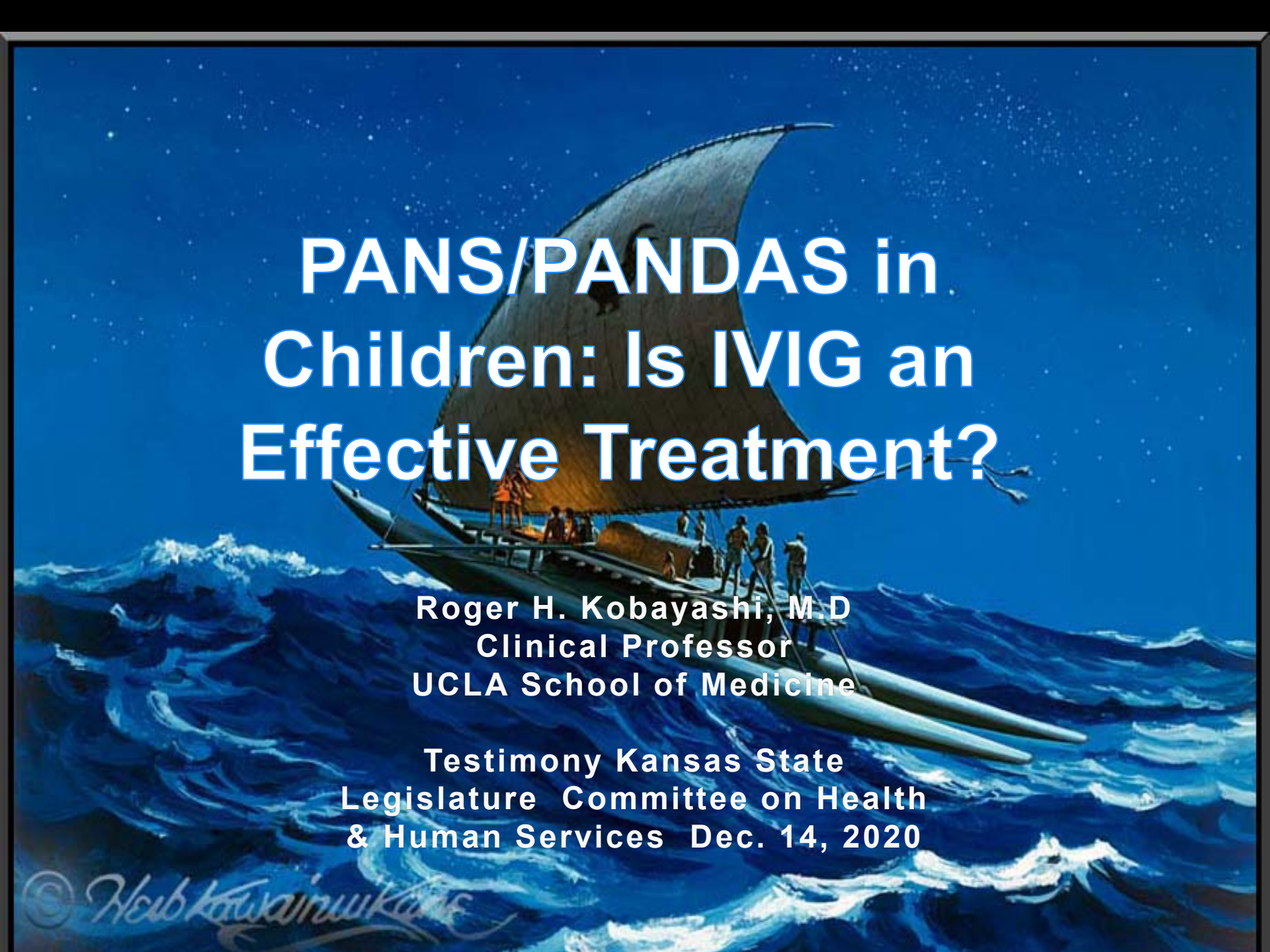


PANS/PANDAS in Children: Is IVIG an Effective Treatment?

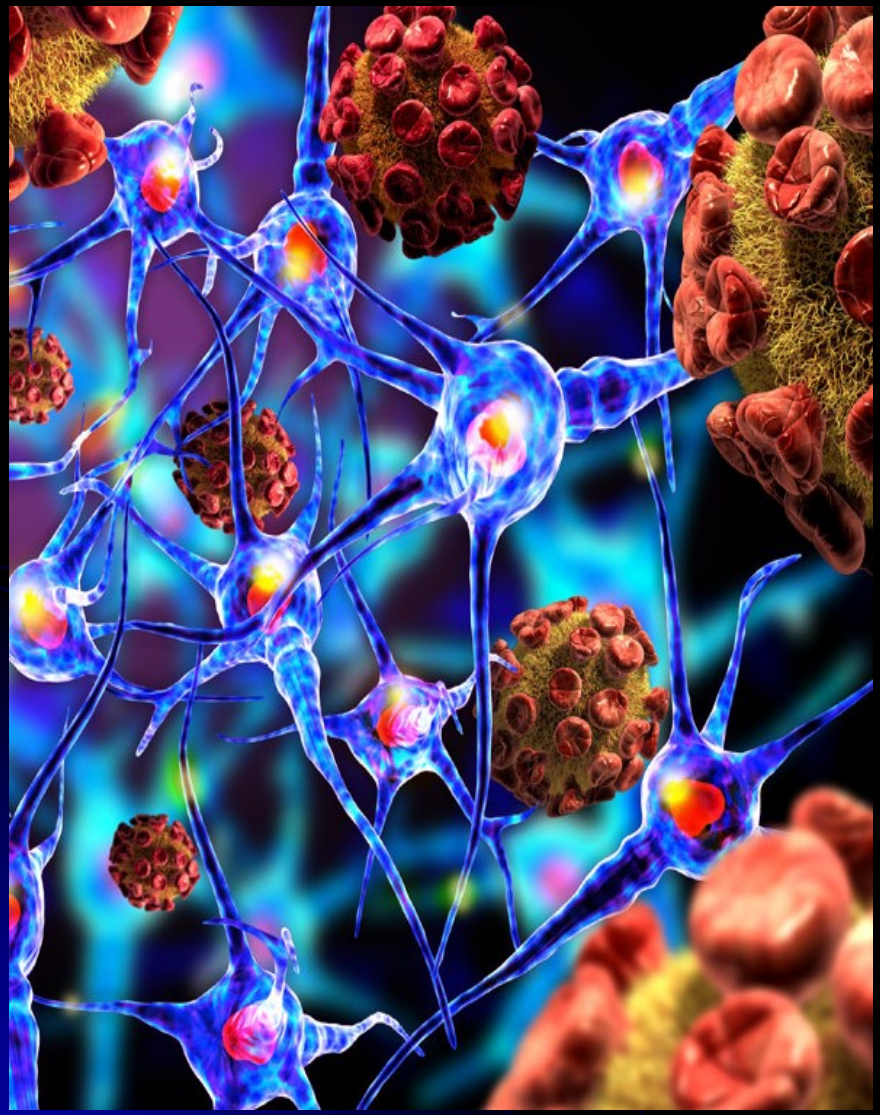
Roger H. Kobayashi, M.D
Clinical Professor
UCLA School of Medicine

Testimony Kansas State Legislature Committee on Health & Human Services Dec. 14, 2020

Humble Country Doctor & Grandfather from Nebraska

- Disclosures
- Immunology/Chronic Infections: AAIA [Ten Doctors & 4 PA's]
- Manage >320 patients on IgG.
- Grant support Octapharma, Shire
- Clinical Professor: UCLA
- Lecturer: MMU Hanoi, Vietnam
- Reviewer: JACI-IP Frontiers
- Consultant IDF, USID. Shire, Octapharma,
- Board Member: IfPA; National Biologic Physicians Working Group, Asian-Pacific Physicians
- Research interests: Primary antibody Immunodeficiencies, Access to affordable care, Immune modulatory treatment for CoVID in rural areas.

Discussion Outline



Purpose: To Discuss whether IVIG is helpful in PANS/PANDAS

- ***Part 1 Working definition of PANS***
- ***Part 2 Suggested pathogenesis of PANS***
- ***Part 3 Treatment of PANS***
- ***Part 4 What is IVIG?***
- ***Part 5 Studies with IVIG in PANS***
- ***Part 6 Questions***

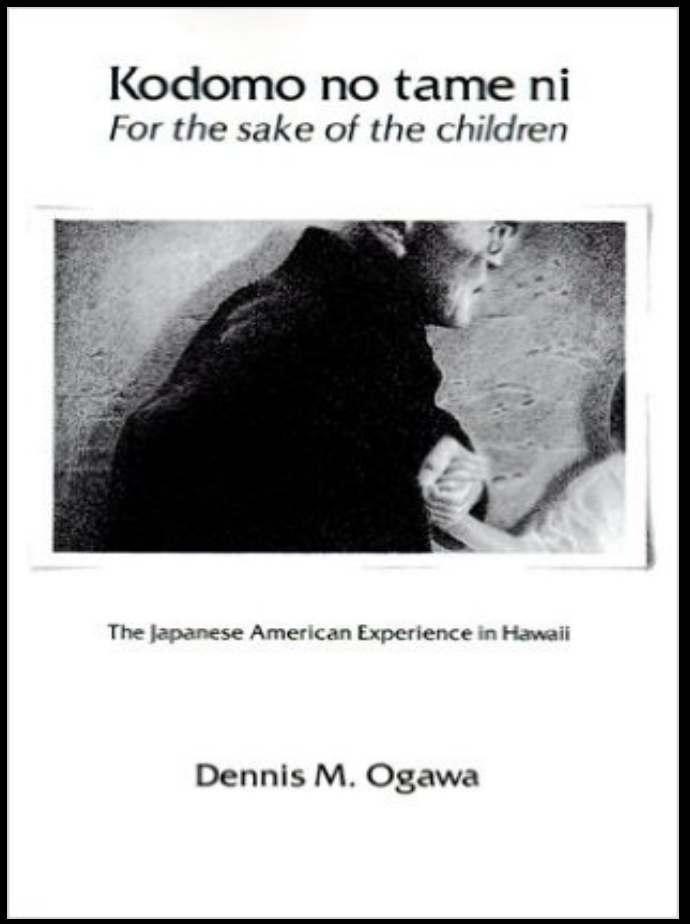
2008 NCAA Basketball Champions
University of Kansas Jayhawks

The National Championship vs. Memphis (Photos by Jeff & Laura Jacobsen)

1969 NCAA Basketball Champions UCLA Bruins

Last Time UCLA Won a Championship Color Film wasn't Invented yet

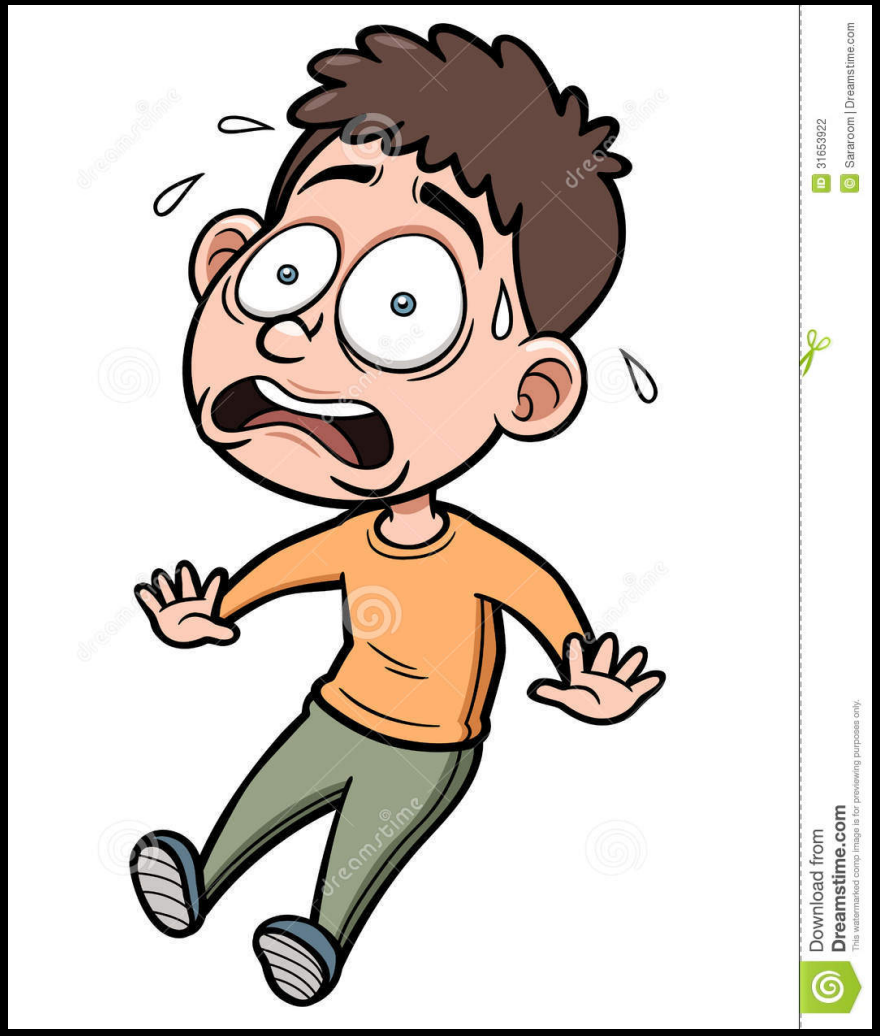
Why Study & Treat PANS?
"KODOMO NO TAME NI"



Case Report 1

- Very well-adjusted 9 y/o W/M history of recent, acute pharyngitis, developed dramatic onset severe compulsive disorder with anxiety, facial TICS, oppositional behavior, sleep disturbances. Taken to emergency room; referred to psychiatrist and placed on SSRI but poorly responsive. Referred and ASO and ASDnaseB > 1000.
- Treated with therapeutic doses of Augmentin, then rotated between amoxillin 500mg daily for 3 weeks and cephalexin 500 mg.
- Responded within 1 week; virtually normal. Cunningham panel elevated. **I COULD NOT BELIEVE THE RESPONSE.**
- After 6 months → no symptoms → antibiotics stopped. 4 months later, strep pharyngitis; **severe flare, incomplete response to beta lactams**, plus steroids, plus ibuprofen, SSRI and antihistamine [Hydroxyzine]. Parents desperate; high-dose IVIG given plus 2 separate monthly doses. ASO/ASD >1400.
- IVIG high dose Excellent response. Now completely normal. Off all medications except rotating antibiotics. Will treat for at least a year.

PANS is Thought to Be Different From Other Disorders Abrupt Onset Dramatic Change in Behavior Autoinflammatory/Autoimmune



NIH 2012 Criteria for PANS

- **Abrupt, dramatic onset OCD &/or Significant eating disorder or OCD &/ or TICS.**
- **Plus At least 2 of the following 7 symptoms**
- ***ALL* other causes excluded**

- **Concurrent presence of additional neuropsychiatric symptoms, with**
- **similarly severe and acute onset, with at least two of the following:**

- **1. Anxiety**
- **2. Emotional lability and/or depression**
- **3. Irritability, aggression and/or severely oppositional behaviors**
- **4. Behavioral (developmental) regression**
- **5. Deterioration in school performance**
- **6. Sensory or motor abnormalities**
- **7. Somatic signs and symptoms, including sleep disturbances,**
- **enuresis or urinary frequency**

Percentage of PANS Children Having Associated Symptoms

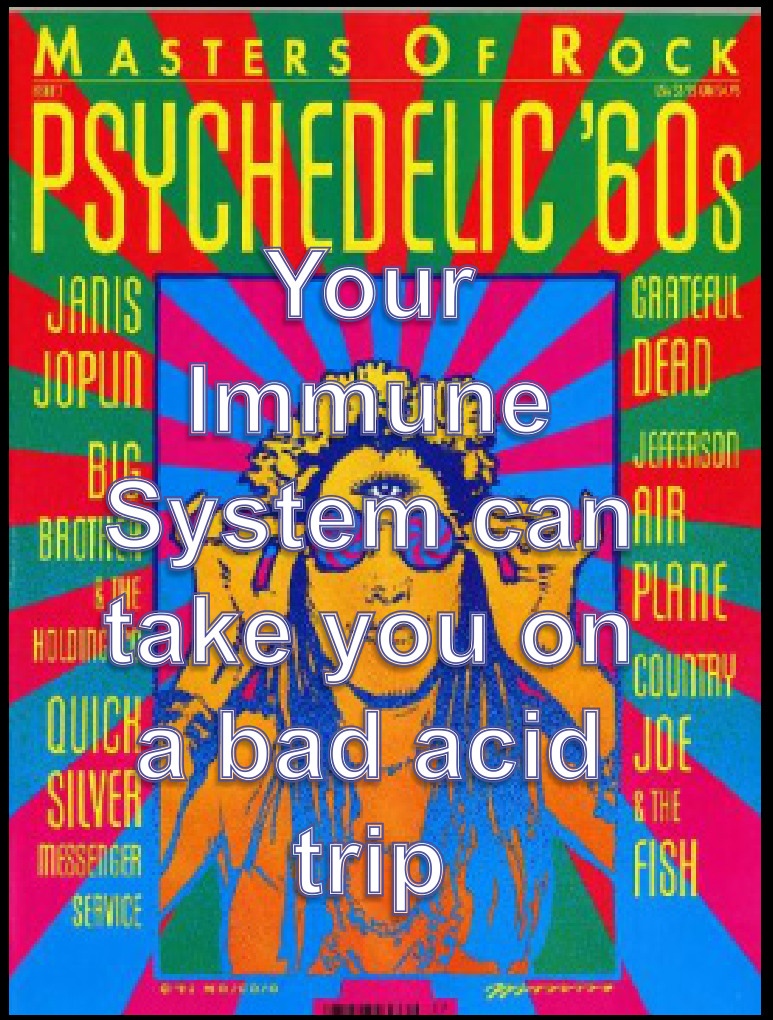
- Anxiety 73 – 95%
- Emotional Lability/Depression 66 -- 94%
- Irritability, aggression, oppositional behavior 26 – 50%
- Behavioral Regression 60 – 69%
- Decline in School Performance 75 – 88%
- Sensory/Motor Abnormalities 77 – 97%
- Somatic Symptoms [sleep, bed wetting] 83 – 98%

Swedo et al JCAP 2015

How the Immune System Is Supposed to Perform

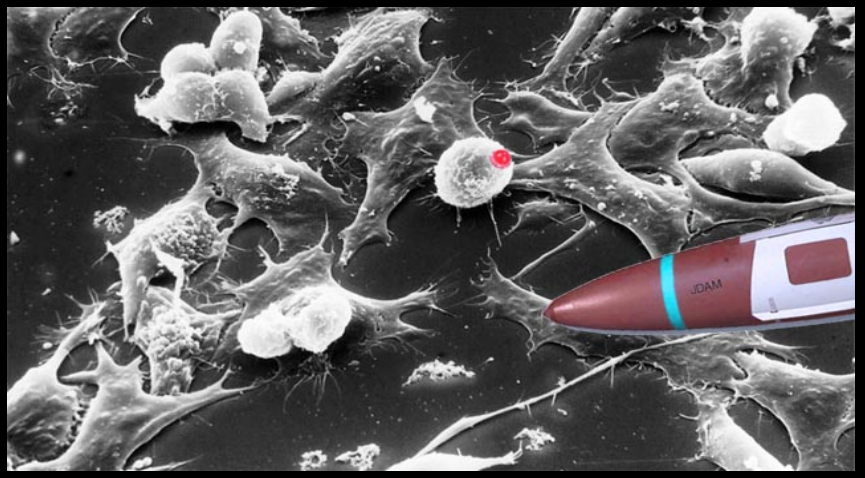
Vienna Philharmonic Ochestra

PIDD: Sometimes your Immune System is "FAR OUT"



The Immune System, Because of Inherent Genetic Mutations, Infectious, Chemical or Physical “Hits” Can Cause Immune Dysregulation, Auto- immunity or Persistent Unbridled Inflammation

Cross-reactivity or Molecular Mimicry/ Immune Dysregulation



Current Theories: Inflammation of Basal Ganglion

- Theory 1: Cross-reacting antibodies [or cells] cause basal ganglia to malfunction
- Theory 2: Neuronal cells in the brain precipitate inflammation in the basal ganglia

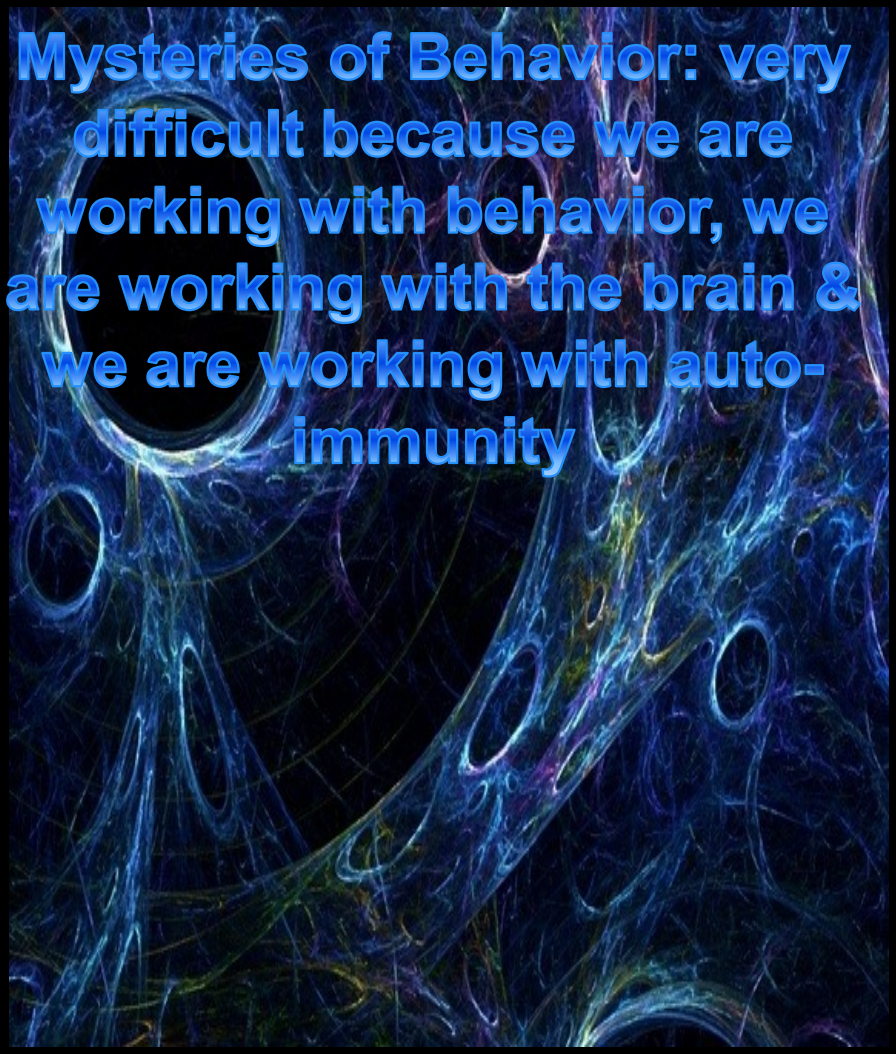
TABLE 1: EFFECTS OF BASAL GANGLIA INFLAMMATION

Basal Ganglia is a Relay Station through which Run Neurons that Control:	Inflammation may cause:
Mood & emotion	OCD, Mood lability, Anxiety
Behavior	OCD, Rage, Developmental regression
Procedural learning	Handwriting changes, Clumsiness
Motor movements	Tics, Choreiform movements
Cognition	Slow processing speed, Memory issues, specific Sensory learning deficits (often Math)
Sensory	Sensitivity to light, sounds, smells, tastes, textures

- M. Pincherio Up to Date

Why is PANS So Difficult to Diagnose and Treat?

- New disease which is still being defined
- Principal manifestations are behavioral
- Involves the brain, which we still don't understand well & is not easy to do laboratory studies on
- Mechanisms [pathogenesis] are not well-understood & are highly controversial
- Treatment: Difficult to treat something you don't understand. Empirical & theoretical treatments----work and don't work.



Suggested Pathogenesis of PANS

- Genetics, Genetics, Genetics
- Infectious etiology: **Group A Strep, mycoplasma, lyme disease, other infections?**
- Autoimmune disease:

  molecular mimicry, auto-antibodies against basal ganglia et al, Sensitized T-cells, immune dysregulation – different cytokine profiles, abnormalities in T-regulatory cells, failure in young children to modulate immune response?

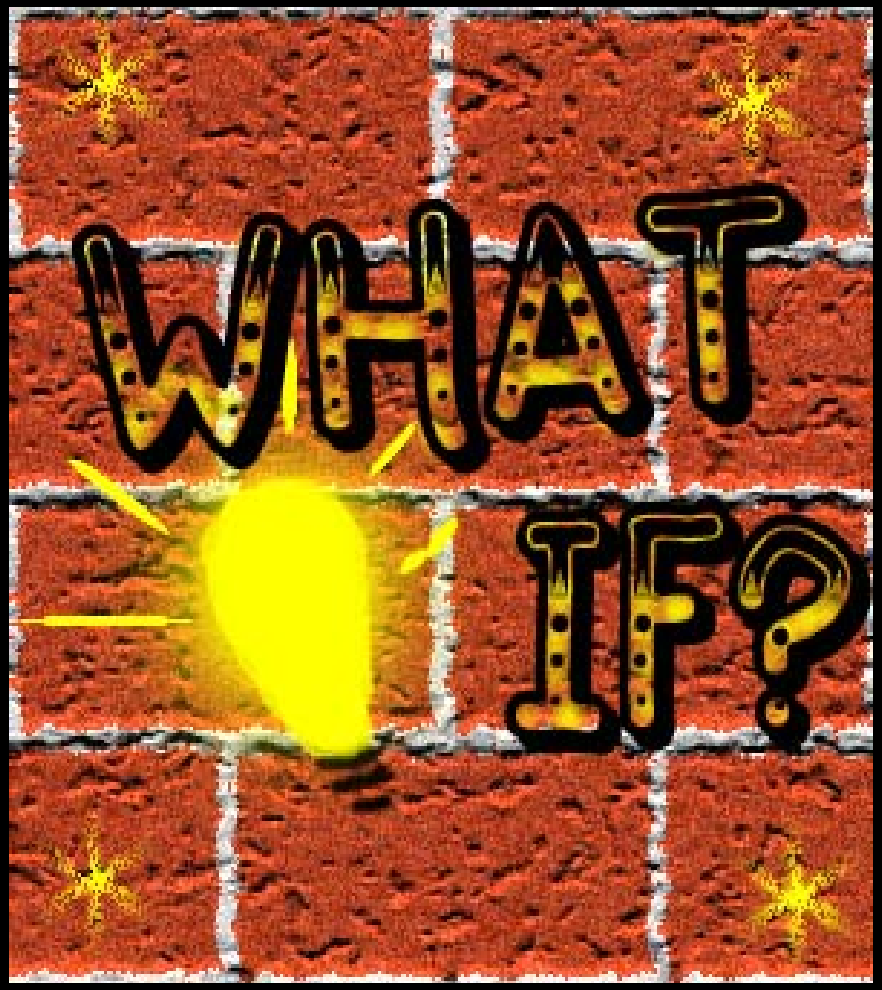
Working Hypotheses but very difficult because we are working with behavior, we are working with the brain & we are working with auto-immunity

Genetics, Infection and Immunity maybe conspiring against these children.

The Working Model is Sydenham's Chorea

What if there might be a small sub-group of Children?

- ***Where*** immune inflammation following infectious stimuli might result in neurologic/behavioral abnormalities?
- ***Where*** investigating inflammation in a small subgroup **might result** in a different therapeutic approach?
- ***Where***, if such a subgroup can be indentified, perhaps **something so simple** as preventing infection, giving antibiotics or immune modulators might result in a normal child?



Precedent Setting Diseases

- Rheumatic Fever
- Rheumatic Heart Disease
- Sydenham's Chorea
- Guillian Barre' Syndrome

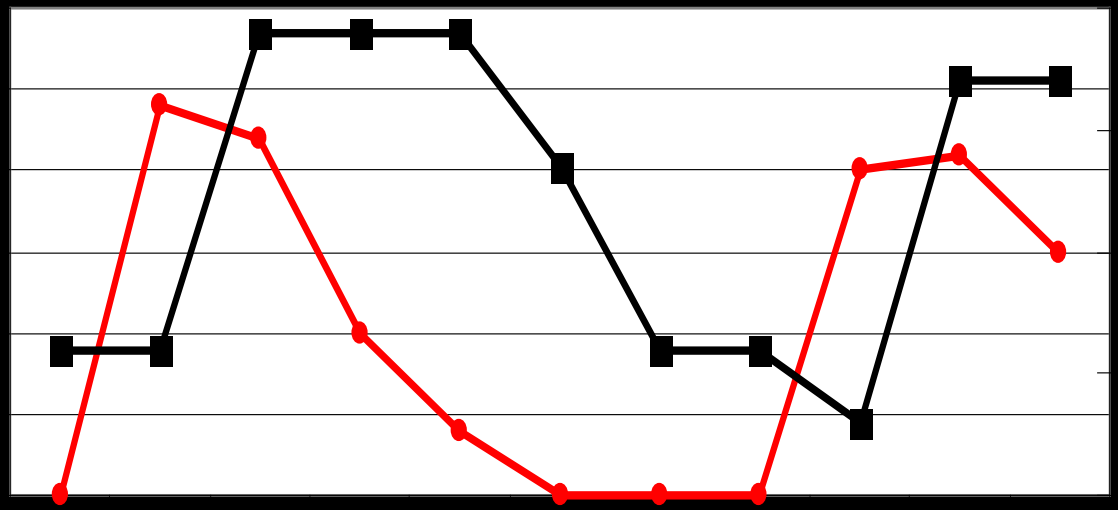
Background

SYDENHAM CHOREA

- Sir William Osler – 1894 "perseverativeness" of behavior in choreic children
- Chapman, Freeman & Grimshaw – increased obsessional neurosis during episode and afterwards
- NIMH: 75% of SC children have OC symptoms
- Sao Paulo (1998): 65% have OCD at initial episode and 100% at recrudescence

OCD/TIC DISORDERS

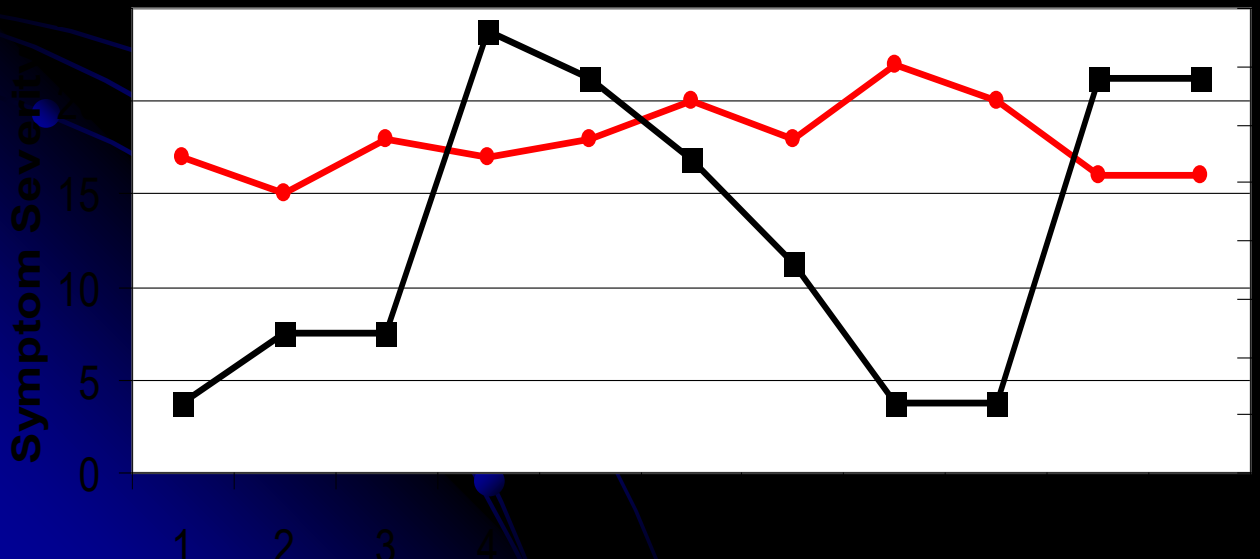
- Post-infectious tics described by von Economo & Sellinger in early 1900's
- Selling [1929] – role of infection in tics – treated
- Kondo & Kabasaba [1978] 11 y/o with TICs 10 days after febrile illness treated with steroids
- Choreiform movements present in 1/3 of children with OCD
- Some children with were different had abrupt-episodic course,
- Kiessling – tics after of GABHS outbreaks; also tic patients have antineuronal antibodies
- Young children with OCD/tic disorders=> exacerbation after streptococcal infections



ASO TITER

Y-B-OCS ---

Disease Severity: PANDAS vs non-PANDAS



ASO TITER

Y-B-OCS ---

**

Antineuronal Antibodies in OCD/Tics

- Kiessling et al. – Serum antibodies recognize human caudate and neuroblastoma cell line
- Singer et al. – Antibodies against human caudate & putamen; but also present in 40% controls.
- Hallett et al. – Serum from patients induces stereotypies in rats infused in basal ganglia
- Morshed et al. – Antibodies against striatum among patients; sera also induces stereotypies [repetitive movements]
- Cunningham et al. – Cross-reactive antibodies present in sera of acutely ill SC patients; appears to affect cell signaling
- Swedo et al [multiple articles] – PANDAS sera & CSF fluid cross reacts with basal ganglia tissue and Gr. A. Strep antigens. Upregulates CKII activity. Depletion of IgG abrogates this activity.

Mouse Model from Columbia University:

Dr. Mady Honig [Mol Psychiatry 2010; 15:712-726]

- Mouse model demonstrating association between GABHS & neuropsychiatric symptoms
- Mice immunized with killed bacteria developed repetitive behaviors [PANDAS-like]
- Serum from immunized mice produced similar symptoms in non-immunized mice
- Antibodies were directed against GABHS matrix protein & cross-reacted with C4/alpha 2-macroglobulin the brain
- Also affected coordination, learning/memory & social interaction

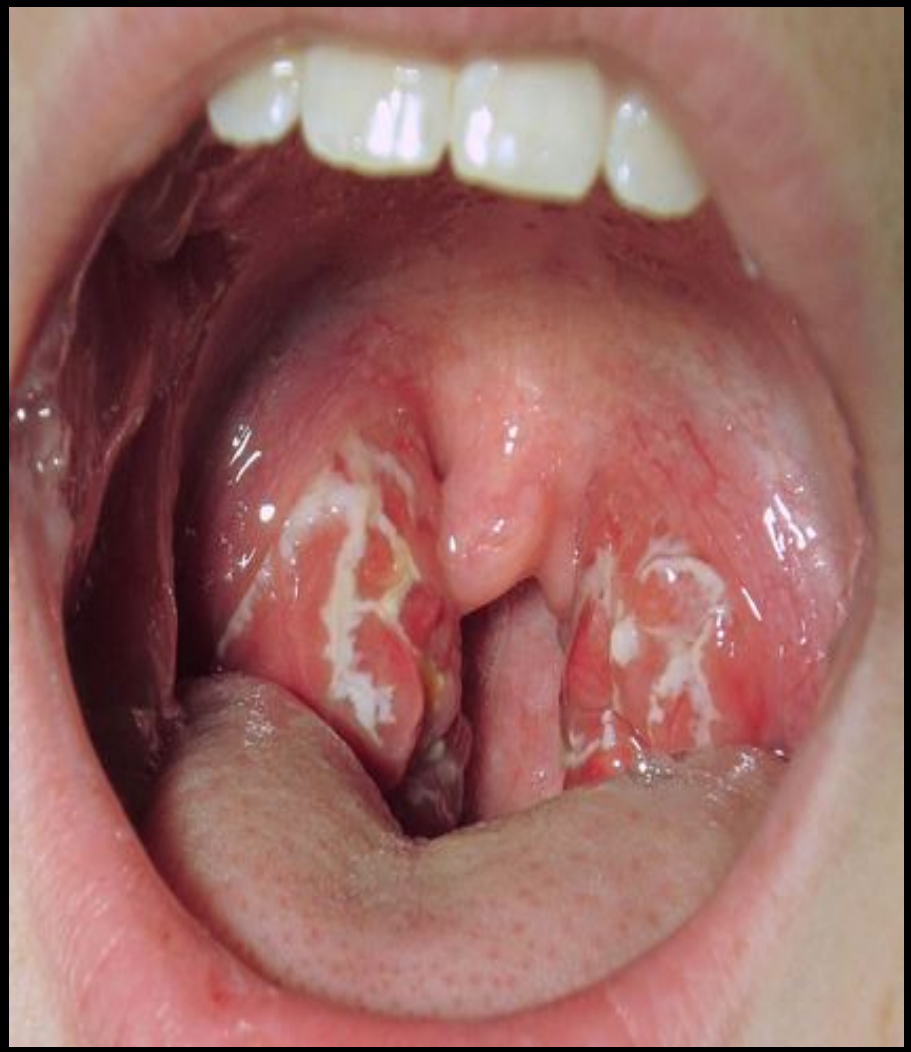
***Depletion* of antibodies from sera *abrogated* the behavioral changes**

How Might PANS/ PANDAS Be Treated?

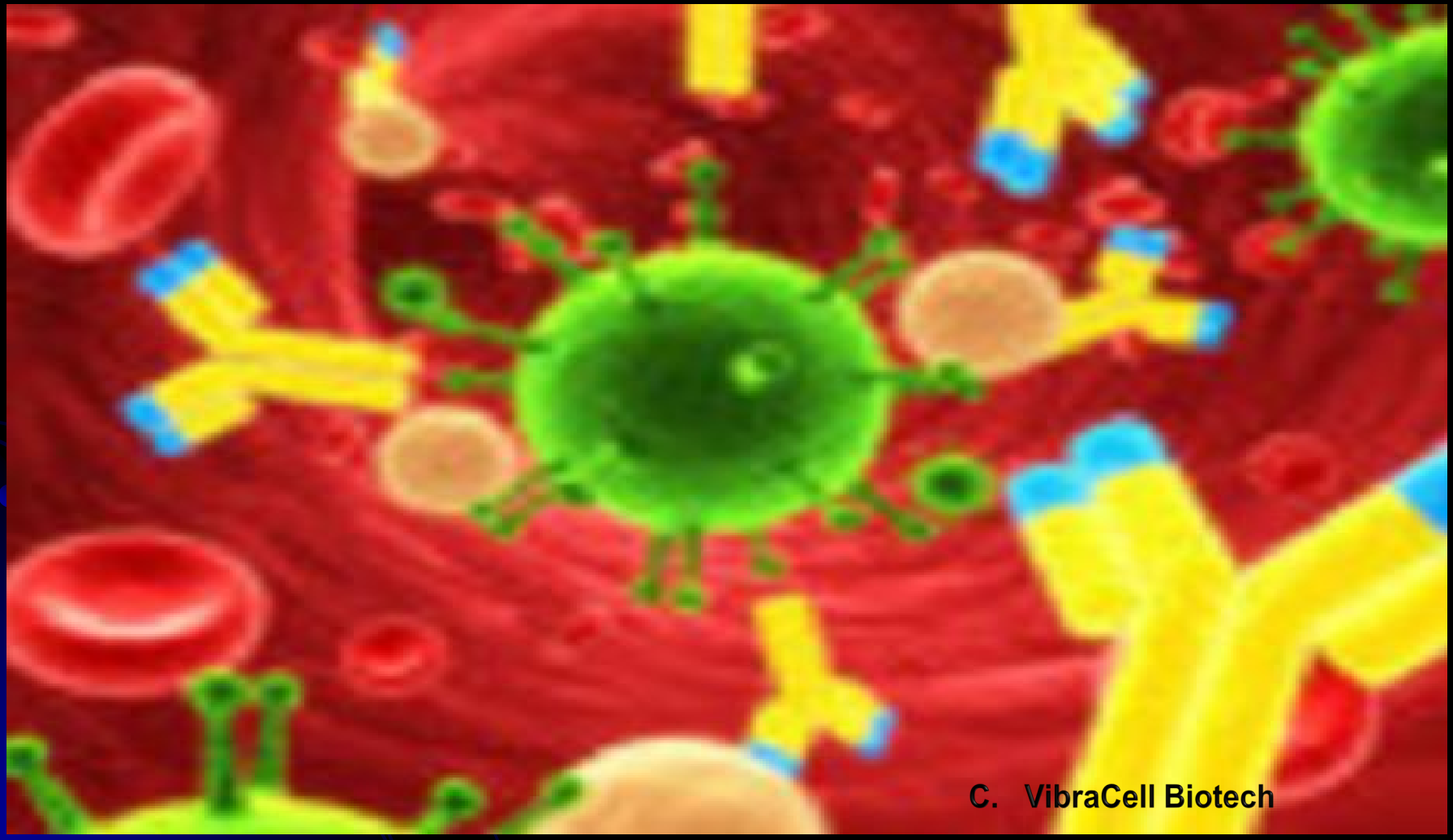
- Antibiotics: Penicillins, Cephalosporins, Macrolides
- Anti-inflammatory/Immunomodulatory: NSAIDS, Steroids, IVIG, Plasmaphoresis
- Selective Serotonin Re-Uptake Inhibitors: fluoxetine, fluvoxamine, sertraline, and paroxetine
- Cognitive Behavior Therapy:
- Other therapies: anti-inflammatory, anti-fungal, anti-histamines et al

Infections

- **Group A Streptococcal Disease**: Rheumatic Heart Disease, Rheumatic Fever, Sydenham's Chorea, Post-Streptococcal glomerulo-nephritis, Pediatric Acute-onset Neuropsychiatric Syndrome [PANS]
- **Camphylobacter & Influenza** [Guillian-Barre Syndrome]
- **Herpes class viruses & Clamydia pneumoniae** [Multiple sclerosis]



Can Immunomodulatory Therapy Reduce Clinical Symptoms?



What is IVIG?

- Highly purified gammaglobulin derived from 1000's of plasma donors. 1% of plasma.
- Gammaglobulin are antibody proteins which help fight infection, are anti-inflammatory and immune modulating.
- It was first used by von Behring & Kitasato in 1901
- First given by injection. Now mostly IVIG/SCIG.
- 30% PID, 70% neurology
- Over 20 million grams used
- Shortages in U.S. 2019-20
- Used in CoVID

Clinical Benefit Established in Controlled Trials

Hematology	Neurology	Rheumatology	Transplant Medicine
•ITP	•Multiple sclerosis •Guillain-Barré syndrome •Chronic inflammatory demyelinating polyradiculopathy •Myasthenia gravis •Multifocal motor neuropathy •Stiff person syndrome	•Kawasaki syndrome •Dermatomyositis (corticosteroid resistant) •Antineutrophil cytoplasmic •Autoantibody-positive vasculitis	•Prevention of graft-versus-host disease in allogenic bone marrow recipients

Clinical Benefit Established in Well-Controlled Trials

•The clinical benefit of IGIV has been established in well-controlled trials for a number of disorders, as shown on the slide.

Orange J et. al. JACI 2006

Diseases Where IVIG Sometimes Beneficial

Hematology	Neurology	Rheumatology	Transplant Medicine
•Hyper-hemolytic transfusion reaction in sickle cell disease	•Lambert-Baton myasthenic syndrome	•Rheumatoid arthritis	•Cytomegalovirus after renal or hepatic transplantation
•Acquired factor VIII deficiency	•Certain childhood seizure disorders	•Systemic lupus erythematosus	•Rescue therapy for renal graft rejection
•Neonatal immune hemolytic jaundice	•Paraproteinemic IgM demyelinating polyneuropathy	•Polymyositis	•Elevated panel-reactive antibody before cardiac transplantation
•Pure red cell aplasia	•Peripheral nerve disorders	•Inclusion-body myositis	
•Phenytoin-induced	•Acute disseminated encephalomyelitis	•Scleroderma	
•thrombocytopenia		•Scleromyxedema	
		•Reactive macrophage activation syndromes	
		•Inflammatory bowel disease	

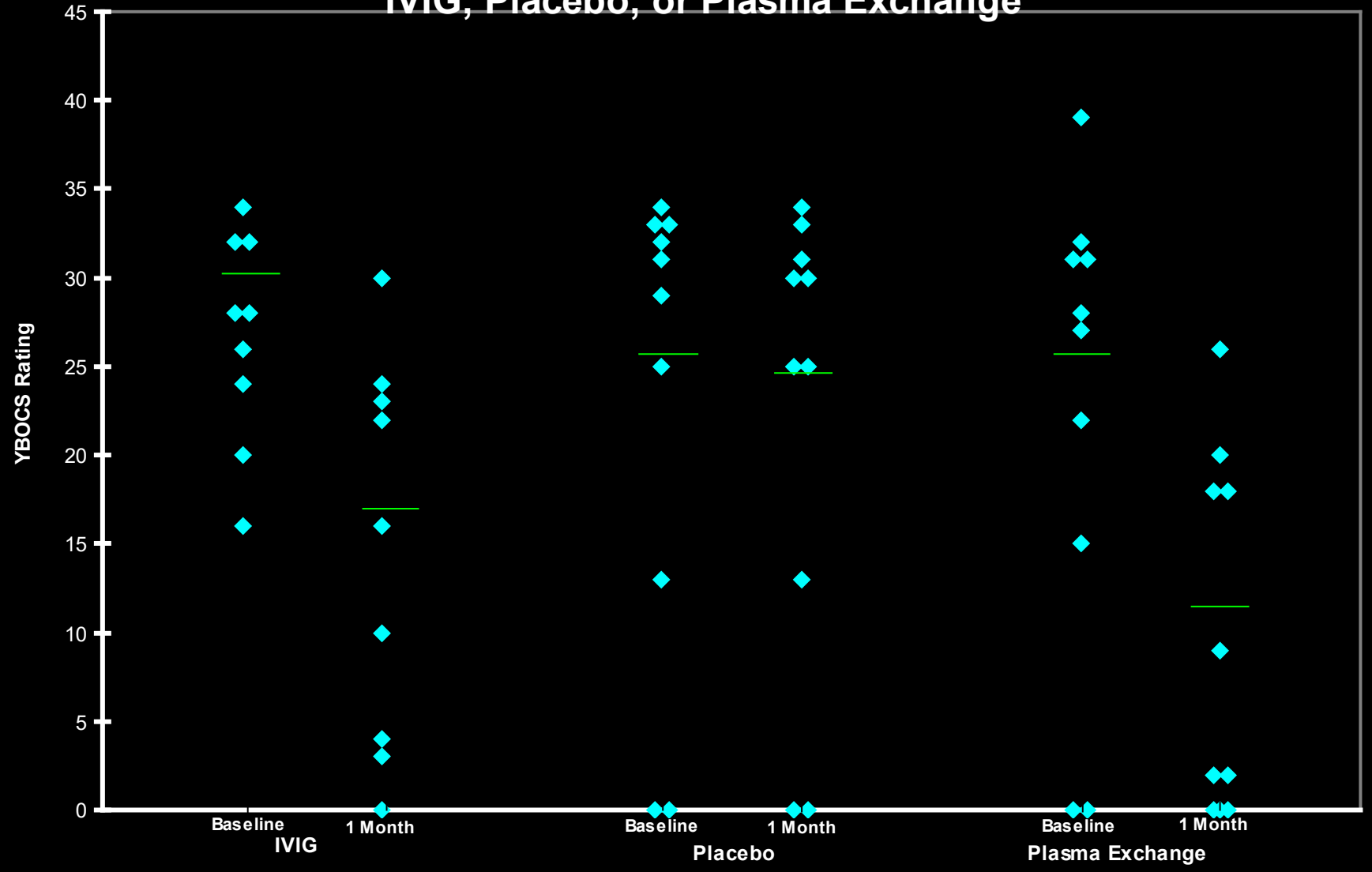
Other Potential Clinical Benefits

In a number of other disorders, clinical benefit for IGIV has been shown in individual case histories, small series of patients, and small trials. These disorders are listed on the slide for hematology, neurology, rheumatology, and transplant medicine.

Other potential clinical settings in which IGIV has been used are infectious diseases, asthma, autoimmune dermatoses such as pemphigus, cardiomyopathy, congestive heart failure, autoimmune eye disease and spontaneous abortions.

Orange J et. al. JACI 2006
Stiehm ER. Textbook of Pediatric Immunology 2004

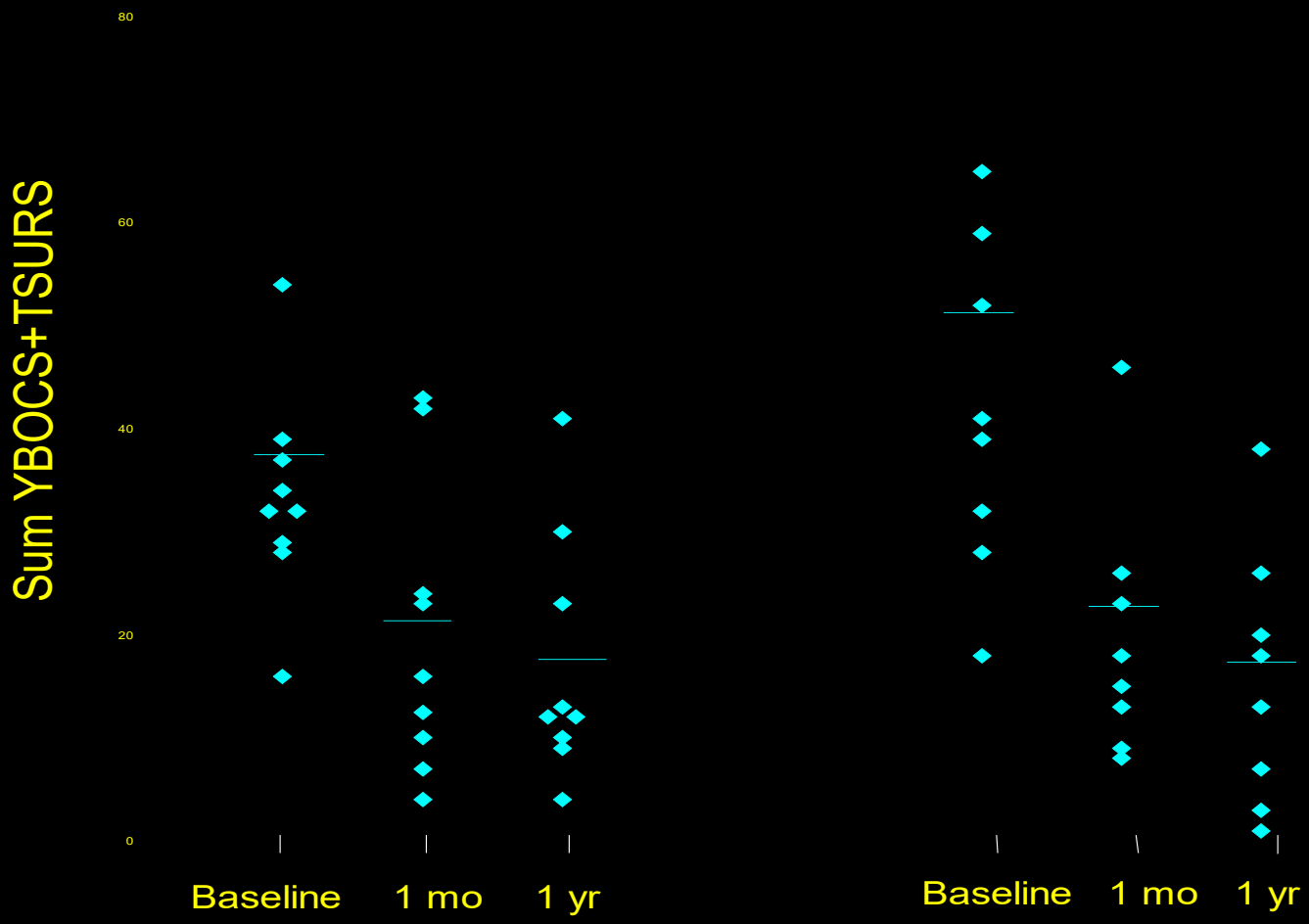
Change in OCD Severity 1 Month Following Treatment With IVIG, Placebo, or Plasma Exchange



Kirvan, et al, J. Neuroimmunol. 179: 173-179

Response to Immunomodulatory Therapy with IVIG (n=9) or Plasmapheresis (n=8)

Small Study Suggesting Prolonged Effect



IVIG Therapy In PANDAS

- 8 Studies in literature with 145 patients total : 4 single cases
- Dose, dosing schedule, length of treatment varied
- Some patients had mild antibody deficiencies
- Younger study largest [non-blinded] 1-2 gm q 1 – 2 months [avg 7.5 doses over 15 months] 64% improved 19% permanent remission.
- 2015 Frankovic and Swedo: double blind – no difference after induction; open label 6 month study 62% improved
- Melamed: 2017 1 year open label study.

- Problem:

  Very few blinded studies and those results varied
- No biologic markers Melamed study proposes markers
- Insurance companies don't cover

Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections.

J Am Acad Child Adolesc Psychiatry. 2016 Oct;55(10):860-867. Williams KA[1], Swedo SE[2], Farmer CA[3]

- 35 children with mod-severe PANDAS with OCD randomized to receive IVIG 2g/kg or placebo
- Measurement: CY-BOCS & Clinical Global Improvement psychometric measurements
- Non-responders [24] placed in open label infusion and retested at 12 and 24 weeks

- IVIG = 24% +/- 31 % resp= 6
- Placebo= 12% +/- 27% resp = 4

- 24 non-responders in open label study and infused with IVIG. Mean improvement from baseline on CY-BOCS
- 12 weeks = 55% +/- 33%
- 24 weeks = 62% +/- 33%

- Conclusions: a] no statistical difference between placebo and IVIG group in DB phase
- Clinical improvement in open label phase suggested more studies need to be done looking at biomarkers as predictors for response to IVIG

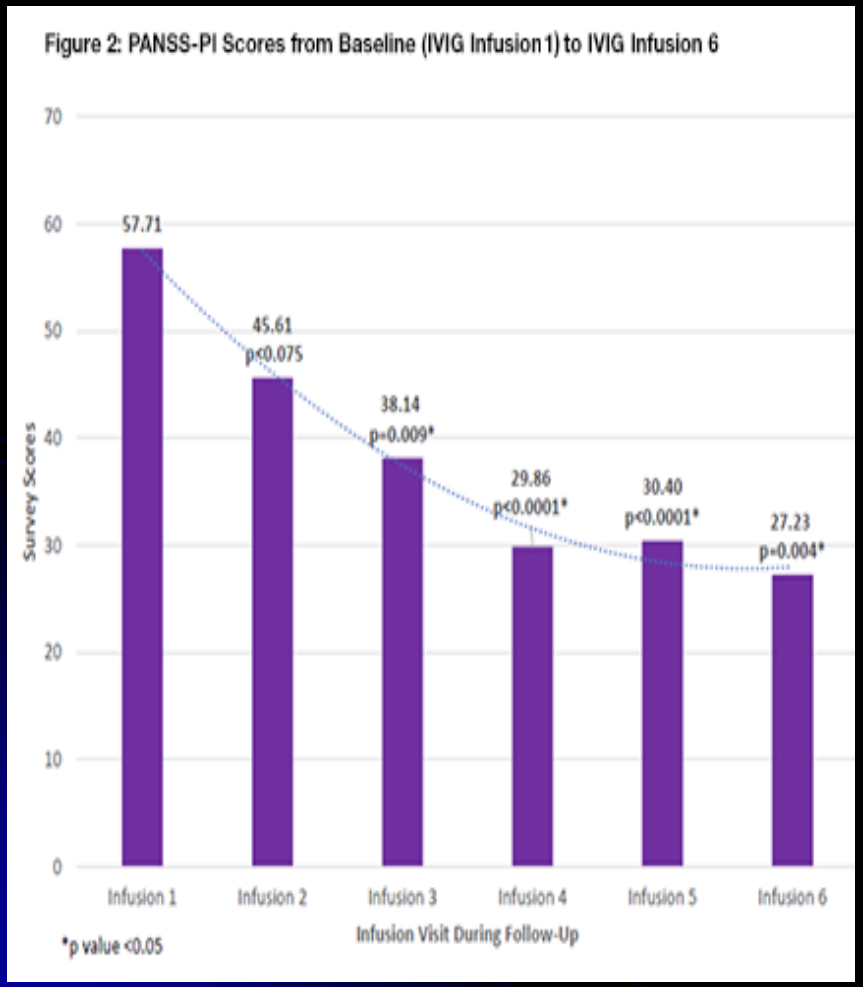
Melamed – Octapharma Study 2018

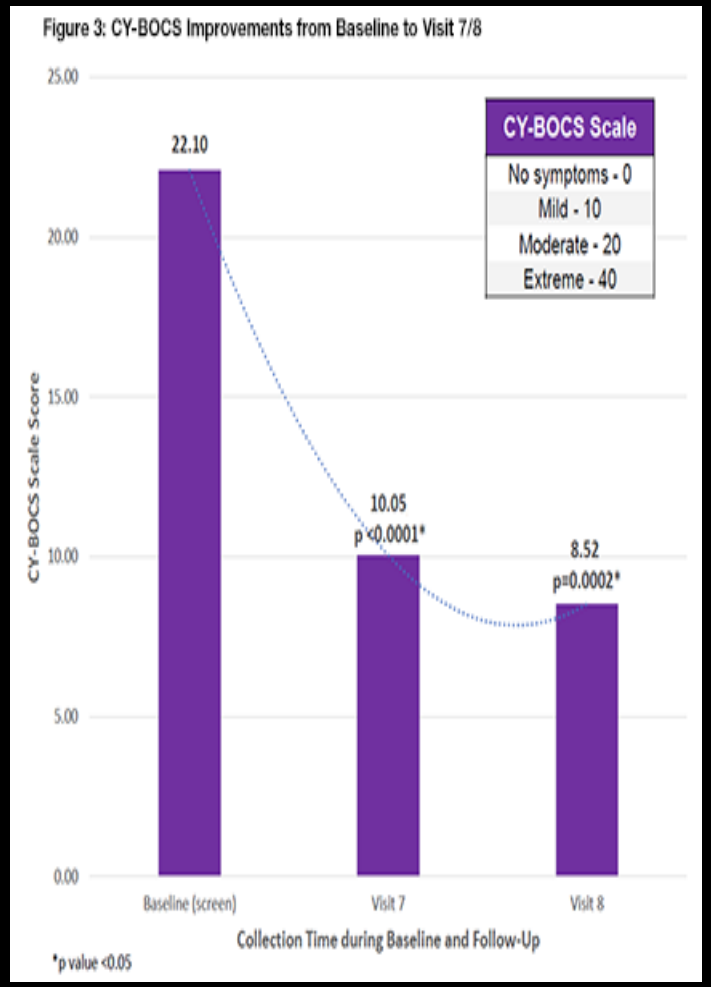
- To determine impact of IVIG [1 gm/kg] on psychiatric behavior during a 8 month 6 infusion study
- Three centers: 21 chidren
- Children with moderate to severe symptoms
- Extensive clinical, laboratory and psychiatric/behavioral assessment by 6 validated instruments
- Measurements before, during, immediately after and 3 to 8 months after cessation of IVIG treatment.

- Pediatric Acute Neuropsychiatric Symptom Scale Phone [PANSS-PI]
- Children's Yale-Brown OC Scale
- Yale Global TIC severity scale
- Anxiety Disorders Interview Scale: DSM IV
- Clinical Global Impression [CGI]
- Parent –Rated Symptom Score [PRSS]

- Comprehensive Laboratory Studies including inflammatory, auto-immune, immune, and allergy labs.

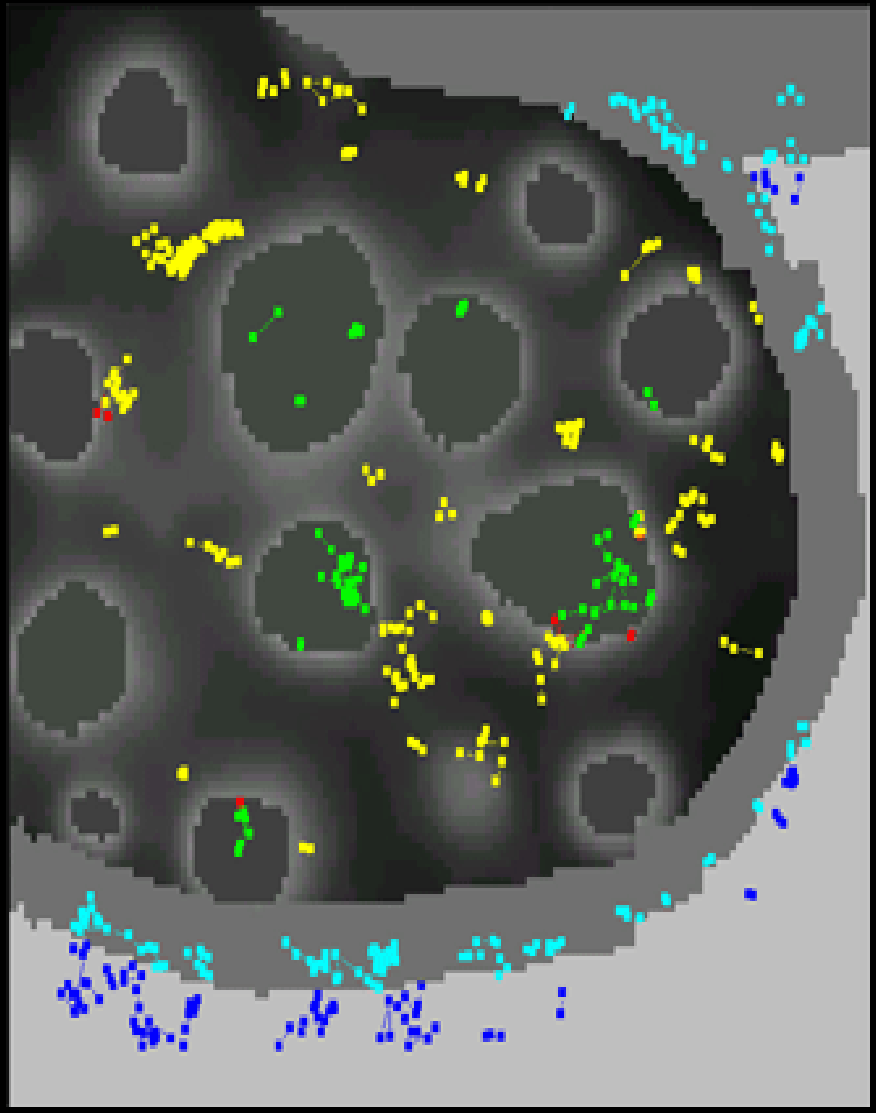
Results: Impressive Improvements in ALL 6 Psychometric measurements





Laboratory Studies

- Cunningham Panel was not helpful in our study.
- Almost 90% of children had positive RAST/Immunoblot for allergy.
- TLR was up-regulated after IVIG; I am unsure what this means.



Questions Our Group is Pursuing

- Does Gammaglobulin have a significant and sustained effect on PANS?
- What dose and how long should children be treated? 1 gm vs 2 gm/kg; 6 months, 12 months; are there important clinical criteria which would guide us to those patients most likely to benefit?
- Do those carefully selected patients with PANS truly have auto-immune or auto-inflammatory disease?
- Are there biomarkers which will guide and monitor therapy?

- **Why Would We Want to See These Children?**
- **The answer is quite simple really: "Kodomo no tame ni"**

Summary Regarding PANDAS

- Need to diagnose on the basis of PANS **criteria**; sudden onset, severe symptoms, undulating course
- Definitive lab studies/ bio-markers lacking
- Response to therapy **variable**, but sometimes dramatic
- Treatment may require **multi-ple modalities**; may take time to respond, may have **exacer-bations** and complete resolution possible.
- Requires a **symptom diary**
- Requires **multi-specialty** approach
- Pathogenesis with **infection** suggestive
- **Auto-immunity/chronic inflammation** suggestive:

  cross-reacting antibodies which stimulate CaM Kinase II & dopamine release, cytore-active T cells?
- Evidence of **basal ganglia swelling** & **inflammation**, in-flammatory cytokines/T-cells
- Evidence of immunodeficiency: increased activated B cells [CD-691] , T-helper cells [CD-951] & decreased T-regs peripherally & locally, decrea-sed serum IgA

Summary Regarding IVIG in PANS/PANDAS

- IVIG must be reserved for children who do not respond to NIH modified therapy or psychiatric medications and counseling
- Strict NIH diagnostic criteria must be adhered to
- To date, this is a behavioral clinically diagnosed disorder.
- To date, there are no reliable laboratory markers to diagnose, monitor or predict disease outcome.

“Ho'okahi ka 'ilau like ana”
Put Your Paddle in and Join the Effort

- However, there are strong evidence in animal models and similar diseases in humans that suggest anti-inflammatory, immune modulatory intervention may be effective.
- IVIG is routinely used in inflammatory/autoimmune diseases
- Where the NIH criteria are fulfilled, other diseases are excluded and other treatments are not helping the child, I strongly believe a trial of IVIG is warranted. All we are asking for is a chance to try.

Why Study & Treat PANS?
"KODOMO NO TAME NI"
Mahalo nui and Ahui Hou