



# PANS/PANDAS Overview

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

# Humble Country Doctor from Nebraska



- Disclosures
- Immunology/Chronic Infections: AAIA [Nine Doctors]
- Manage >300 patients on IVIG [over 500 during career]
- Grant support Octapharma, Baxter, ADMA
- Currently, Clinical Professor UCLA
- Consultant, Expert Panel IDF
- Exec. Board Member, Consortium Indep Clinical Immunologists
- Board Member, National Biologic Physicians Working Group
- Previously, Consultant for Bayer-Talecris, CSL/Sandoz, Baxter, Shanghai Red Cross, American Red Cross



# Frustration & Despair

- PANS/PANDAS is not well-known & is controversial
- The Disease itself causes great stress in families
- Diagnostic criteria & Laboratory tests are not well-established
- Treatment protocols are not well established
- Insurance Companies are reluctant to pay
- Outcomes are uncertain



# I BELIEVE

- Started out as a laboratory immunologist so I was very skeptical and even annoyed
- But the more I read and talked to very bright people ....
- And just as importantly, I saw parents at wits end and children who would be normal except for an abrupt alteration in behavior, then
- .....I began to believe that such a disease existed
- 61<sup>st</sup> Annual Meeting of Am Acad Child Adol Psychiatry in San Diego, CA October 20 -25, 2014
- Participants from NIH, Harvard, Columbia, Stanford, and other major medical centers



## ***Clinical Perspectives Program***

Diagnosis and Treatment of Children With Pediatric Acute-Onset Neuropsychiatric Syndrome

Saturday, October 25, 2014: 8:30 AM-11:30 AM

Chair: Tanya K. Murphy, MD

Discussant: Susan E. Swedo, MD

## **Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) vs. Non-Pans Obsessive Compulsive Disorder**

Tanya K. Murphy, MD University of South Florida, St. Petersburg, FL

## **Clinical Decision-Making and Dilemmas in Diagnosing and Treating Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)**

Margo Thienemann, MD Private Practice and Stanford University School of Medicine,  
Palo Alto, CA

## **Prospective and Retrospective Study of 52 Consecutive Patients With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Symptom Complex Including Results of Medical Evaluations**

Jennifer Frankovich, MD Stanford University, Palo Alto, CA

## **Mood Symptoms in Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Differentiating From Depression and Bipolar Disorder**

Kiki Chang, MD Stanford University School of Medicine, Stanford, CA

## ***Symposium Program***

PANDAS/PANS: Answered Questions and Questions to Be Answered

Wednesday, October 22, 2014: 8:00 AM-11:00 AM

Chair: Susan Swedo, MD National Institutes of Health, Bethesda, MD

Discussant: Kiki Chang, MD, Stanford University, Palo Alto, CA

### **Baseline Characteristics of the PANDAS/PANS Phenotype**

Tanya K. Murphy, MD University of South Florida, St. Petersburg, FL

### **Inflammation and Immunomodulation in Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections (PANDAS)**

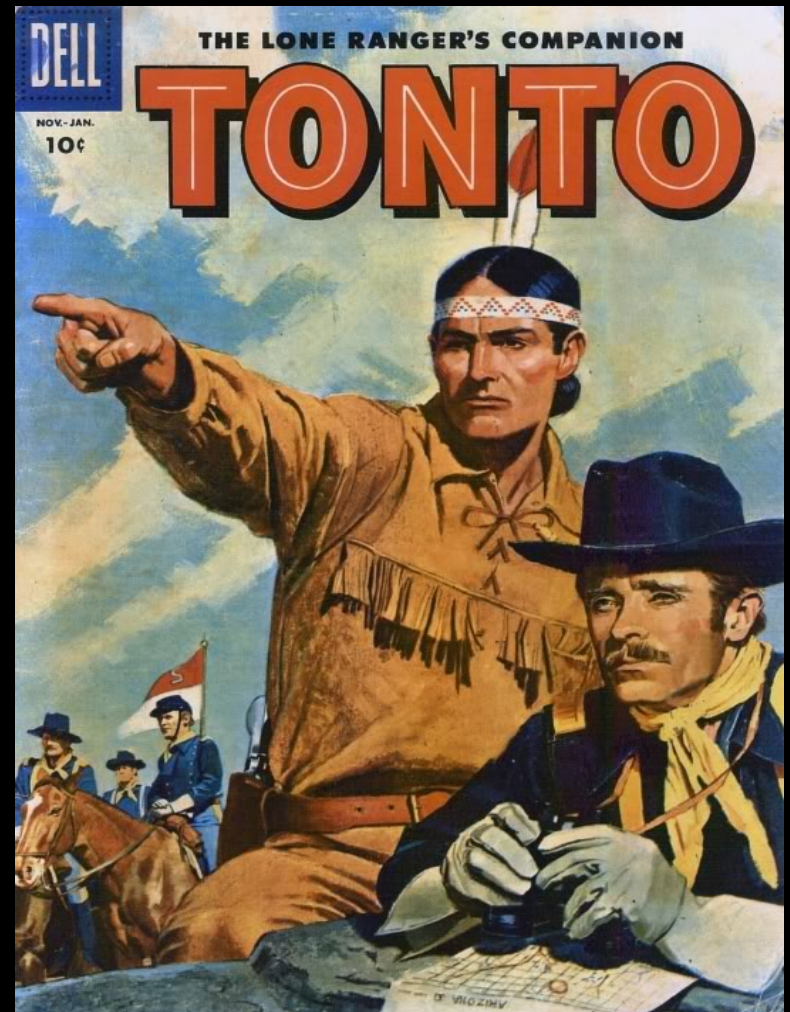
Kyle Williams, MD Massachusetts General Hospital, Boston, MA

### **Brain-Immune Interactions in Animal Models of Immune-Mediated Neuropsychiatric Disorders**

Mady Hornig, MD Columbia University, New York, NY

# SO WHAT NOW KEMO SABE?

- What is PANS/PANDAS?
- What evidence is there for an auto-immune inflammatory syndrome?
- What treatments are available & what are the rationale?
- Where might help be available?





# Case Report

- 9 y/o WM previously well, happy, active in school.
- Sore throat 3 weeks before, not treated; began having eye twitching and facial grimacing Friday, got progressively worse, became extremely anxious and fearful. Hiding under bed, repeated questions about safety
- Parents took to emergency room, admitted to CMH; extensive evaluation not remarkable. Placed on anti-anxiety medications
- PCP thought might be PANDAS; started empirically on Augmentin=> improved on 10 day course. Behavior recurred after antibiotics stopped.
- Referred to for evaluation and possible treatment

# From PANDAS to PANS

- Criticism resulted from limiting to GABHS infections, age restrictions, time relation to antecedent GABHS infection, difficulty correlating infections with exacerbations, lack of reliable laboratory studies, lack of suitable experimental models to demonstrate pathogenesis, difficulty in separating “dramatic acute onset TICS in PANDAS vs non-PANDAS patients, variable effect of prophylactic antibiotics and/or immuno-modulators [expensive /associated with risks] etc.
- Workshop of clinicians & scientists met July 2010: expanded “working” definition to PANS
  - \* **Abrupt, dramatic onset of OCD - Primary criterion**
  - \* **Concurrent presence of at least 2 additional acute onset neuropsychiatric symptoms**
  - \* **Vigorous exclusion of other disease entities** S.Swedo [NIH], J. Leckman [Yale] N. Rose [Johns Hopkins] 2012  
\*full list see handout

# NIH 2012 Criteria for PANS

- **Abrupt, dramatic onset**
- **At least 2 of the following 7 symptoms**
- **All other causes excluded**
- Concurrent presence of additional neuropsychiatric symptoms, with
- similarly severe and acute onset, from 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



# What's So Fascinating About PANS/PANDAS?

- Small subgroup with **acute onset** , **severe behavior changes** following infection
- **Autoimmunity?** Clinical Precedents: SC GBS RF
- Suggestive but controversial evidence **for autoimmunity and exuberant inflammation**
- **Anti-infective and anti-inflammatory** intervention appear to result in improvement in some children, sometimes so dramatic that hard to believe
- **Tonsillectomy** sometimes results in improvement

## Complex Puzzle

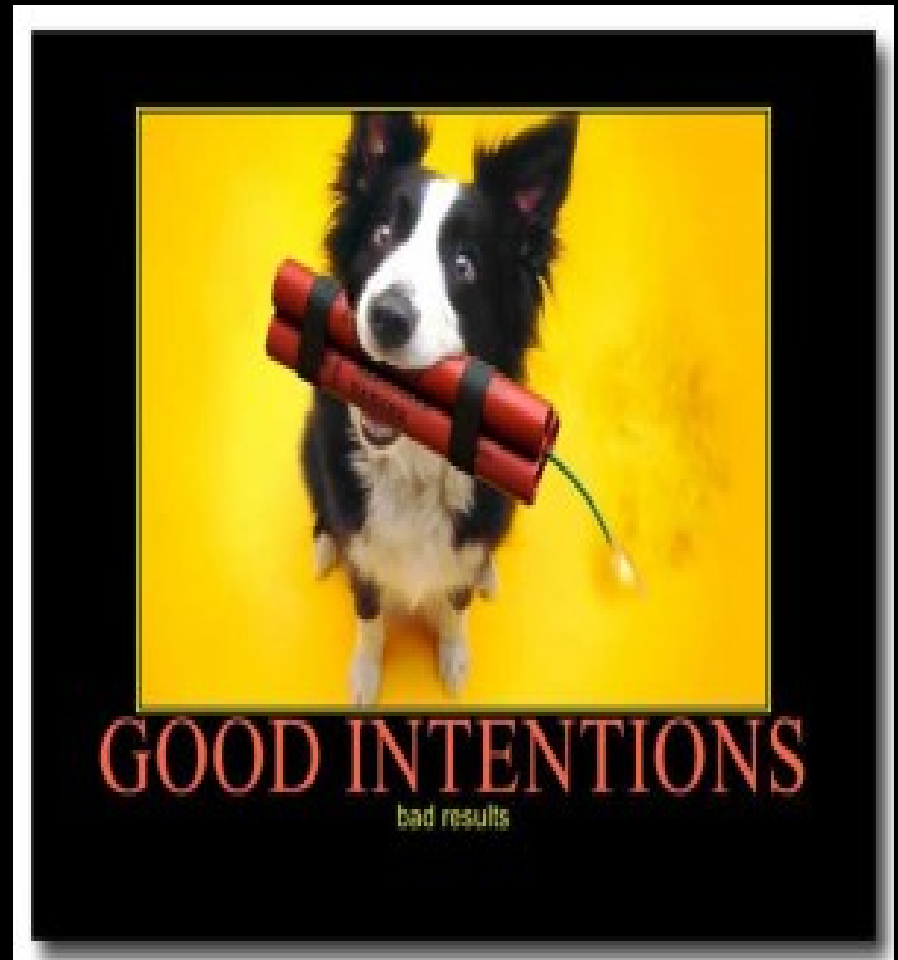


**What is  
going on?**

# Autoimmunity/Exuberant Inflammation

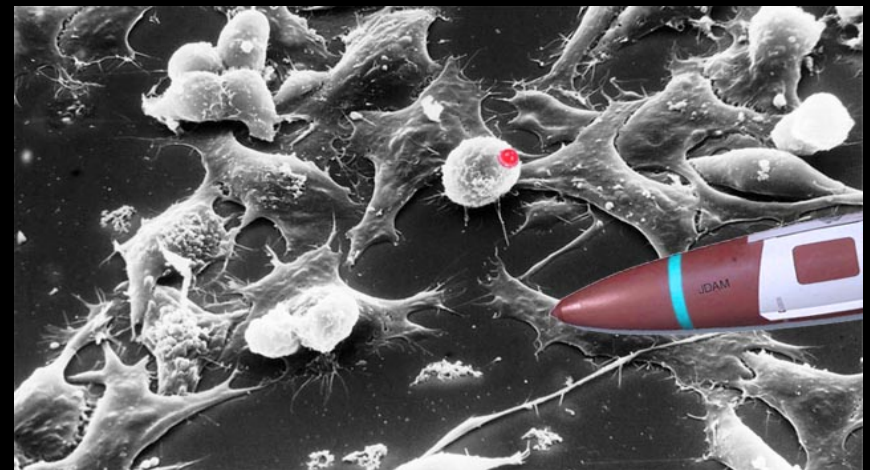
AHHH...  
I see the screw up fairy  
has visited you again...

JESDESIGNZ.COM



# Young Children's Immune System Are Developing & Can Sometimes Make Mistakes

Cross-reactivity  
or Molecular  
Mimicry





# Is There an Infectious/Autoimmune Subgroup of Acute Neuropsychiatric Disease?

- NIH described similarities between PANDAS & Sydenham's Chorea
  - Distinguished an OCD sub-group with **acute onset** and co-morbid symptoms including separation anxiety, ADHD & TICS which seemed to follow infections
  - NIH also observed that **65 -70%** of children with Sydenham's had **OCD** and many developed symptoms 2 – 4 weeks before chorea
  - **OCD often followed viral/bacterial infections:** influenza, EBV, varicella, GABHS
  - Gr. A Strep was of intense interest
- Swedo S et al 1998, 2012
- Concept of **molecular mimicry** with cross-reacting antibodies
  - **Auto-immunity**, inappropriate immune activation
  - Gr. A Strep is an ancient organism adapting to humans
  - Over the millennia, if you were a germ, you'd adapt to the host
  - The “building blocks” are similar & in some hosts, **the immune system may recognize both**



Credit: Dr. Bac Nguyen

# Precedent Setting Diseases

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



"A sore throat  
can lead to a  
broken heart"



# PANDAS – Is There A Host Susceptibility?

- **Increased familial rates of OCD & tics**

- 36/50 (67%) of PANDAS probands had an affected 1<sup>o</sup> relative
- 15% of relatives had OCD
- 15% of relatives had tic disorder (Lougee et al, 2000)

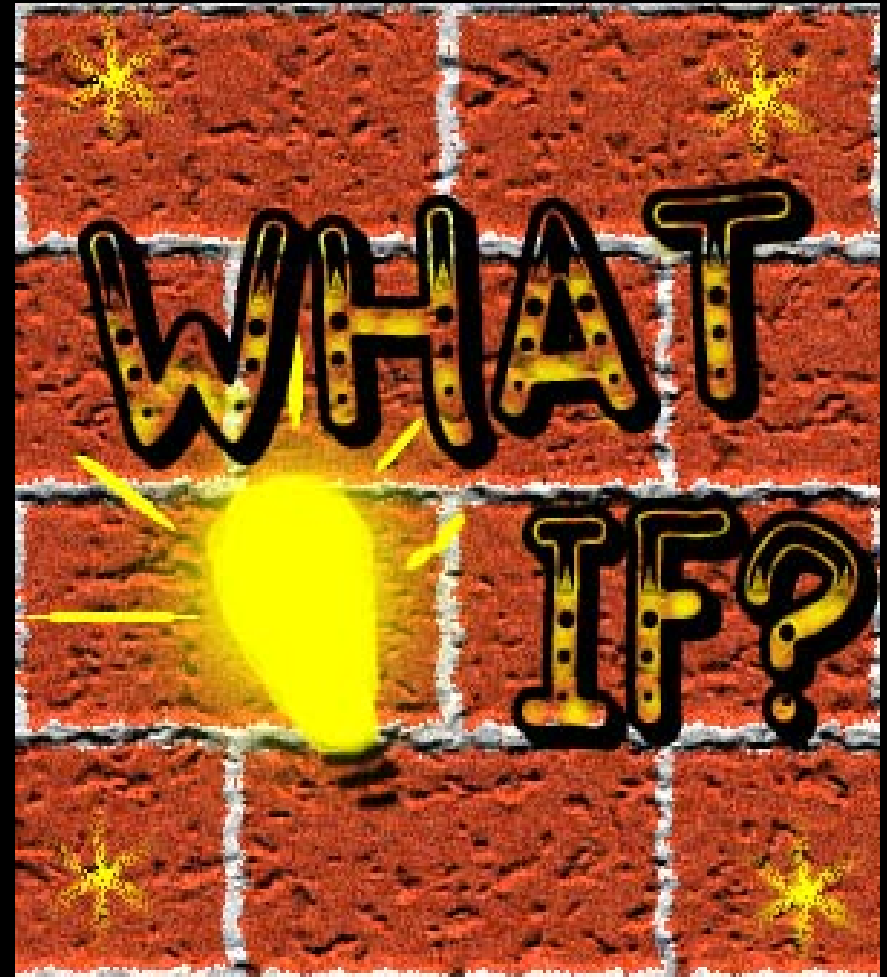
- **Increased familial rates of rheumatic fever**

- 5/126 (4%) PANDAS parents/grandparents affected
- 6/90 (7%) of Sydenham parents/grandparents affected
- 3/210 (1.4%) of controls parents/grandparents affected
- D8/17 prevalence significantly greater among patients with OCD/tics or rheumatic fever than controls \*\*



# 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 identified, perhaps **something so simple** as preventing infection, giving antibiotics or immune modulators might result in a normal child?



c. Terry Harper 2009

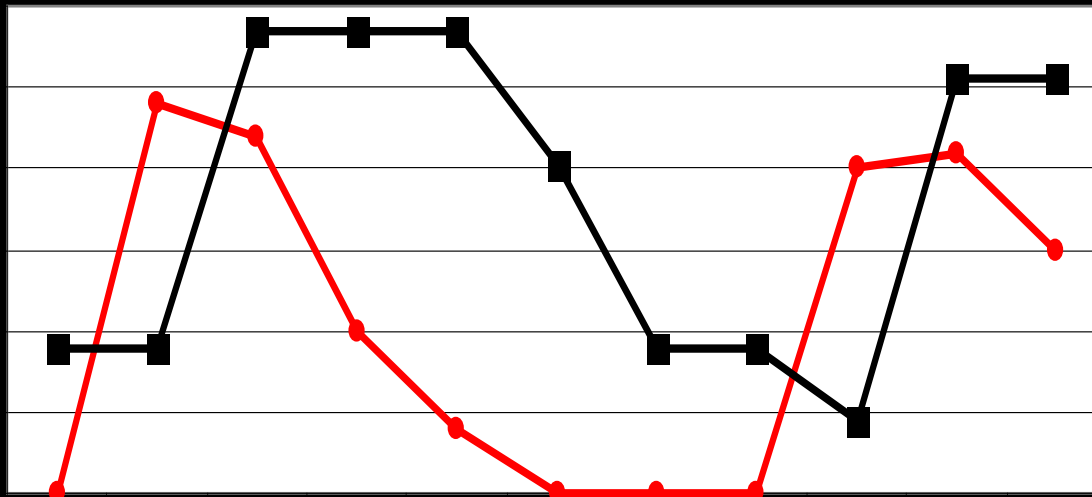
# Background

## 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

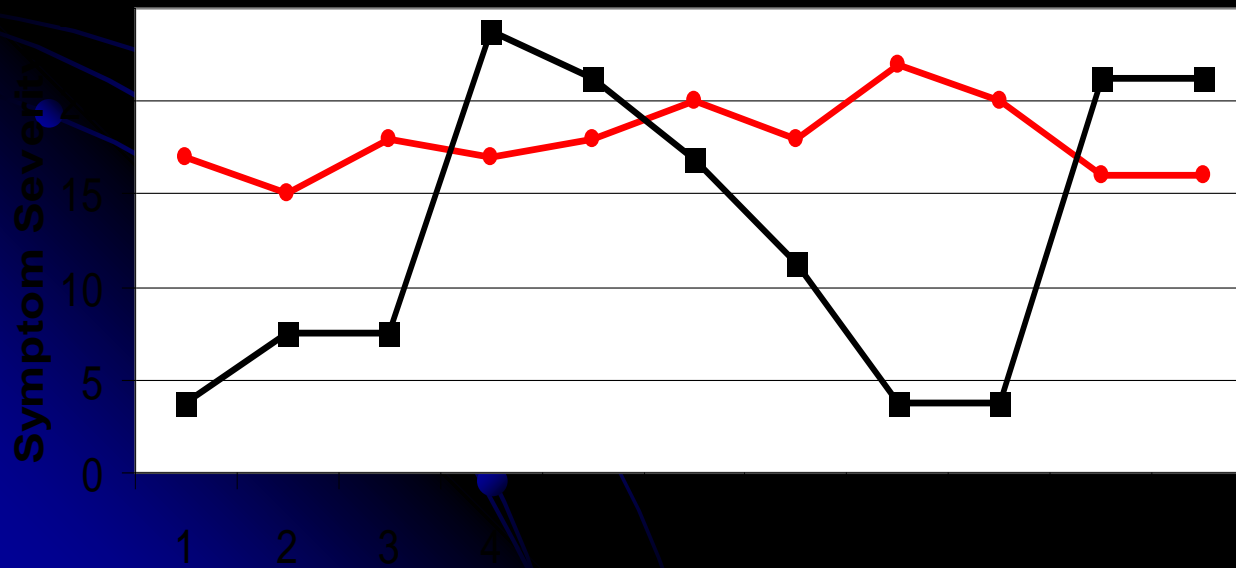
- Post-infectious tics described by vonEconomo & Sellinger in early 1900's
- Selling [1929] – role of infection in tics – treated
- Kondo & Kabasaba [1978] 11 y/o with TICs 10 days after febrile illness treated with steroids
- Choreiform movements present in 1/3 of children with OCD
- Some children with 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-BOCS ---

## Disease Severity: PANDAS vs non-PANDAS



ASO TITER

Y-BOCS ---

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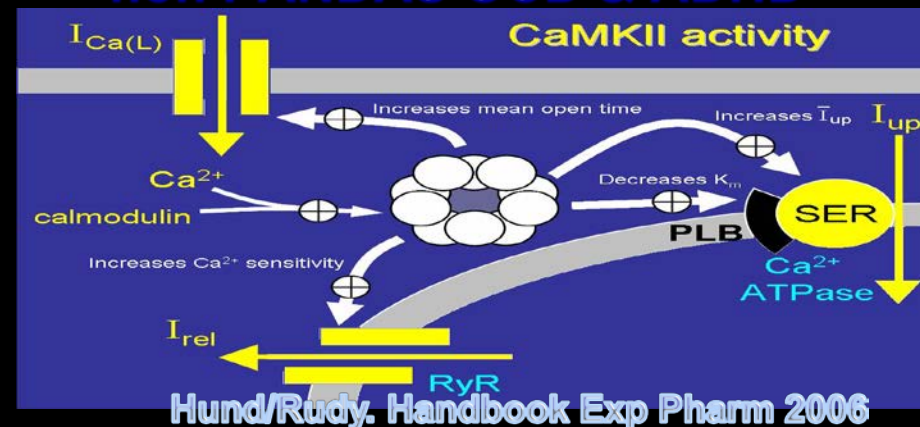
# Antineuronal Antibodies in OCD/Tics

- **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 \*\*

# Putative Auto-antibodies in Sydenham's & PANDAS [?]

- **47% of SC patients had auto-antibodies** against subthalamic and caudate nuclei; severity correlated with titers [Husby 1976 [J Exp Med]
- **64% vs 9% anti-neuronal antibodies** in **PANDAS** vs those with Gr. A Strep but without PANDAS
- **Several subsequent studies => no difference**
- **Auto-antibodies** in **SC** might **block** neurotransmitters N-acetyl-beta-D-glucosamine (GlcNAc) & lysoganglioside GM1 and **induce** CaM kinase II activation which increases dopamine release
- **Auto-antibodies** to GABHS cross react with **basal ganglia/D2&D5** receptors in mouse models, producing PANDAS-like behavior [Honig 2009; Murphy 2010]

- **CaM kinase II important in signaling in heart & brain**
- **CaM kinase II activity and dopamine release increased by auto-antibodies found in PANDAS & Sydenham's**
- **Sera from PANDAS patients induced much higher levels of CaM Kinase II levels than non PANDAS OCD & ADHD**



# 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**





# Rat Model: Tel Aviv U. & NIH

Swedo, Cunningham, Joel

Neuropsychopharmacology 2012; 37:276-287

- Male Lewis Rats injected with GABHS antigen => motor dysfunction [impaired food handling & beam walking] & compulsive behavior [increased grooming]
- Alleviated by D2 blocker [haloperidol] & SSRI [paroxetine]
- GABHS exposure resulted in IgG in striatum, thalamus & frontal cortex ~SC & PANDAS
- IgG reacted with tubulin and increased CAM protein kinase II signaling ~ SC & PANDAS
- Suggests IgG auto-antibody against D1 & D2 receptors

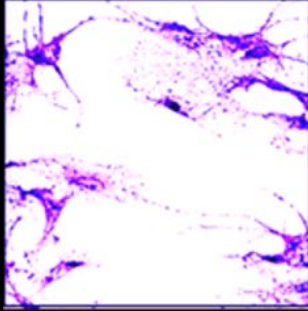




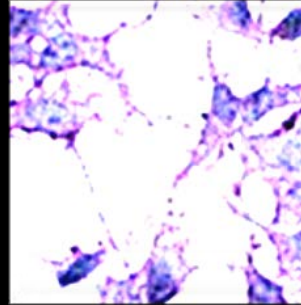
# Reactivity with Neurons and Caudate/Putamen

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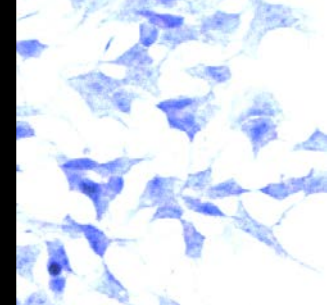
PANDAS



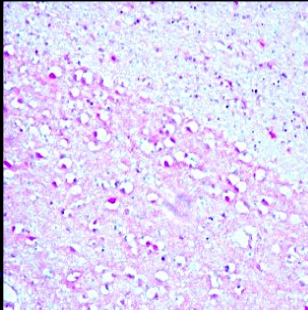
SC



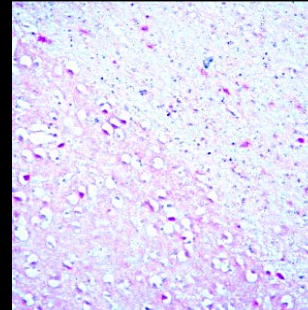
Control



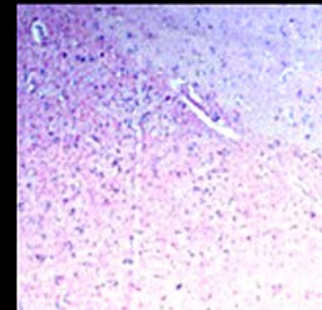
PANDAS



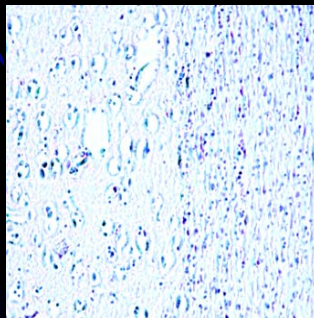
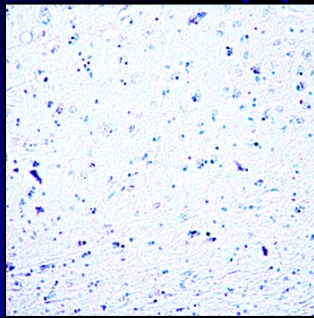
PANDAS



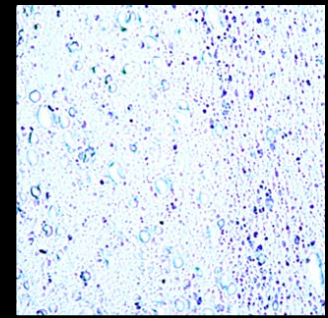
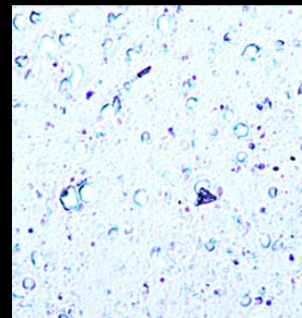
SC



Controls



Controls



# Measuring Auto-antibodies: The Cunningham Panel

- lysoganglioside
- tubulin
- dopamine receptor D1
- dopamine receptor D2
- calcium/calmodulin-dependent protein kinase activity using a neuronal cell line to test for function
- As of September 2014 we have done the test on 4 patients:
  - 2 Brothers – one off therapy & one being treated
  - 1 with PANS/PANDAS
  - 1 with autism but developed PANS

# How Might PANS/ PANDAS Be Treated?

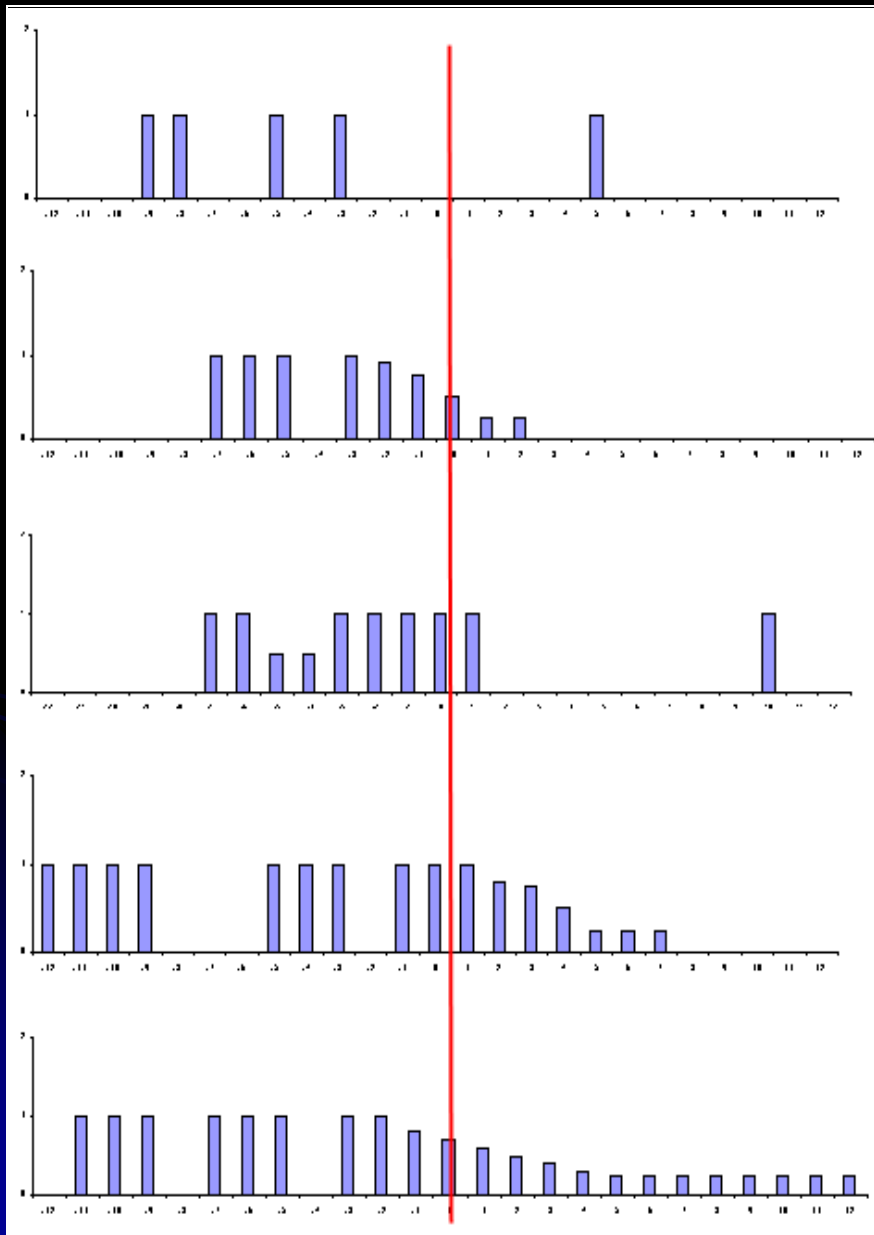
- Antibiotics: Penicillins, Cephalosporins, Macrolides
- Anti-inflammatory/Immunomodulatory: NSAIDs, Steroids, IVIG, Plasmaphoresis
- Selective Serotonin Re-Uptake Inhibitors: fluoxetine, fluvoxamine, sertraline, and paroxetine
- Cognitive Behavior Therapy:
- Other therapies: anti-inflammatory, anti-fungal,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

# Antibiotics Prophylaxis Trial – Study Design

- Double-blind, parallel-design study of azithromycin (500 mg q week) and penicillin (250 mg po bid)  
(Note – All Children received antibiotics)
- One year long trial with monthly visits for throat culture, titers and symptom ratings
- Comparison of symptom course year prior to study, with course during prophylaxis.
- Assessment of GABHS infections via titers

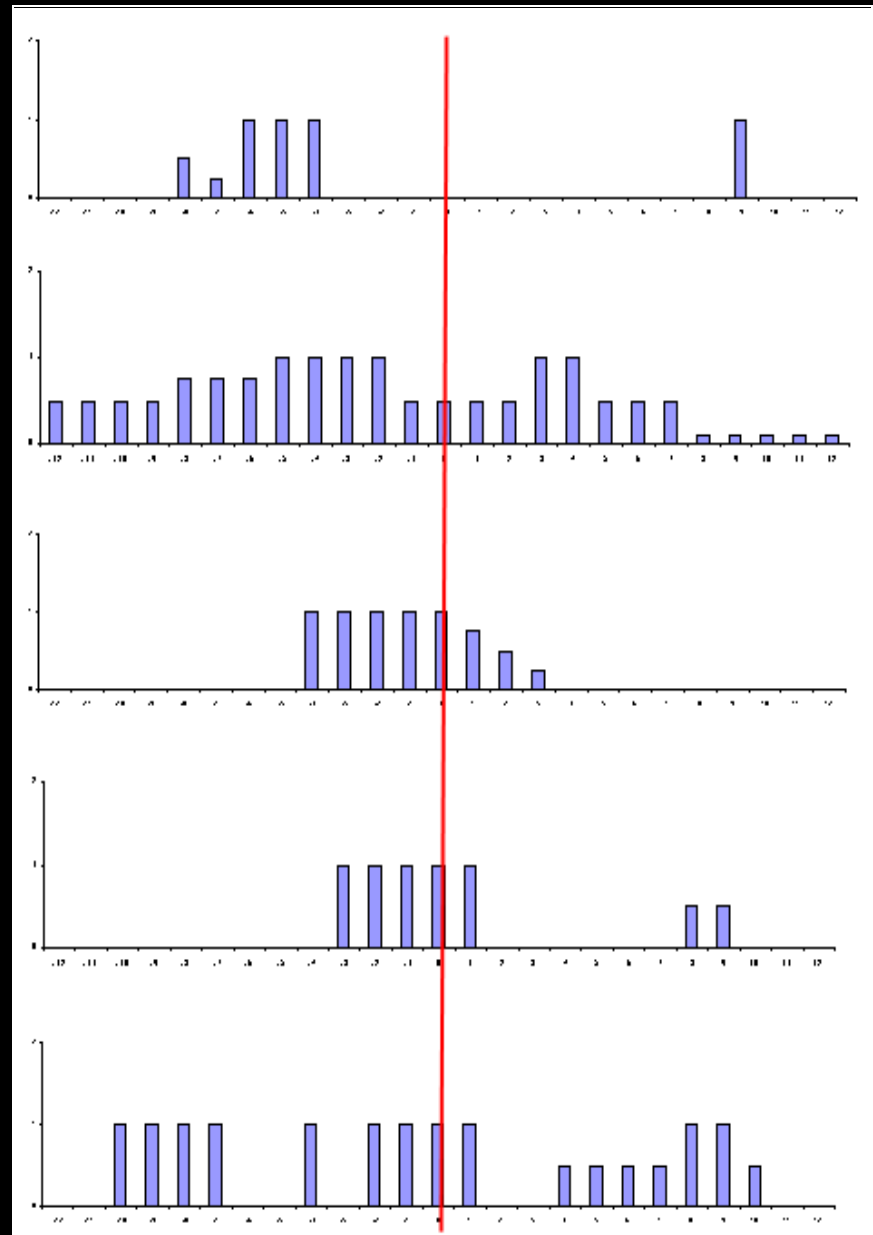


# PCN

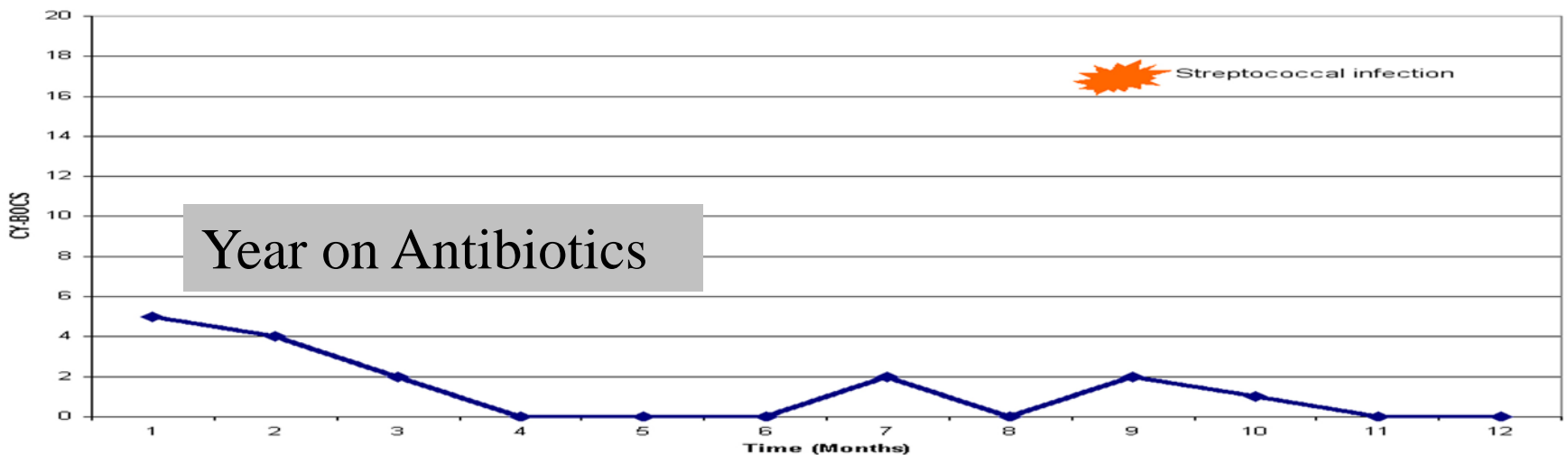
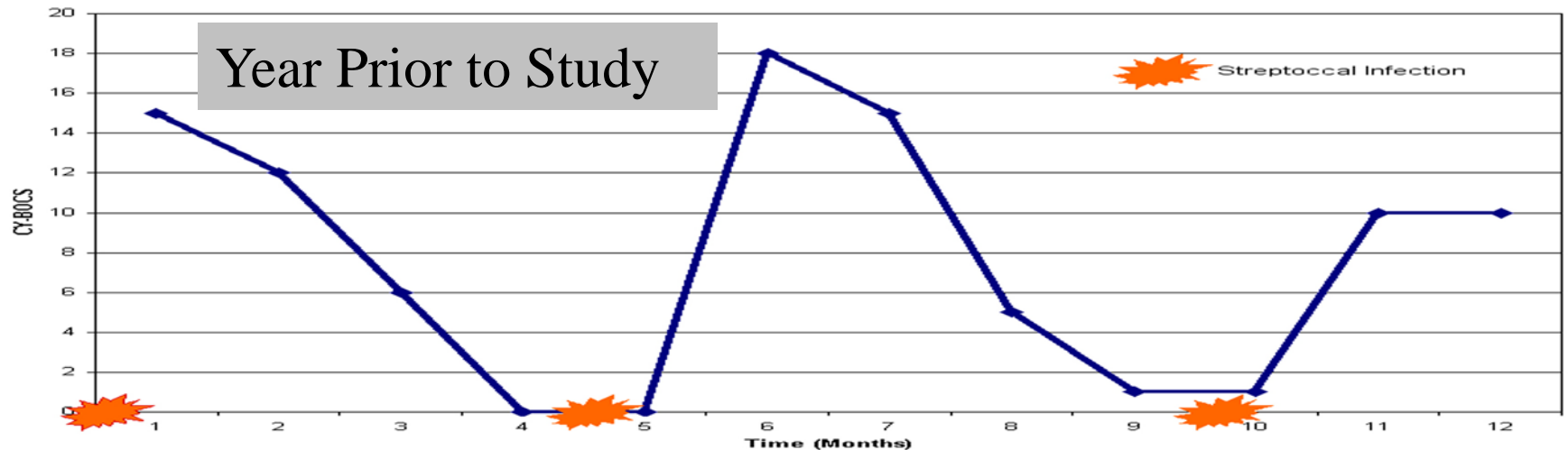


# AZITHROMYCIN

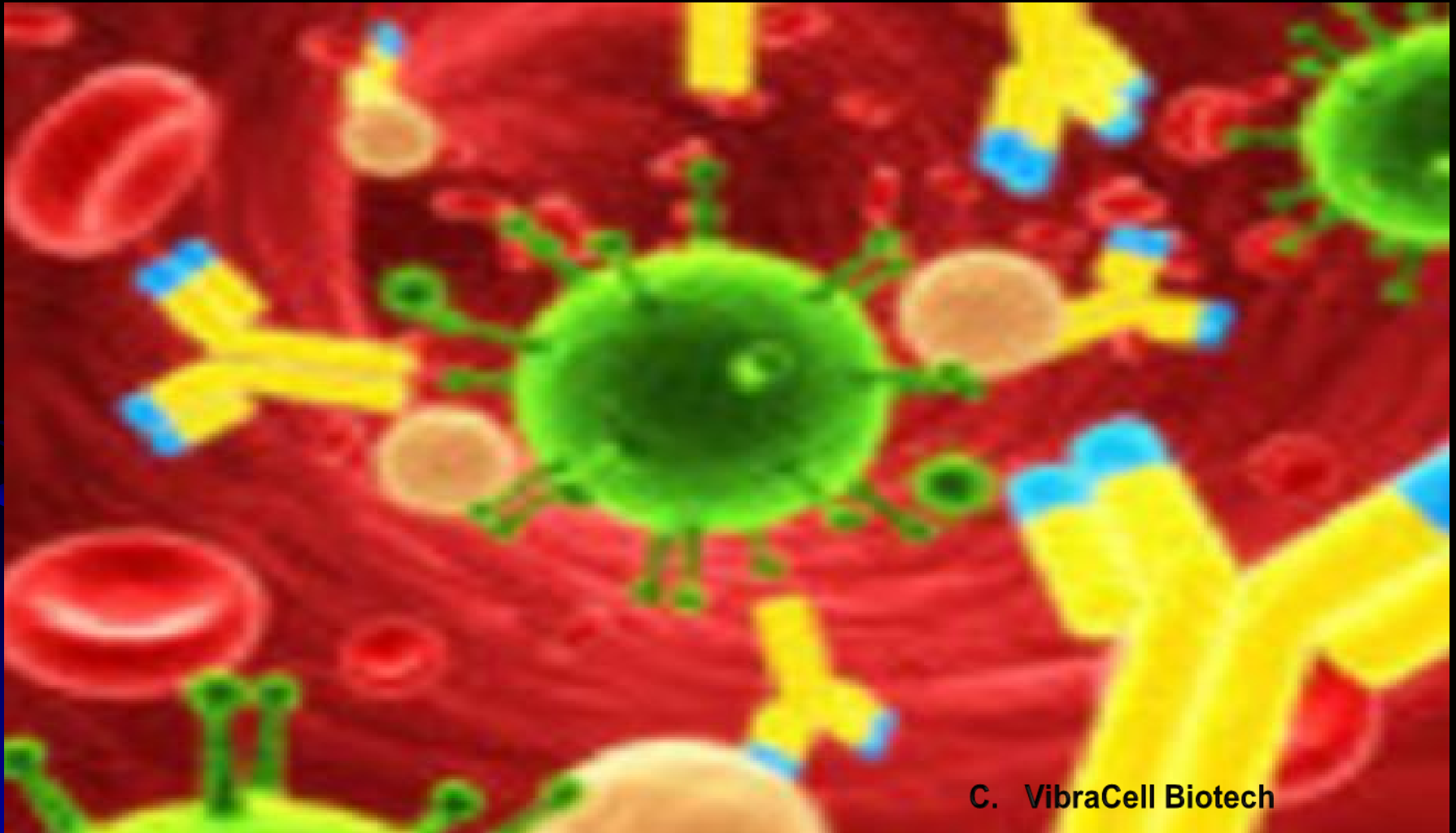
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# Effectiveness of Antibiotic Prophylaxis \*\*



# Can Immunomodulatory Therapy Reduce Clinical Symptoms?



C. VibraCell Biotech

# Immunomodulatory Treatment Trial

## Plasma Exchange vs. IVIG vs. Placebo

\*\*

**RANDOMIZATION**



```
graph TD; A[RANDOMIZATION] --> B[Plasma Exchange  
N = 10]; A --> C[IVIG  
N = 9]; A --> D[SHAM IVIG  
N = 10];
```

The diagram illustrates the randomization process for the trial. A central box labeled 'RANDOMIZATION' branches into three treatment groups: Plasma Exchange (N=10), IVIG (N=9), and SHAM IVIG (N=10). The Plasma Exchange group is highlighted with a blue dot and a curved line pointing to it from the left side of the slide.

**Plasma Exchange**

N = 10

**IVIG**

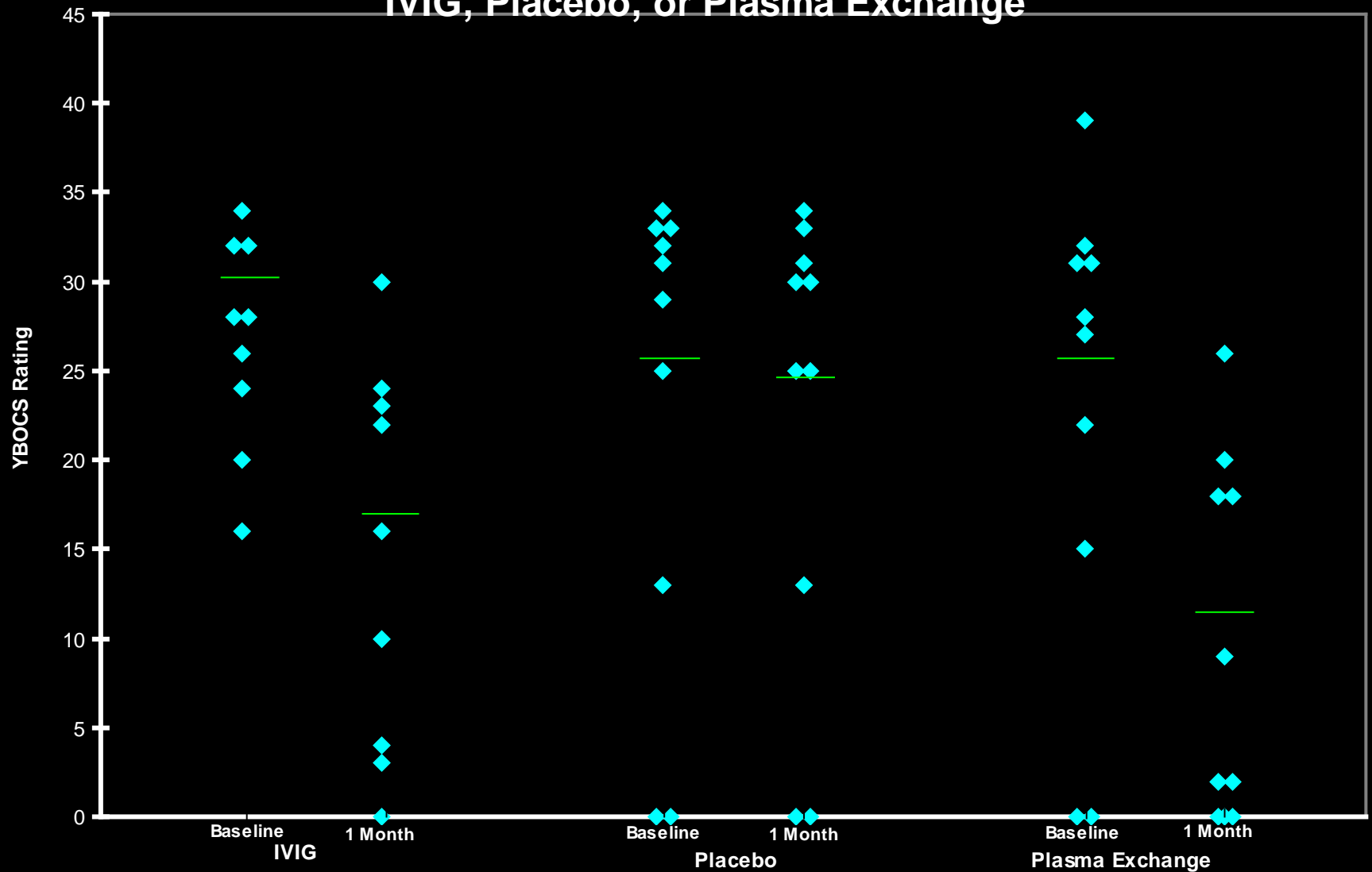
N = 9

**SHAM IVIG**

N = 10

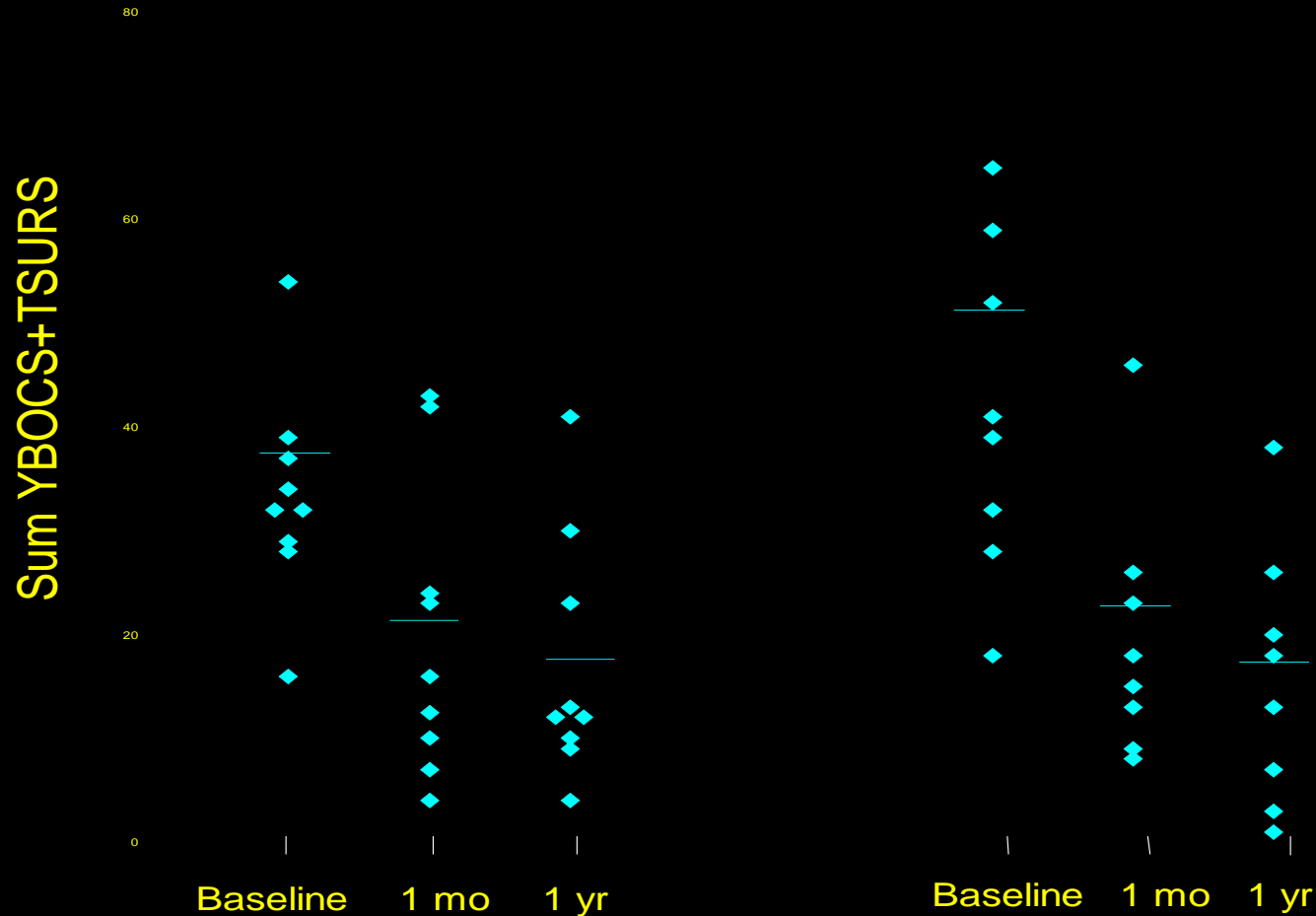


# Change in OCD Severity 1 Month Following Treatment With IVIg, Placebo, or Plasma Exchange



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# Response to Immunomodulatory Therapy with IVIG (n=9) or Plasmapheresis (n=8) Small Study Suggesting Prolonged Effect



***MRI scans of a PANDAS patient, showing reduced inflammation in the caudate nucleus (area circled just to the left of black area in center of brain), part of the basal ganglia, following IVIG treatment. Evidence suggests that this brain structure is targeted by errant anti-brain antibodies, triggered by a strep infection, in PANDAS.***



# 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 might be unusual.
- 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
- Evidence of **basal ganglia swelling & inflammation**, inflammatory 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



# Questions Our Group is Pursuing

- Evaluating these children as best we can, from an immune, autoimmune & immune activation perspective
- Explore the syndrome from an ENT standpoint with our friends at Boys Town
- Specifically, is there evidence for inflammation?
- What is the role of tonsillectomy/adenoidectomy?
- Are there Biofilms and could it be driving an inflammatory response?
- **Why Would We Want to See These Children?**
- **The answer is quite simple really: “Kodomo no tame ni”**



# What We Try to Do

- Evaluate carefully from an immune/auto-immune perspective
- Have Pediatric Neurology, ENT & Psychology/Psychiatry evaluate
- Have parents keep a symptom diary [see attached]
- **CBC, CRP**, QIG's, antibody function, ANA, **ASO, anti-DNAase, throat cultures\***, EBV, DHT, anti-neuronal antibodies
- **Frequently:** IL-2, INF-gamma, TNF-a,
- **Occasionally:** allergy skin testing, Lyme, Mycoplasma
- **Ideally:** anti-Dopamine receptor antibodies, anti-basal ganglia cell antibodies, IL-12, Lymphocyte subsets [T-regs?, activated B-cells, NK cell activity?]

# RESOURCES FOR PANS/PANDAS SUPPORT

- **NIH:**

[http://www.nimh.nih.gov/  
labs-at-nimh/research-  
areas/clinics-and-  
labs/pdnb/web.shtml](http://www.nimh.nih.gov/labs-at-nimh/research-areas/clinics-and-labs/pdnb/web.shtml)

- **PANDAS Physicians**

- **Network:**

- <https://www.pandasppn.org/>

- [http://pandasnetwork.  
org/](http://pandasnetwork.org/)

## **State Groups:**

NE:[pandasnebraska@cox.net](mailto:pandasnebraska@cox.net)

IA:[iowapandas411@yahoo.com](mailto:iowapandas411@yahoo.com)

KS:[kcareapandas@gmail.com](mailto:kcareapandas@gmail.com)

MO:[kristenmarsh1@hotmail.com](mailto:kristenmarsh1@hotmail.com)

“That’s All Folks!”

