, teeth, etc.
  - Biofilm = extracellular polymeric substance (EPS) matrix ("SLIME") + attached microorganisms that created the EPS
  - A biological system and coordinated functional community
- Microbial cells growing in biofilm are phenotypically DIFFERENT from free-floating planktonic organisms of that SAME organism
- PURPOSE: Promote growth and survival of organisms in the biofilm
  - Protection from the host's immune system and antimicrobials
- Can be a persistent source of infection and PANS/PANDAS flares
  - May need T&A
- Implicated in many chronic diseases

ORGANISMS THAT CREATE BIOFILMS

- Pretty much all!
- Gram-positive bacteria (Streptococcus spp, Staphylococcus spp, Bacillus ss, Listeria monocytogenes, Enterococcus spp, Lactobacillus spp, etc.)
- Gram-negative bacteria (Escherichia coli, Klebsiella spp, Pseudomonas spp, Haemophilus spp, etc.)
- Fungi (Candida spp, Cryptococcus spp, etc.)
- Spirochetes (Borrelia spp)
- Viruses (HTLV-1)

frontiers in
CELLULAR AND INFECTION MICROBIOLOGY

REVIEW ARTICLE
published: 11 February 2015
doi: 10.3389/fcimb.2015.00015

Streptococcus pyogenes biofilms—formation, biology, and clinical relevance

Tomas Fiedler, Thomas Köller and Bernd Kreikemeyer*

Institute of Medical Microbiology, Virology, and Hygiene, Rostock University Medical Centre, Ros

Edited by:
Pietro Speziale, Università degli Studi di Pavia, Italy

Reviewed by:
Vincent Joseph Starai, The University of Georgia, USA
Sabine Hunke, University of Osnabrueck, Germany

***Correspondence:**
Bernd Kreikemeyer, Institute of Medical Microbiology, Virology and Hygiene, Rostock University Medical Centre, Schillingallee 70, 18057 Rostock, Germany
e-mail: bernd.kreikemeyer@med.uni-rostock.de

Streptococcus pyogenes (group A stre
pathogen. The virulence potential of this
range from asymptomatic carriage over r
membranes up to systemic purulent t
the latter are a severe threat for predisp
worldwide. This places GAS among the n
Many recent reviews have highlighted th
and regulatory circuits/networks that er
all levels of the host immune defense.
animal infection studies based on mice
appreciated that GAS, like many other
live in a planktonic lifestyle. GAS is capa
cells and tissues. We are now beginn
contributes to GAS pathogenesis. In thi
on GAS biofilm formation, the biofilm-phenotype associated virulence factors, regulatory
aspects of biofilm formation, the clinical relevance, and finally contemporary treatment
regimens and future treatment options.

GAS is capable of microcolony and biofilm formation on host cells and tissues. We are now beginning to understand that this feature significantly contributes to GAS pathogenesis…

GAS organized in biofilm structures are able to survive antibiotic treatment that is adequate for planktonic GAS.

GENERAL BIOFILM PROTOCOL

- Step 1: Mucolytic, proteolytic, fibrinolytic enzyme and/or NAC on empty stomach (nattokinase, serrapeptase)
  - GOAL: "Punch holes" in biofilm to allow antimicrobial penetration
- Step 2: 1 hour later: Antimicrobial agent
  - GOAL: Kill the bugs living in biofilm
- Step 3: 1 hour later: Binding agent
  - GOAL: Mop up microbial toxins and reduce "die-off"

CAUTION: Reduce burden of FREE-FLOATING organisms FIRST before attacking biofilm and releasing SESSILE organisms

BIOFILM BUSTERS – REFERENCES

- Dinicola S et al. N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. Eur Rev Med Pharmacol Sci. 2014 Oct;18(19):2942-8.
- Zapotoczna M et al. An Essential Role for Coagulase in Staphylococcus aureus Biofilm Development Reveals New Therapeutic Possibilities for Device-Related Infections. J Infect Dis. 2015 Dec 15;212(12):1883-93.
- Hogan S et al. Novel Treatment of Staphylococcus aureus Device-Related Infections Using Fibrinolytic Agents. Antimicrob Agents Chemother. 2018 Jan 25;62(2).
- Hogan S et al. Potential use of targeted enzymatic agents in the treatment of Staphylococcus aureus biofilm-related infections. J Hosp Infect. 2017 Jun;96(2):177-182.

SECONDARY HYPERCOAGULABILITY

- Coagulation cascade initiated by Tissue Factor (TF)
  - End result: Generation of Thrombin with subsequent conversion of Fibrinogen → FIBRIN CLOT formation
- TF primarily expressed by endothelial cells and perivascular fibroblasts
- TF also expressed at low levels → MONOCYTES and NEUTROPHILS
- Immune system activation of the coagulation cascade
  - Seen with bacterial infections
  - Including Strep spp, Staph spp, Yersinia spp

- Delvaeye M and EM Conway. Coagulation and innate immune responses: can we view them separately? Blood 2009 114:2367-2374.

SECONDARY HYPERCOAGULABILITY

- Immune system activation of the coagulation cascade – the PROS
  - Limits pathogen dissemination
  - Supports pathogen killing
  - Promotes tissue repair
- Immune system activation of the coagulation cascade – the CONS
  - Chronic activation leads to thrombosis
  - Literally keeps immune system "STUCK"
  - Walls off pathogens to evade immune system
  - Impedes nutrient and waste flow in and out of cells
  - RESULT → Increasing inflammatory/toxic and infectious burden
    - Antoniak S. The coagulation system in host defense. Res Pract Thromb Haemost. 2018 Jul; 2(3): 549–557.

HYPERCOAGULABILITY WORKUP

Hypercoagulability labs:

- ❑ Fibrinogen
- ❑ Prothrombin fragment 1 + 2
- ❑ Thrombin-Antithrombin complex
- ❑ Antithrombin III
- ❑ D-Dimers
- ❑ Protein C activity
- ❑ Protein S activity
- ❑ Plasminogen activator inhibitor-1 activity (PAI-1 activity)
- ❑ Homocysteine
- ❑ C-reactive protein

Nakashima MO and HJ Rogers. Hypercoagulable states: an algorithmic approach to laboratory testing and update on monitoring of direct oral anticoagulants. Blood Res. 2014 Jun; 49(2): 85–94.

TREATING IMMUNE-SYSTEM ACTIVATED HYPERCOAGULABILITY

- Lumbrokinase
  - Fibrinolytic + Thrombolytic
  - Only use if evidence of elevated Hypercoagulability panel
    - Otherwise use fibrinolytic nattokinase and serrapeptase
- Hypercoagulability protocol similar to Biofilm protocol
  - Mucolytic, proteolytic, fibrinolytic enzyme on empty stomach (lumbrokinase, nattokinase, serrapeptase)
    - GOAL: "Punch holes" in biofilm to allow antimicrobial penetration
  - 1 hour later: Antimicrobial agent
    - GOAL: Kill the bugs living in biofilm
  - 1 hour later: Binding agent
    - GOAL: Mop up microbial toxins and reduce "die-off"

CAUTION: Reduce burden of FREE-FLOATING organisms FIRST before releasing a deluge of organisms hiding behind clots…

R.M. – "NOT A HEME ISSUE"

- Almost 10 y/o with h/o apraxia presenting with depression/anxiety and "fits" of "tongue groping" and emotional/physical tantrums, cognitive decline especially in math
  - ASO 219 (N150), anti-DNAse B ab 422 (<376)
- Significant improvements on azithromycin
  - Normalized strep titers, no more "fits,", doing well in math
- Further improvement with treatment of treatment of dientamoeba fragilis (metronidazole) and candida (itraconazole) gut dysbiosis
- Transitioned off azithromycin to Biocidin LSF
- Got into desired private high school and doing great on foundational supplements
  - Fish oil, probiotic, vitamin d3/k2, magnesium, food-based multi, SPM, LDN
- Parental separation → extreme psycho-emotional stress, inconsistent supplements and sleep

R.M. – "NOT A HEME ISSUE"

- 7 months later…
  - Itchy swollen tender "purplish" feet for 7 months
  - Multiple urgent care visits treated with lotrimin for possible athlete's foot, hydrocortisone and calamine for possible chilblains
  - Podiatrist consultation → referred to vascular surgeon for possible Raynaud's
  - PE: cap refill ~3 seconds on feet, legs and fingers, feet moderately edematous and pink, cool to the touch
  - Labwork:
    - ANA negative
    - Prothrombin Fragment 1.2 1072 HIGH (41-372 pmol/L)
    - Thrombin-Antithrombin (TAT) Complex 29.8 HIGH (<4 mcg/L)
    - D-Dimer 8.10 HIGH (<.50 mcg/ml)
    - Normal: Protein C + S activity, AT III activity, fibrinogen, homocysteine, ESR, CRP
- I call LPCH Heme…

R.M. – "NOT A HEME ISSUE"

- LPCH Heme Fellow/Attending:

  Why did you order these labs?

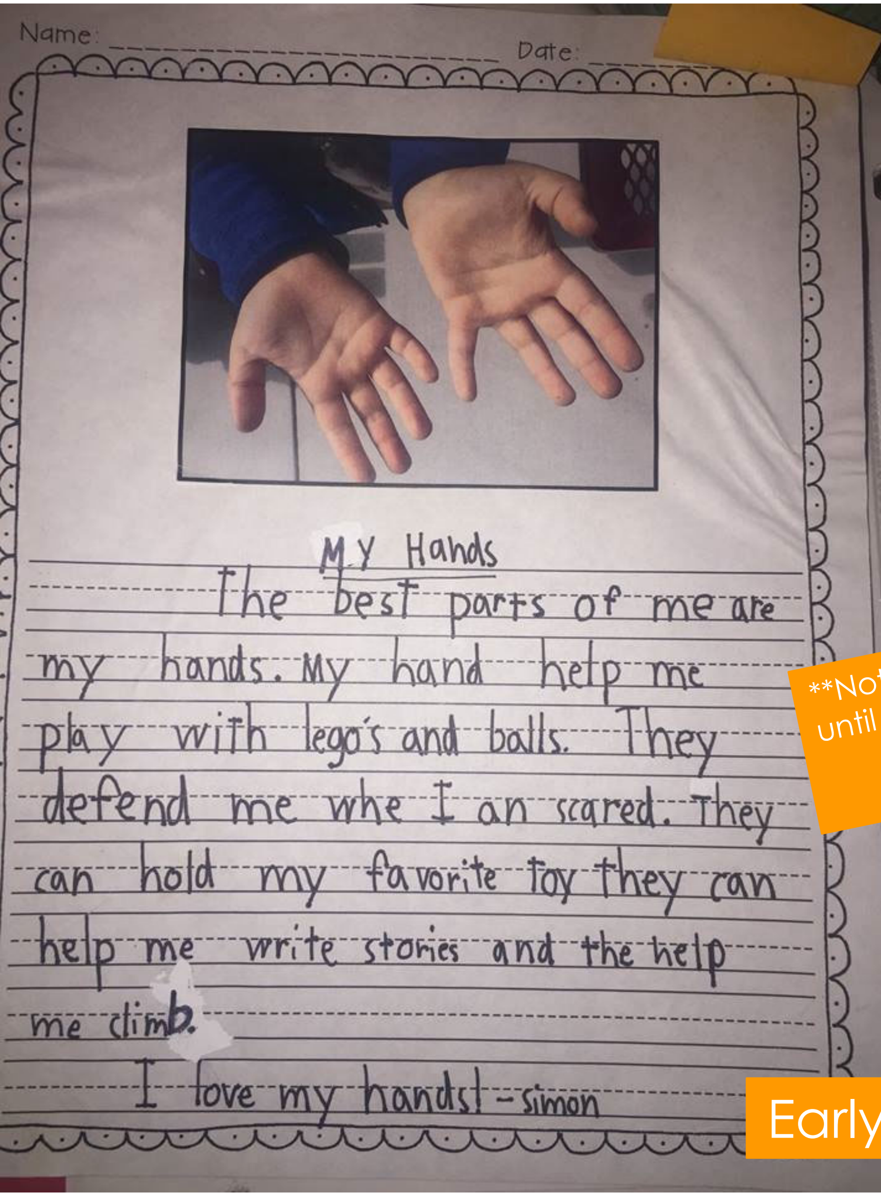
  I'm not really familiar with them…

  She doesn't have any signs of DVT or family history of coagulopathy, so…

  It's not a Heme Issue

- Treatment Plan
  - Nattokinase/Serrapeptase on empty stomach
- 3 months later
  - CRT <2 seconds
  - Labs normalized
    - TAT Complex 2.8, PT Frag 1.2 253, D-dimer 0.54 sl high (<0.50)

MORE CASES…



Name: Date:

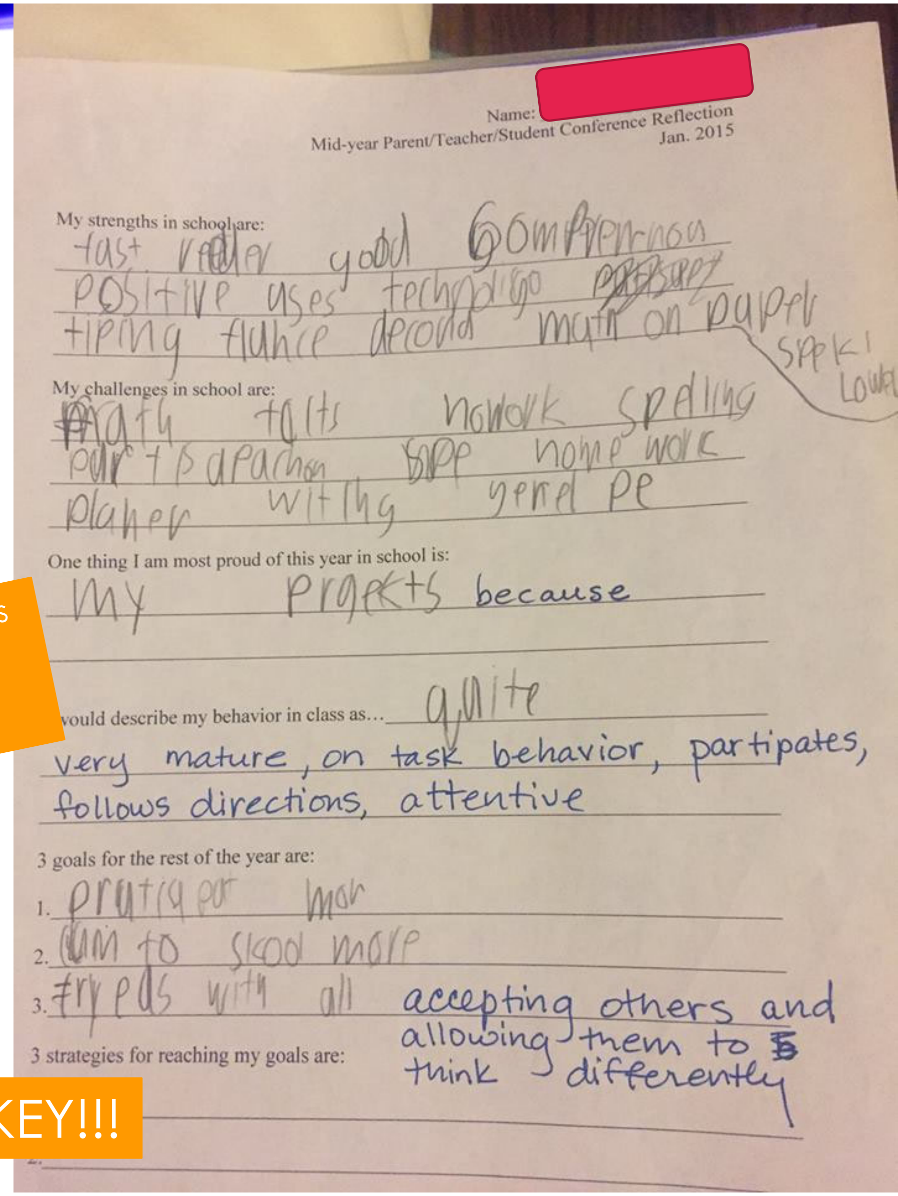
My Hands

The best parts of me are my hands. My hand help me play with lego's and balls. They defend me whe I an scared. They can hold my favorite toy they can help me write stories and the help me climb.

I love my hands! - simon

← Before PANS
(2nd grade)

After PANS →
(3rd grade)



Name: [redacted]
Mid-year Parent/Teacher/Student Conference Reflection
Jan. 2015

My strengths in school are:
fast reder good comprenhsion
positive uses technology [illegible]
tiping fluncie decod math on paper
[illegible]

My challenges in school are:
math falts nowork speling
part 1 s [illegible] [illegible] home work
planer witing yenel pe

One thing I am most proud of this year in school is:
my progects because

[I w]ould describe my behavior in class as… quite
very mature, on task behavior, partipates, follows directions, attentive

3 goals for the rest of the year are:
1. pratiq [illegible] [illegible]
2. [illegible] to skool more
3. frends with all
accepting others and allowing them to think differently

3 strategies for reaching my goals are:

Not dx'ed for over 2 years until I saw him Jan 2017

STILL STRUGGLING…

Early diagnosis is KEY!!!

LK – HISTORY

12 year-old previously healthy girl, in 6th grade

- Seen for well-care through 2nd grade when family moved to Texas
- History of intermittent abdominal pain
  - → ?Underlying gut dysbiosis
- Carb/sugar junkie
  - → ?Yeast dysbiosis
- Mild OCD behaviors in 2nd and 3rd grade – touching certain items
- But a sweet, happy, smart, athletic kid with lots of friends
- Moved back to Bay Area for 5th grade (about a year prior to our first visit)
  - Things dramatically worsened…
  - → An abrupt change… Think possible PANS

LK – HISTORY

- Anxiety and OCD behaviors really ramped up at end of 5th grade
  - Tumbling everywhere, touching things around the house, turning lights on and off, not wanting to step over lines
- Sleep has become really challenging, taking hours – making anxiety worse
- Big decline in executive function skills, organizing backpack, binders, room
- Cognitive processing and memory declining
- Clumsier, increased accidents, competitive cheer suffering
- Not yet affecting grades, but everything seems CHAOTIC
- Handwriting is terrible now
- Last time patient remembers being really happy and relaxed:
  - When she went to Disneyland with friend's family in 5th grade
  - During that trip had a high FEVER and needed to stay in hotel for a couple of days
  - About a week after coming home, anxieties started to ramp up with eventual suicidal ideation and cutting behaviors
  - → ?Possible PANS trigger
- That's when parents decided to start Paxil for past few months and sleeping med (hydroxyzine) which have helped significantly

All possible PANS symptoms

"I wish I could go back to how I used to be"

LK – HISTORY

- Diet –SAD
  - Chooses sweets, breads, junk food
  - Despite household full of fruits and vegetables, nuts, healthy options
  - Anxiety worse when eats lots of junk food
  - → highly pro-inflammatory diet, suspect nutritional insufficiencies
- FHx
  - Significant atopic history on both sides
  - Twin brother with sensory processing issues, ADHD, severe sensitivity to dyes, food additives, chemicals
  - → FHx of immune dysregulation, neurodevelopmental disorders, detoxification problems

LK – SIGNIFICANT EXAM FINDINGS

- Pupils dilated
  - → "Fight-or-Flight" typical of a PANS flare
- Intermittent "jerking" off whole body
- Tremoring of hands
  - → choreiform movements and motor tics common in PANS
- Mental status
  - Delayed response to questions, poor eye contact
  - NOT the "same" girl I knew 4 years ago…
  - → cognitive processing delays can be startling

INITIAL TESTING PLAN

- Testing
  - Cultures of nares, throat and anus for strep
  - Antibody titers for ASO, anti-DNAse B, EBV, mycoplasma, coxsackie, parvo-B19, HHV-6, HSV 1/2, Lyme immunoblot
  - Vitamin D, RBC zinc, RBC magnesium, Ferritin, CBC, CMP
  - MTHFR status
  - Copper, Zinc, Ceruloplasmin
  - TSH, Free T4, Free T4, Reverse T3 (symptoms coincided with pubertal changes)
  - Comprehensive Stool analysis
  - Urine Organic Acid Test
  - Food IgG sensitivity panel
  - Moleculera Cunningham panel (per parent's request)

INITIAL RECOMMENDATIONS

- NEED TO CLEAN UP DIET – eliminate processed artificial foods, add fruits/vegetables
  - Focus in ADDING before taking away
- Prioritize SLEEP – sleep supplement with melatonin, 5-HTP, theanine, curcumin
- Fish oil, food-based green multivitamin/mineral with methylfolate and mb12
- Inositol for OCD and anxieties

SIGNIFICANT LAB FINDINGS

- TSH 1.88, FT4 0.9 LOW-NL (0.9-1.4), FT3 3.2 LOW (3.3-4.8), RT3 11
  - → need thyroid support for proper immune functioning
- Pathogen titers
  - ASO 918 high (<150), Anti-DNAse B ab 354 HIGH (<95)
  - Parvo B-19 IgG 8.6 HIGH (<0.9); IgM negative
  - → PANDAS, possible viral component
- RBC zinc 8.4 LOW (9.0-14.7)
  - → contributing to immune dysfunction, sensory issues, picky eating, leaky gut
- 25-OH Vitamin D 23 LOW (30-100)
  - → contributing to immune and hormonal imbalance
- MTHFR heterozygous C677T mutation
  - → methylation stress
- Food IgG panel HIGH egg white/yolk, gluten
  - → leaky gut
- Urine OAT high bacterial dysbiosis markers, HIGH quinolinate
  - Gut dysbiosis, neuro-inflammation

PATIENT REPORT

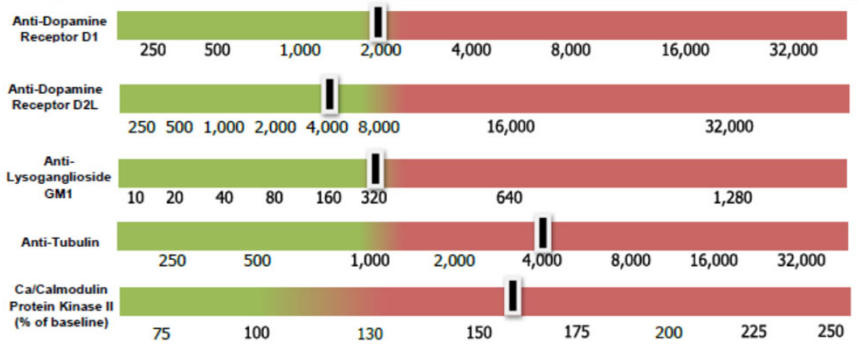
Submitting Prescriber: Elisa Song, MD
Date of Collection: 05/22/2017
Date of Receipt: 05/23/2017

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 II (% of baseline)
Patient Result	1:2,000	1:4,000	1:320	1:4,000	159
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	BORDERLINE	NORMAL	BORDERLINE	ELEVATED	ELEVATED

***Report Guidance:** If any 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 which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS



The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D1 Receptor (DRD1), Dopamine D2L Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). ELISA results are determined by measuring the colorimetric intensity at a specific wavelength which is directly proportional to the amount of antibody in the sample. The fifth assay of this panel 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 controls. 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.

PLAN

- Continue fish oil, multivitamin, inositol, sleep reset packet
- Gluten-free, egg-free diet
- Eliminate artificial dyes, flavors, preservatives
- Add zinc
- Add curcumin
- Add SPM for immunomodulatory support
- Add strep-free probiotic
- Add Vitamin D3
- Add Nature-Throid ½ grain qam
- Add Azithromycin 500mg loading dose then 250mg qd

6 WEEKS LATER…

- "Enormous improvements" – acting and feeling like the "old Lily"
  - Anxiety and OCD are almost gone
  - Clumsiness totally gone
  - Mood is great
  - Patient feels so much better physically and emotionally

"It's like a night and day difference"

- Psychiatrist does NOT believe patient has PANS – and told her so! ☹

STOOL TEST RESULTS BACK!

- Significant findings:
  - HIGH streptococcus species
  - + Chilomastix mesnelli
  - Pancreatic elastase 129 Low (>500)
- Plan:
  - Continue azithromycin
  - Parasite cleanse – antiparasitic herbs, Alinia

2 MONTHS LATER

- Still doing great!
  - Diet loosened up, and anxiety creeps back when too much gluten or junk food
- Successfully weaned OFF Paxil and hydroxyzine
- Sleep is great!
- Going on school trip to Costa Rica

- Ongoing plan/goals
  - Wean off azithromycin and switch to herbals
  - Healthy eating choices to reduce inflammation and keep PANDAS in remission
  - Continue fish oil, vit D, probiotics, MVI, SPM
  - Treat acute illnesses quickly with natural/homeopathic medicines to prevent flares
  - Quickly address flares with ibuprofen +/- prednisone

As good as it gets!

AK – HISTORY

- 6.5 year old boy consulting for sensory processing disorder and emotional regulation issues
  - Referred by OT – "there's something more going on…"
  - Always "rough and tumble" but did well in preschool
  - Then in Kindergarten, things became really rough
    - → no clear illness trigger, but things CHANGED…
    - Quick to anger, constantly wiggling, touching others, lots of fears and anxiety
    - Heightened sensory issues
      - Can't stand touch, can't stand smells, loud sounds freak him out
      - → zinc deficiency
    - Very HIGH PAIN THRESHOLD – could run into walls or have huge falls and not notice
      - → gliadorphins or casomorphins
    - Low energy and endurance compared to peers, wiped out at end of soccer game
      - → mitochondrial dysfunction
    - Sleep disturbance, waking multiple times to urinate
  - Environmental allergy symptoms showing up
    - → histamine issues
  - Tendency toward constipation
    - → gut dysregulation

INITIAL PLAN

- Fish oil, vitamin D3, Zinc, Epsom salt baths
- Move toward GFCF diet
- No artificial dyes, flavors, preservatives
- Testing
  - Anti-DNAse B
  - ASO
  - CBC
  - RBC zinc
  - RBC mg
  - Ferritin
  - Vitamin D
  - MTHFR mutation panel
  - MMA and homocysteine
  - Comprehensive stool analysis
  - Urine organic acid test

FOLLOW-UP #1

- Since last visit, a LOT of improvements
  - Just with change in diet, fish oil, vit d, zinc, Epsom salt baths
  - A lot less explosive, able to control emotions better, taking thinks more in stride
  - Sensory issues much better
    - Doesn't rub off mom's kisses, asks for hugs
  - Still easily tired and poor endurance
- Lab results
  - Urine OAT with HIGH gut yeast dysbiosis, methylation issues, mitochondrial dysfunction, oxidative stress, low amino acid profile
  - Refusing blood and stool testing
- Plan:
  - Add magnesium malate, broad spectrum probiotic + saccharomyces boulardii,, protein powder

FOLLOW-UP #2

- More willing to try new foods, and enjoying them!
- Sleep still really disturbed
  - Over last 1-2 months, now waking to pee at least 3-4 times at night
    - Thinks he's wet, doesn't like feeling, gets up to pee, and has to change all clothes
    - In bed 12 hours, but interrupted multiple times
- Still low energy/endurance
- Moving and twitching nose frequently - ?allergies ?tic

Plan:

- Strongly encouraged getting bloodwork
- Add coQ10, quercetin, sublingual MB12
- Add inositol for tics and help staying asleep

FOLLOW-UP #3

- Doing really well – has some days where he's "Amazing Alex" and so cute
- Other days he's "Angry Alex" – screaming from morning till night
- Still twitching nose a lot and having headaches
  - Restarted quercetin which is helping
- Still has fatigue
  - Theanine helping a lot with sleep and not waking to pee but still waking several times at night
  - Mood is good because he's sleeping better, but sometimes energy so low he just flops down
- Plan:
  - Encouraged bloodwork again, add respiratory allergy panel
  - Increase quercetin
  - Increase coq10
  - Add adrenal supports

BLOODWORK DONE (ALMOST 1 YEAR AFTER 1ST VISIT…)

- Significant findings
  - ASO 290 HIGH (<150), Anti-DNAse B ab 545 HIGH (<376)
  - MTHFR homozygous A1298C mutation
  - RBC Zn 9.7 LOW-NL
  - IgG food panel HIGH CASEIN
  - Respiratory allergy panel totally negative, total IgE 9
- Plan:
  - Discussed PANDAS
    - Waxing and waning course, need to avoid strep exposures at school and home, longterm antimicrobials and need to protect gut microbiome, potential future treatments including ibuprofen/steroid bursts for flares and IVIG
  - Add Azithromycin
  - Add curcumin
  - ADD L-Methylfolate
  - Add probiotic specifically to reduce gliadorphins and casomorphins
  - Eliminate dairy, continue elimination of gluten and artificial flavors/dyes/preservatives

6 WEEKS POST- ANTIBIOTICS

- "A different kid" in a positive way
  - More clear and focused, better eye contact, less volatile
  - More willing to do what's asked even if he things it's hard or challenging
  - A lot more flexible, can negotiate and reason better
  - Not melting down when things don't go his way
  - More accepting of touch and giving parents hugs - NEVER did this before
  - More giggly and goofy and trying to crack jokes
  - Asking for more playdate and more flexible in his play and willing to do what friends want
- Energy better but still tires more easily than peers
- Sniffing tic is gone and seems clearly dairy-related
- Still spitting with bad smells
- Still waking throughout night and can't fall back asleep

FIRST SIGNIFICANT FLARE

- Grandmother visiting
  - Pt had return of sniffles, really volatile and tantrums
  - Grandmother broke out in shingles next day
- Ibuprofen 10mg/kg tid x 5 days
  - Flare resolved
  - No need for prednisone

ALTITUDE TROUBLES…

- Parents notice worsening when they went to Arnold (~4000 feet altitude at base)
  - Mood regression, anger, meltdowns
  - As soon as they got to Pleasanton on drive back home, mood totally changed and mom "felt like I had my child back"
  - → increased mitochondrial and oxidative stress
- Next Arnold trip
  - Ramp up coQ10, ribose, Vitamin C
  - MUCH BETTER

STILL FLARING…

- Overall better but…
  - Still some tics
  - Getting more obsessive over Ipad
  - Has to change pants as soon as there's a little wetness
  - When stools, can't get himself clean enough – uses nearly whole roll of toilet paper, mom has to check, and pt has to change clothes
  - Often won't sleep in own room – never had to sleep with parents when young
  - New fears about noises

MORE INVESTIGATION…

- Nasal swab + aeromonas and MARCONS (Multiple Antibiotic Resistant Coagulase Negative Staphylococci) often seen in mycotoxin illness
  - Won't do BEG (Bactroban, EDTA, Gentamicin) spray – burns too much
- Additional testing
  - Do comprehensive stool analysis NOW
  - C4a level for mold screen
  - Additional infections – EBV, mycoplasma pneumonia, hsv6, coxsackie A+B, HSV 1/2, cmv, parvo b-19, Lyme and coinfections, IgG and IgG subclasses, IgA
- Plan:
  - Add SPM (but won't swallow it, and can't tolerate taste)
  - Consider LDN
  - Has been on azithromycin for 4 months – try changing to cefdinir
    - (In restrospect, probably not a good idea. KEEP on the initial antibiotic that helped, then layer in different antimicrobials if needed)

LAB RESULTS

- Total IgG 574 LOW (673-1734); IgG subclasses wnl
- Total IgA 28 LOW (41-368)
  - ??? Does patient have immunodeficiency due to chronic infections, OR does patient have underlying CVID or other immunodeficiency predisposing him to PANS/PANDAS???
- Infection panel: POSITIVE Bartonella Quintana IgG antibodies, IgM negative
- Functional stool analysis: MODERATE YEAST, no strep
- PLAN:
  - More specialized Lyme/coinfection testing
  - Add Fluconazole for yeast
  - Big flare despite Omnicef (dad had a cold?) → change to Augmentin
  - Add homeopathic detox supports and strep/staph nosodes

FOLLOW-UP

"Alex has been DELIGHTFUL since changing his supplements. He was great on Wed night and all day yesterday - like a different kid. Kind, no yelling, no complaining to take his meds, etc."

- Short-lived
- A month later, mood improved but biggest concerns right now are OCD type behaviors, anxiety and general lack of interest in doing things (almost as if things are too hard and take too much energy).
- Awaiting specialized Lyme/coinfection testing
- ??? Time to consider IVIG to "reboot" immune system

LAB RESULTS

- ASO and anti-DNAse B now NORMAL
- Bartonella Quintana IgG 1:128 HIGH; IgM negative
  - → significant given low IgG
- Lyme IgG western blot REACTIVE 41kda, 58kda, 93kda bands; IgM nonreactive
- Questions:
  - Do we need to treat Bartonella now?
  - Do we push forward for IVIG?
  - Where are the lingering neuro-inflammatory triggers?
- Plan:
  - T&A scheduled for 1 month to remove potential biofilm and hidden strep source
  - Consider prednisone taper
  - Retry SPM, add Chinese Skullcap
  - Consider LDN
  - Change back to azithromycin
    - No appreciable change on cefdinir or amox-clav, and zmax has anti-inflammatory effects

POST-T&A AND RESTARTING SPM

- Just finished 2nd grade and did GREAT – perfect report card!
- Last 2 weeks – sleeping in OWN BED and ALL NIGHT LONG!
  - Hasn't been in own room for 6 months!
- Happier, more calm, easier transitions, giggle and laughing more
- Has made some good friendships
- Remaining issues
  - Still wants Ipad all the time
  - Still tired a lot of the time
  - Still occasional headaches
- IVIG scheduled for next month…
- PLAN: Start Low-dose naltrexone

POST-LDN

- Very positive results
- Titrated up to 3mg QHS
- A lot less explosive
- Still wants Ipad, but not as desperate, and can put down if asked
- Way more social and cooperative with friends
- Anxiety much better at night and in room alone

POST-IVIG

- Doing GREAT!
- Sleeping through the night
- Much less anxious
- A “different kid”
- BUT had also started low-dose naltrexone

CURRENT COURSE

- Overall SO much better!
- In school, much more regulated emotionally, sensory issues nearly resolved, HAPPY
- Continues with intermittent flares
  - Triggered by exposures to strep, viral illnesses, altitude
  - Flares typically respond to 5-7 day course of Ibuprofen
  - +/- Prednisone burst (2mg/kg/day x 3-5 days) occasionally needed

AAH, PREDNISONE…

Dr. Song, Wanted to share some good news (a small win) this week with Alex. I am in love with prednisone but understand that he can't always be on it. However, he is so good when he is on it, its awesome. He came home today with his paper from school and he got "role model" which is an indication of his behavior for the week. He's never gotten that and was so super happy that he had stepped it up. The smile was BIG! He's been much calmer, less fears, etc. Let's see what happens when we stop the 5 day dosage tomorrow, but hopefully we've put out the fire in his brain for now. Thanks! Amy

CURRENT COURSE…

- ASO and anti-DNAse B titers continue to be normal!
- Last cold that mom and sister had → patient NEVER flared – didn't "turn crazy" and never got sick!!!
- Huge flare in tics over the Spring
  - No response to quercetin or Benadryl
  - Resolved with fluconazole!
  - → REMEMBER Yeast Dysbiosis can easily occur given longterm antibiotic use
- Beginning work on Bartonella…
  - Another rocky road…

I'm getting the kid back that I always knew he was…

PHEW!

- TAKEAWAYS:
- Have a HIGH index for suspicion
  - Early diagnosis is KEY for early success
- Be PATIENT and PERSISTENT
- You DON'T have to treat everything at once!
  - Take a stepwise approach
    - Always build up immune reserves (optimize diet, nutrient levels, gut, etc.)
    - Fight the battle
    - Rest, recover, rebuild
- Always LOOK at your patient, not the numbers

HEALING PANS/PANDAS

Identify the Trigger(s)

- Diagnostic trial of ibuprofen, prednisone, antibiotics
- Throat/Nose/Anus/Skin cultures
- Titers: ASO, Anti-DNAse B, Lyme + coinfections, EBV, HSV 1/2, HHV-6, Coxsackie A+B, Parvo B-19, Influenza, Candida…
- Baseline CBC, CMP, Vit D, RBC Zn, RBC Mg, ferritin
- Comprehensive stool analysis
- Food IgG testing
- Urine Organic Acid test
- Copper, Zinc, Ceruloplasmin (r/o pyroluria)
- +/- Heavy metals
- +/- Mold
- +/- Cunningham panel

Initial Treatment Plan

- ANTI-MICROBIALS
- ANTI-INLAMMATORIES
  - Ibuprofen, Curcumin, Prednisone
- Omega-3 EFAs
- Vitamin D3
- +/- Probiotics
- GFCF diet
- NO artificial dyes, flavors, preservatives
- Whole foods, organic, phytonutrient-rich diet
- Refer for CBT and other therapies

Treat the Trigger(s)

- Pharmaceutical or Herbal Antimicrobials
- Reduce frequency of secondary illnesses
- Treat close contacts
- Treat non-infectious triggers (allergies, EMF, mold, metals)
- Consider Biofilms & Secondary Hypercoagulability

Put Out the Fire

- For flares: Ibuprofen, Prednisone bursts
- EFAs, Naprosyn, Curcumin, Quercetin, Antioxidants
- Anti-inflammatory diet
- Stress reduction

Keep the Fire Down

- SPM, LDN, CBD Oil, Chinese Skullcap
- Consider IVIG, plasmapheresis, Rituximab

Address Core Clinical Imbalances

- Nutritional Insufficiencies
- Gut dysbiosis, Leaky gut/food sensitivities
- Cell Danger Response (mitochondria & mast cells)
- Methylation stress
- Detoxification concerns

Restore & Rebalance

- Cognitive Behavioral Therapy (CBT)
- Family/sibling counseling
- Mindfulness, meditation, stress reduction

Complementary/Alternative Medicine

Dr. Song's 6-Step Approach to PANS/PANDAS

Download here:
https://healthykidshappykids.com/6-step-pans-pandas/

THANKS FOR JOINING ME TODAY!

Questions?