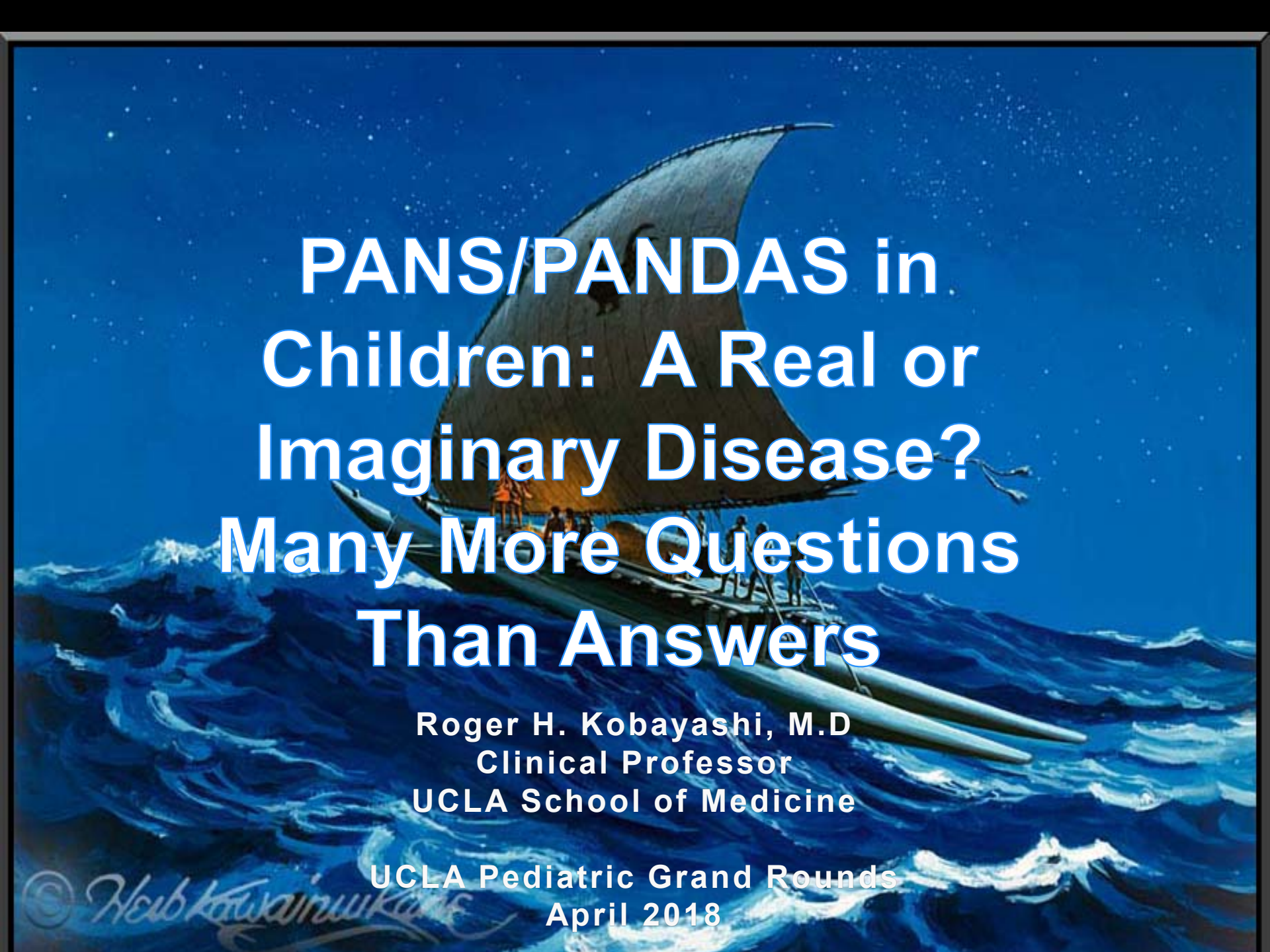


PANS/PANDAS in Children: A Real or Imaginary Disease? Many More Questions Than Answers

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

UCLA Pediatric Grand Rounds
April 2018

“Okage Sama De” I am what I am because of you

- Dr. Sheldon C. Siegel

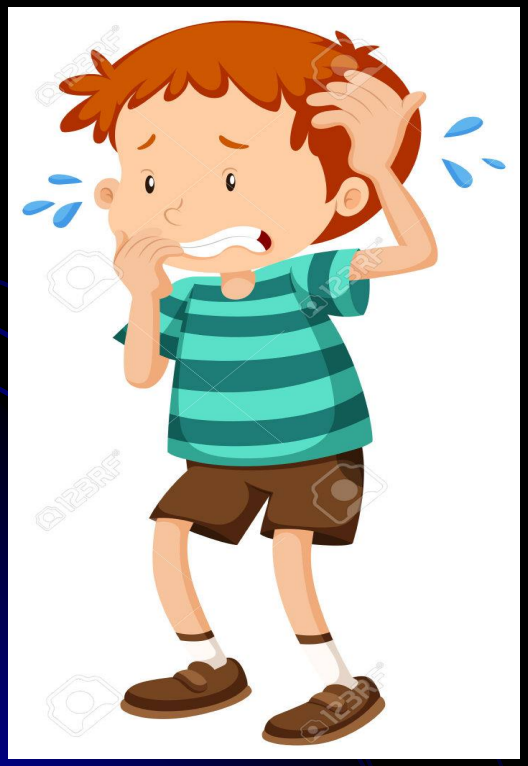
Co-founder & Director of Allergy UCLA

- Dr. E. Richard Stiehm

Emeritus Director of Allergy UCLA

Dr. John Fahey: Director CIRD UCLA School of Medicine

- "Young Man, Where Did You Read That? That is the dumbest Thing I Ever Heard" "Young Man, Stop! Where did you read that?"

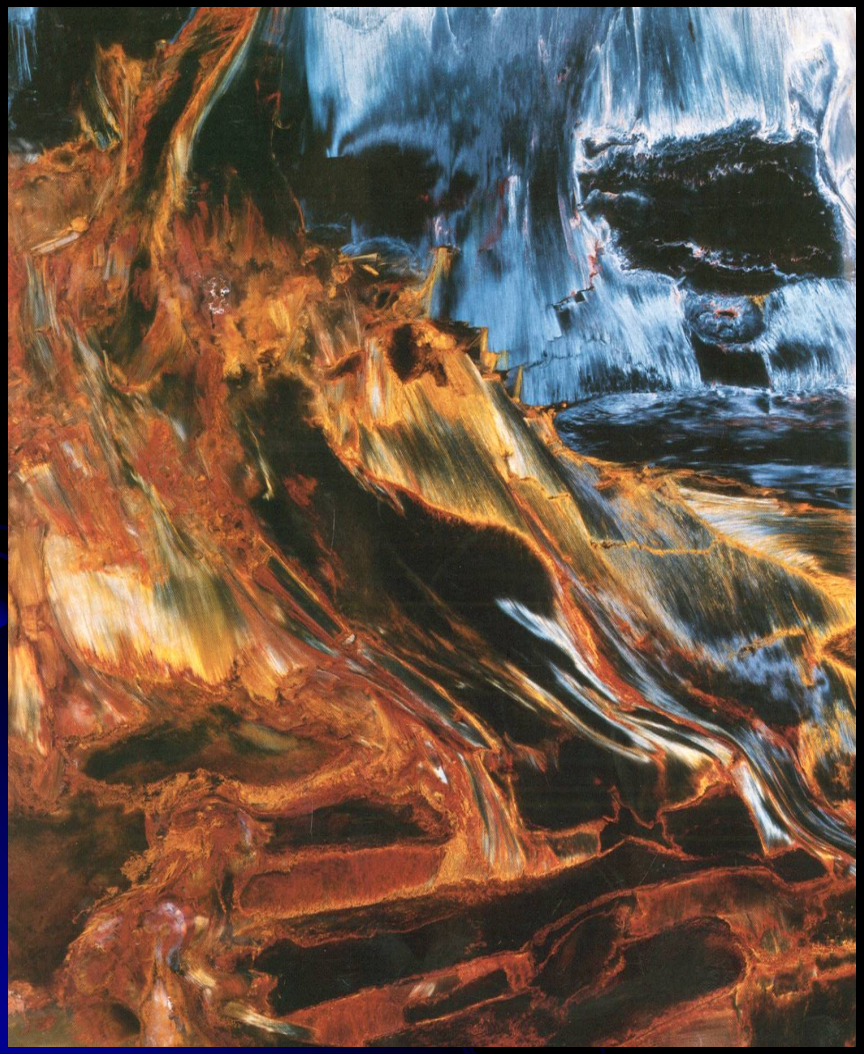


- During this lecture there will be some young investigators in the audience today who will say, "Old man, Where did you read that? That is the dumbest thing I ever heard"

Humble Country Doctor from Nebraska

- Disclosures
- Immunology/Chronic Infections: AAIA [Eight Doctors & 3 PA's]
- Manage >320 patients on IVIG
- Grant support Octapharma, Shire
- Clinical Professor: UCLA
- Lecturer: MMU Hanoi, Vietnam
- Consultant IDF, USID. Shire, Octapharma,
- Exec. Committee: CIIC
- Board Member: IfPA; National Biologic Physicians Working Group, Asian-Pacific Physicians
- Previously, Consultant for Bayer, Talecris, CSL/Sandoz, Baxter, Shanghai Red Cross, American Red Cross

Discussion Outline

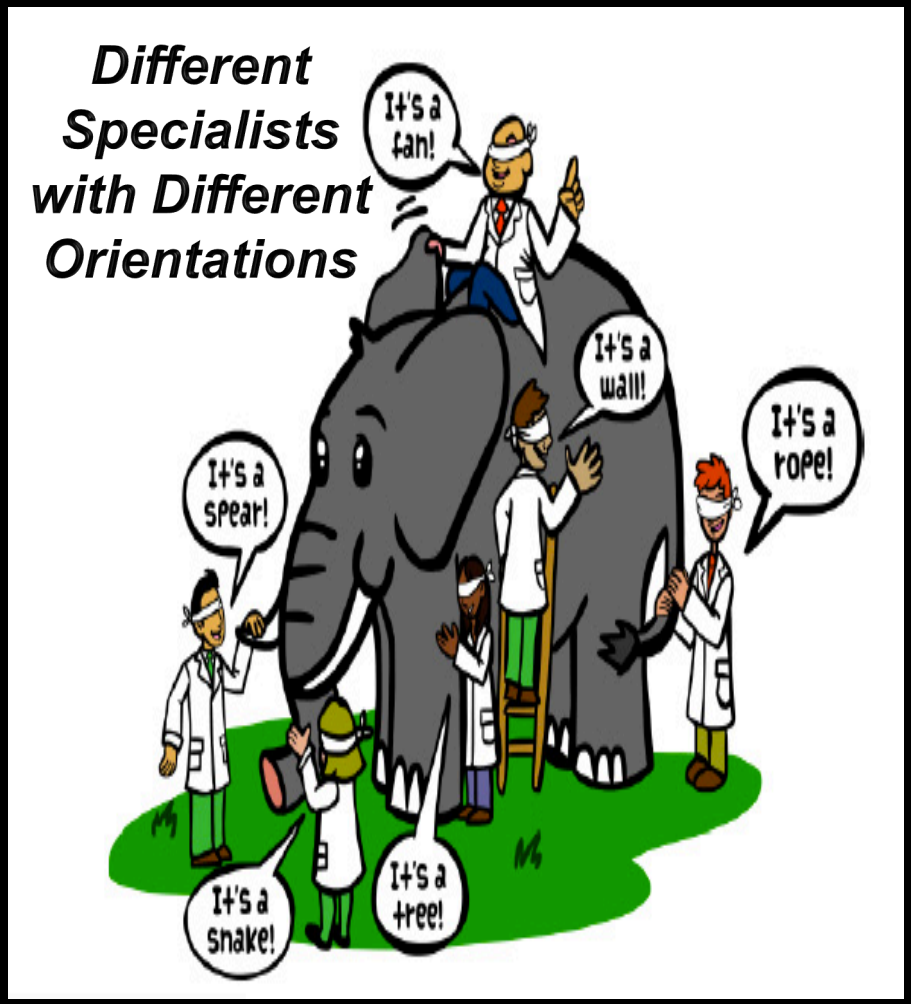


Purpose: To help the audience imagine that such a disease might exist & to keep an open mind.

- ***Part 1 Working definition of PANS***
- ***Part 2 Suggested pathogenesis of PANS***
- ***Part 3 Why is PANS such a difficult disease to define and treat?***
- ***Part 4 What treatment modalities are available? How might they work and why sometimes they don't work?***
- ***Part 5 Summary***

Disclosures & Confessions

- I am a Clinical Immuno-logist and Allergist in private practice with an interest in PIDD & Immune Dysfunction.
- I stumbled into caring for PANS patients [referrals for IVIG]. I am *not* an expert & prefer PIDD.
- So if this lecture junk, it is not my fault.



Questions Where I Will Need Help

- How do you distinguish PANS/PANDAS from other behavioral or neurologic diseases?
- Is PANS/PANDAS an auto immune disease and if so, how do you prove it?
- Is there credence to the laboratory studies, particularly dealing with infections, auto-immunity and animal models?
- Are the demonstration of auto-antibodies against basal gang-lion tissue diagnostic?
- What therapeutic options are appropriate for these children?
- How do antibiotics work in this supposed auto-inflammatory disease?
- What is the role of IVIG, plasmapheresis, high dose steroids, rituximab, cellcept?
- How do you interpret the Cunningham Panel and is it a test upon which you can base your diagnosis upon?
- These patients are very high maintenance; who is willing to take them on?

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 & anti-psychotic medications. Did not improve.
- PCP thought might be PANDAS; started empirically on Augmentin=> improved on 10 day course. Behavior recurred after antibiotics stopped.
- Referred for evaluation and possible treatment

Case Report 2

- 8 y/o W/F previously happy, well-adjusted developed sore throat 3 weeks prior to the onset of sudden symptoms.
- Normal and well the night before, woke up the next morning suddenly crying, obsessive thoughts, anxiety. Fearful and constant rubbing of nails on the door; outbursts.
- No head trauma, vaccines, viral infections associated with encephalitis.
- Extensive laboratory studies revealed increased ASO, normal CRP, CBC, negative anti-neuronal antibodies, ANA , chem profile , EBV, West Nile. Cunningham Panel not done.
- Started on antibiotics, prednisone and ibuprofen.
- Amazing response within one week to almost normal behavior.
- Placed on antibiotics for 1 year and discontinued. Normal behavior, no OCD/TICs or other abnormalities.

Case Report 3

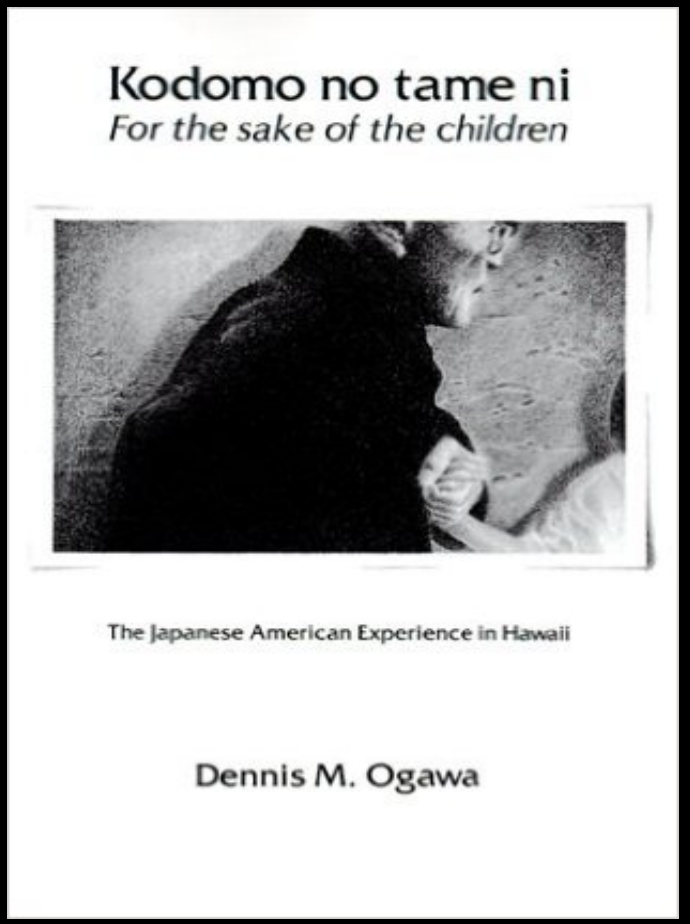
- Very well-adjusted 9 y/o W/M history of recent, acute pharyngitis, developed dramatic onset severe compulsive disorder with anxiety, facial TICS, oppositional behavior, sleep disturbances. Taken to emergency room; referred to psychiatrist and placed on SSRI but poorly responsive. Referred and ASO and 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 where 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.

Extreme Skepticism to Belief

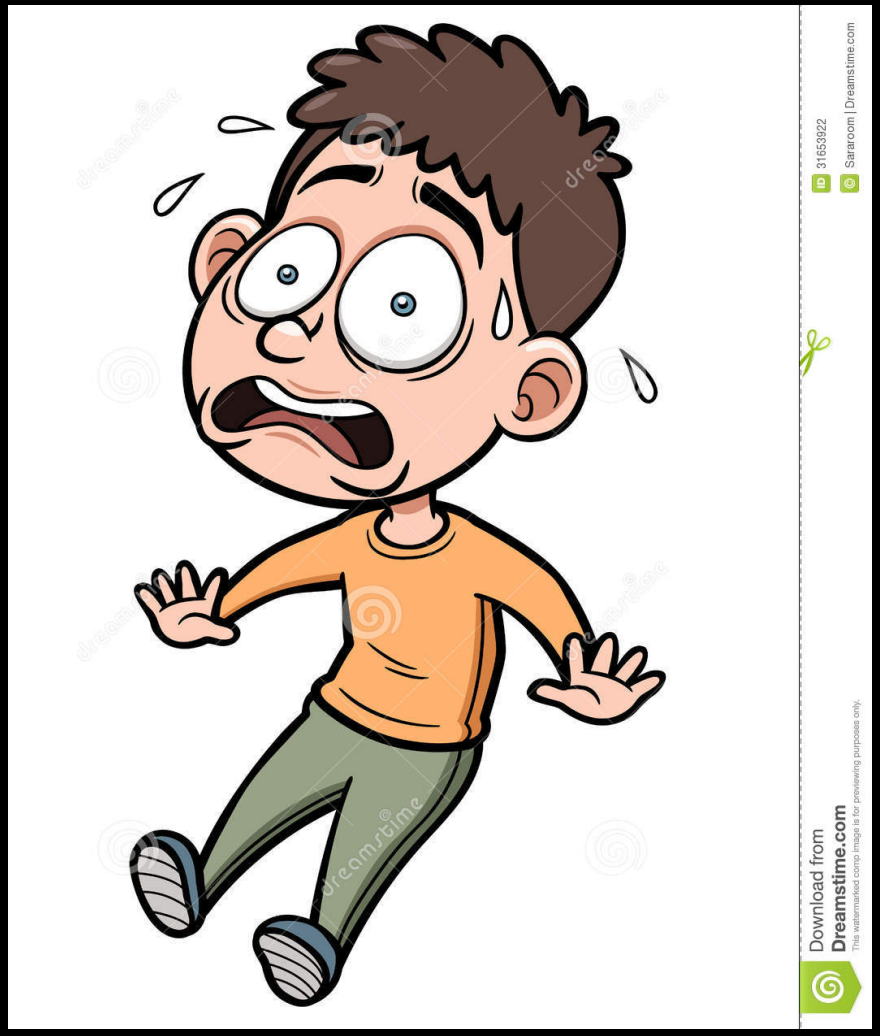
- **I am a clinical immunologist so I was very skeptical and even annoyed. I hated psychiatry in Medical School.**
- **But the more I read and talked to very bright people..**
- **…and just as importantly, I saw parents at wits end and children who would be normal except for an abrupt alteration in behavior, then**
- **…..I began to imagine that such a disease might exist**
- **We have now evaluated over 120 children from NE, IA, KS, MO, SD, ND, CA, IL, MN, OH, & Hawaii.**

- 61st Annual Meeting of Am Acad Child Adol Psychiatry in San Diego, CA October 20 -25, 2014
- Participants from NIH, Harvard, Columbia, Stanford, Johns Hopkins, Yale and other major medical centers

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



Abrupt Onset Dramatic Change in Behavior



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 & symptoms… sleep disturbances, eating disorders**
- **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

PANS & PANDAS

- PANDAS
- Typically associated with antecedent Gr. A Strep infection
- Main criteria TICS or OCD
- Appears to be responsive to antibiotics, often dramatically
- In a placebo controlled study, patients seemed to do better while on antibiotics.
- In a study where TICS/OCD was associated with Gr. A Strep compared with a controlled group where infection was not a factor, the antibiotic group did significantly better.
- JAMA.Psych. 2017; 74:740 – Danish study in 1,067,743 children. 638,245 had strep screen. Those with positive strep had higher incidence of any mental disease than those negative.

- PANS
- Redefined in 2012 NIH criteria
- Group A Strep infection is not a criteria; other infections [myco-plasma, EBV, Lyme, West Nile, In-fluenza] or no precipitating cause
- Main criteria: sudden, dramatic onset of OCD and/or severe eating disorder; **WAXES & WANES**
- Treatment may be more geared towards anti-inflammatory, anti- TIC and anxiety medications and behavioral management.
- Antibiotics here are controversial.

PANS Questionnaire

PANDAS / PANS New Patient Questionnaire:

Who referred you here today?

_____

PANDAS/PANS Primary Criteria: circle yes or no

YES / NO Was there an abrupt and/or dramatic onset of symptoms? **WHEN:** _____

YES / NO Movement Tics ? (F95.8) and/or Compulsive Behavior (F42.8)

PANDAS/PANS Secondary Criteria: circle yes or no

YES / NO Anxiety? (F41.8)

YES / NO OCD symptoms? (F42.8)

YES / NO Emotional Liability and/or Depression? (sudden unexpected changes in moods) (F33.1)

YES / NO Irritability and/or severely oppositional behaviors? (F91.3)

YES / NO Behavioral (developmental) Regression? ("baby-talk") (F89)

YES / NO Deterioration in school performance? (handwriting, coloring) (F81.89)

YES / NO Sensory or motor abnormalities? (textures, movements) (F82)

YES / NO Somatic signs and symptoms? (sleep disturbances) (G47.01)

When did the symptoms start (date) and what are the symptom(s)?

_____

_____

_____

Has any treatment helped? If yes, please list:

_____

_____

Has the patient been placed on antibiotics? If yes, please list:

_____

Has the patient had a Tonsillectomy and/or Adenoidectomy: If yes, please list surgeries and dates:

_____

1

rev. 12/16

PANDAS / PANS New Patient Questionnaire:

_____

_____

How many times has the patient had strep throat? _____ JO2.0 (CURRENT) HX OF (Z87.09)

Do family members get strep frequently? If yes, list relation to patient: _____

History of Immune Problems? _____ Recent Lab Work Done? **YES / NO**

If Yes, Where was it done at? _____

History of familial OCD, TICS, ANXIETY: If yes, please list:

_____

_____

CURRENT MEDICATIONS and DOSE:

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Has the child been evaluated or treated by the following:

Primary Doctor: _____ Last Seen: _____

Testing done: _____

Neurologist: _____ Last Seen: _____

Testing done: _____

Psychiatrist/Psychologist: _____ Last Seen: _____

Testing done: _____

Immunologist: _____ Last Seen: _____

Testing done: _____

Dr. Signature _____ Date/Time_____

2

KB-rev. 2/15

What's So Fascinating About PANS/PANDAS?

- Small subgroup with acute onset , severe behavior changes following infection
- Autoimmunity? +FH 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

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

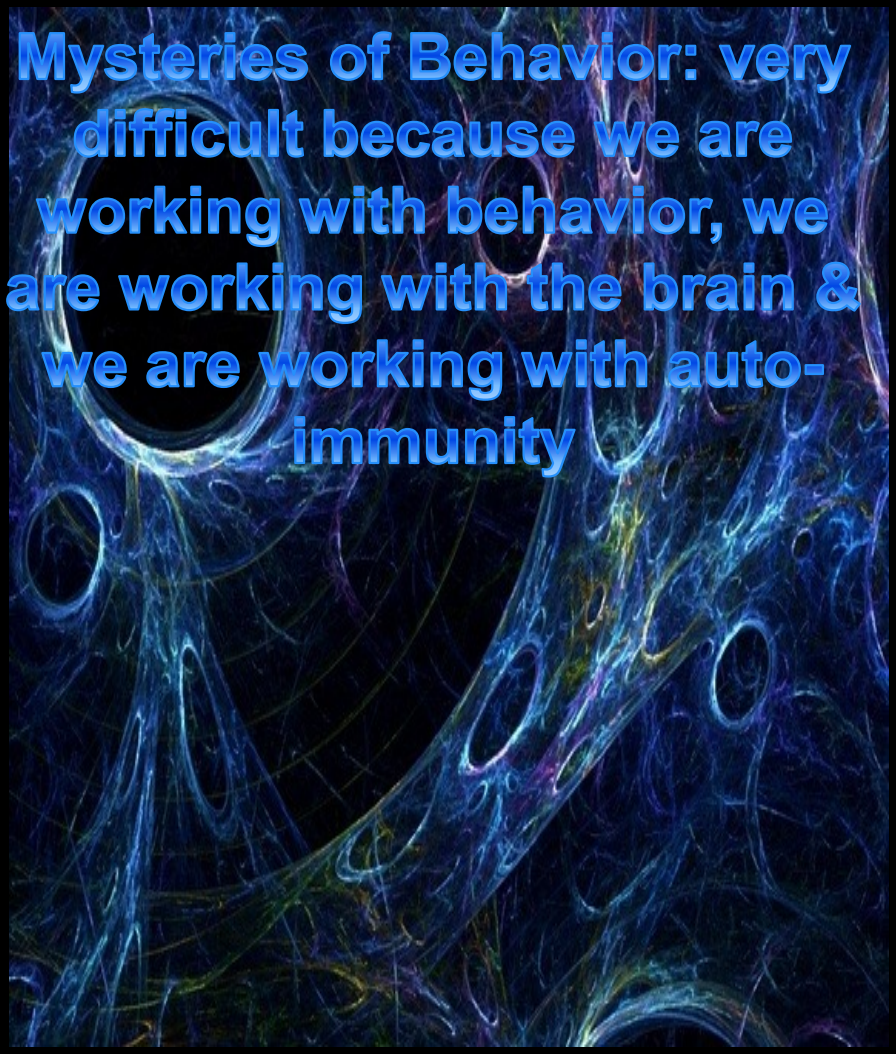
TABLE 1: EFFECTS OF BASAL GANGLIA INFLAMMATION

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.



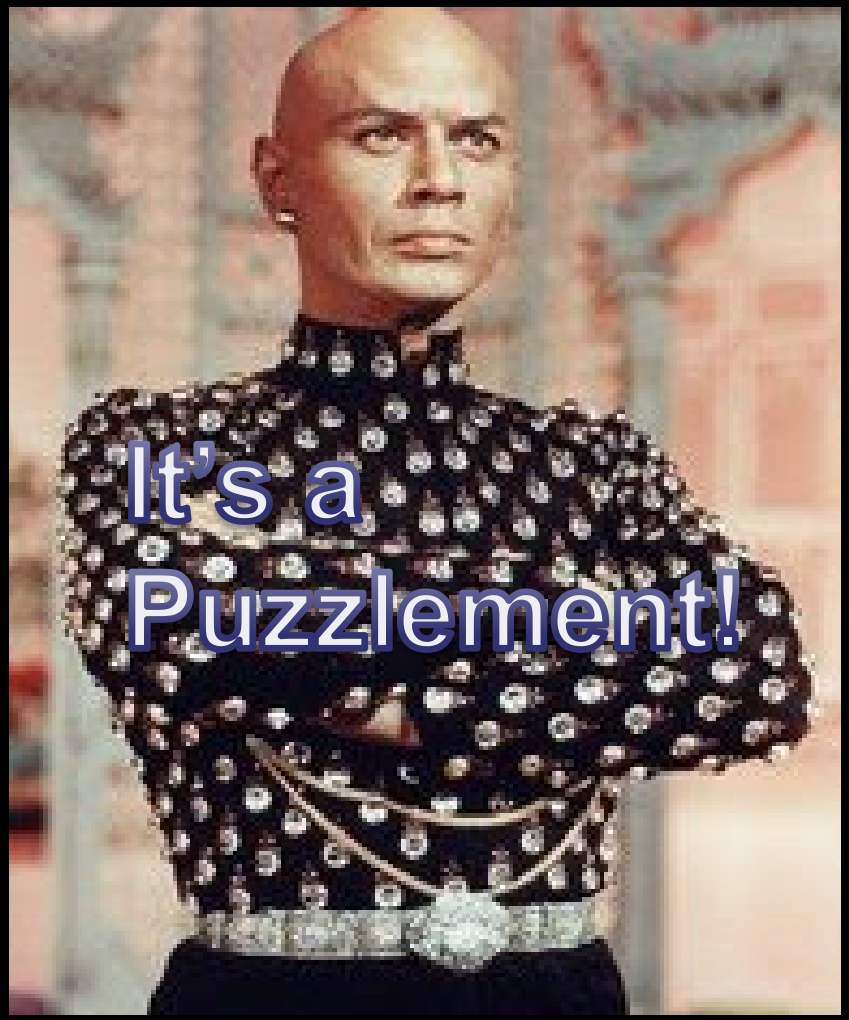
Kapakahi

- Group A Strep Infections very common in children ~ 25 %
- Assymptomatic Strep carriage common ~2.5 – 4%
- Transient minor TICS common in children ~ 25%
- OCD is not uncommon in children ~ 1-2%
- Behavior problems common in children

- **BUT TO BLOCK OUT ANY IMMUNO-CHEMICAL PATHOGENSIS IS NOT LOGICAL. THERE HAS TO BE A REASON FOR SUDDENT ONSET, DRAMATIC CHANGE IN BEHAVIOR.**
- **MAY BE IMPORTANT TO DISTINGUISH PANS/ PANDAS BECAUSE *TREATMENT MAY BE DIFFERENT***

Must Differentiate from Other Behavior Disorders

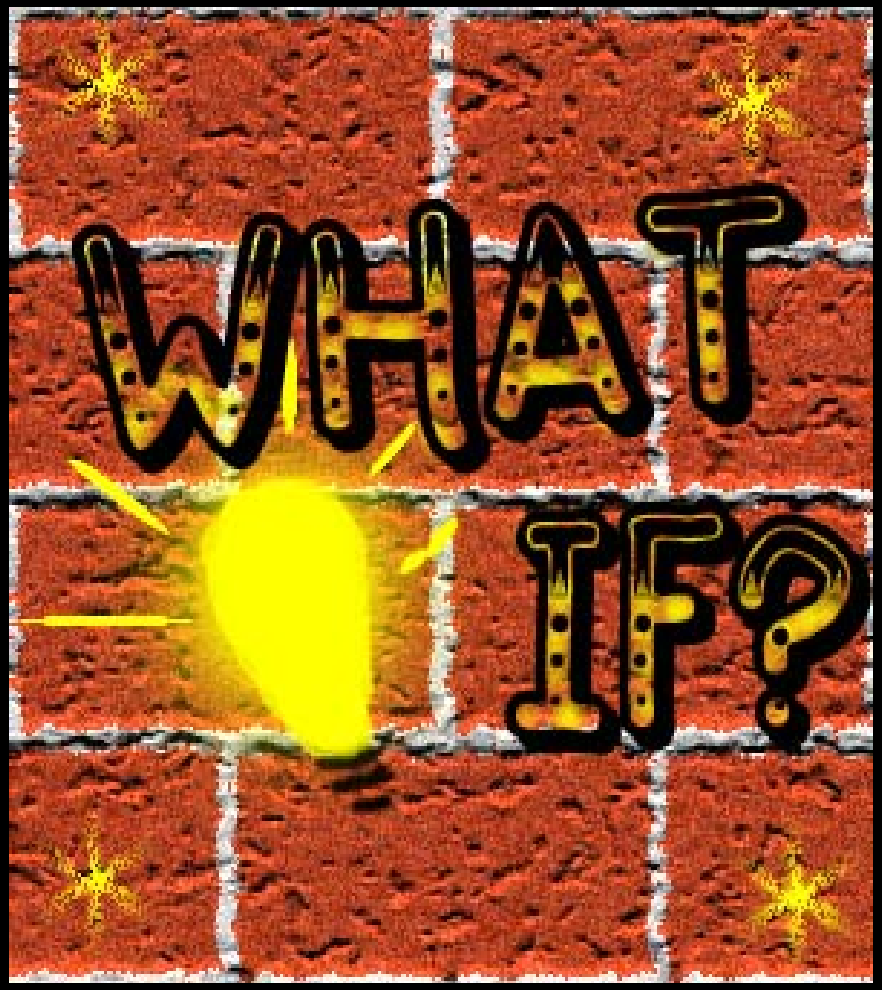
- OCD
- Neuropsychiatric Disorders
- Anorexia nervosa
- Tourette Syndrome
- Transient TIC Disorder
- Bipolar Disorder
- Sydenham's Chorea
- Autoimmune Encephalitis
- Systemic Autoimmune Disorders



K.Chang JCAP 2014

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?



PANDAS – Is There A Host Susceptibility?

- **Increased familial rates of OCD & tics**
  - 36/50 (67%) of PANDAS probands had an affected 1º 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 [D8/17 is a known marker on B-cells for Rheumatic Fever] **

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

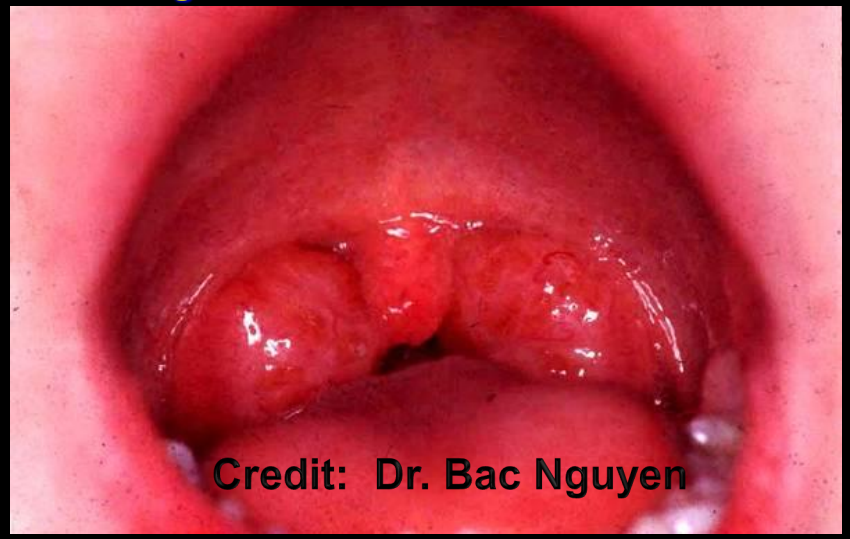
OCD/TIC DISORDERS

- 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

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

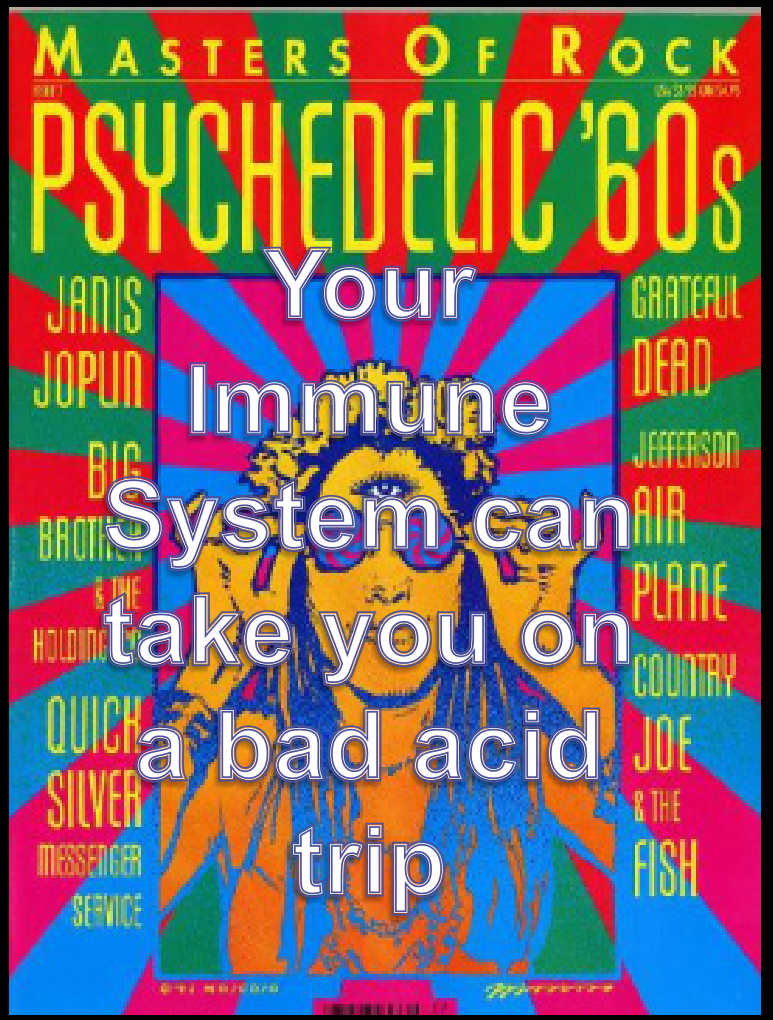
- NIH described similarities between PANDAS & Sydenham's Chorea
- Distinguished an OCD sub-group with *acute onset* and co-morbid symptoms including separation anxiety, ADHD & TICS which seemed to follow infections
- NIH also observed that 65 -70% of children with Sydingham's had OCD and many developed 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



How the Immune System Is Supposed to Perform

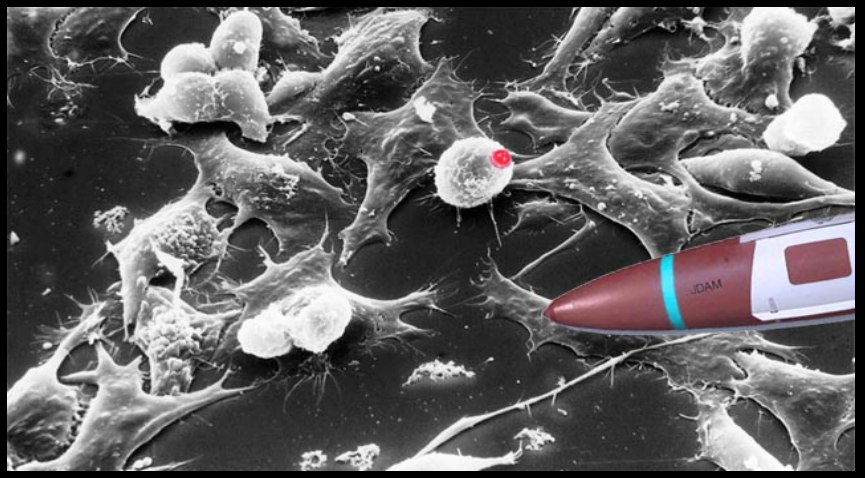
New York Philharmonic



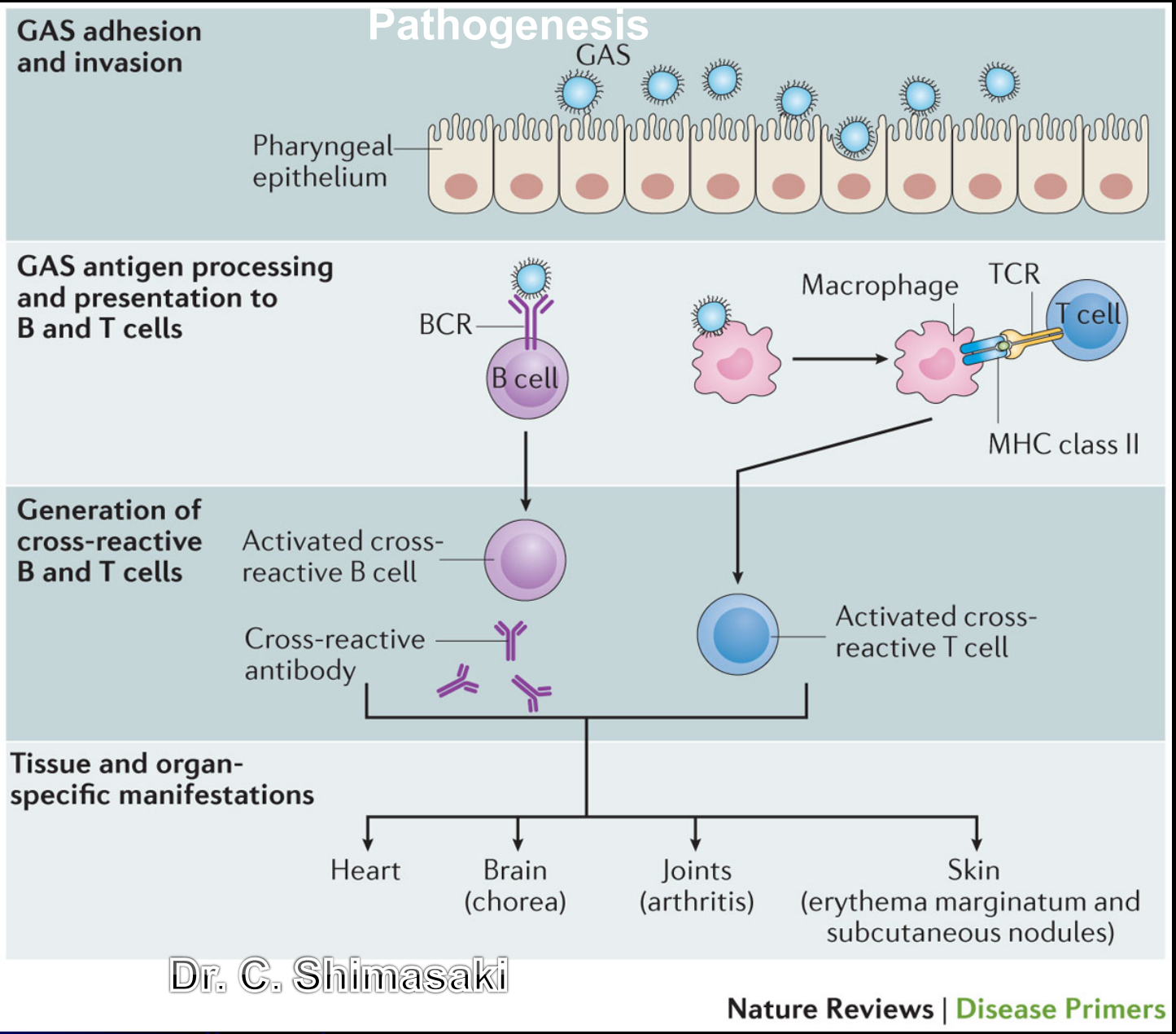
PIDD: Sometimes your Immune System is "FAR OUT"

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

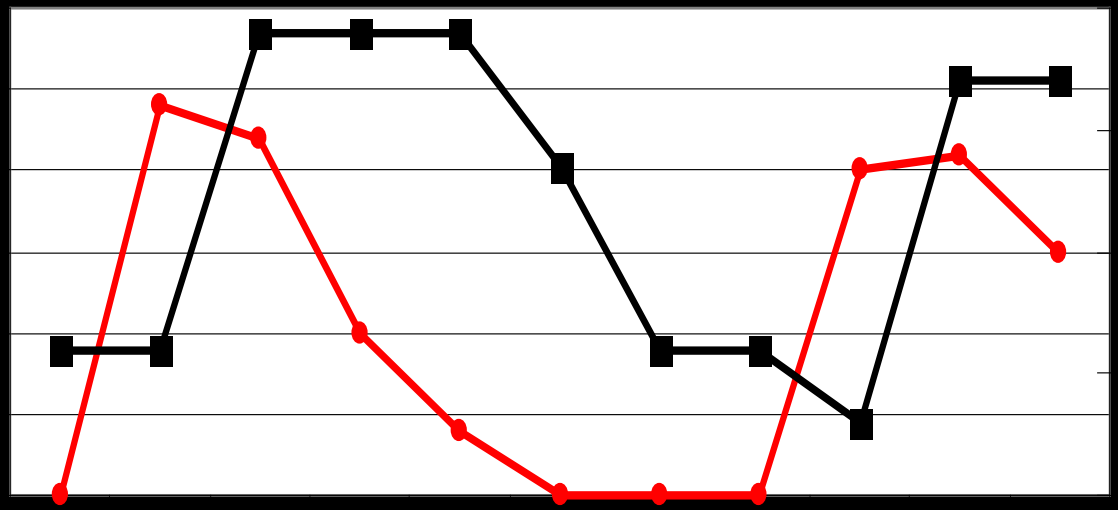
Cross-reactivity or Molecular Mimicry/ Immune Dysregulation



Pathogenesis



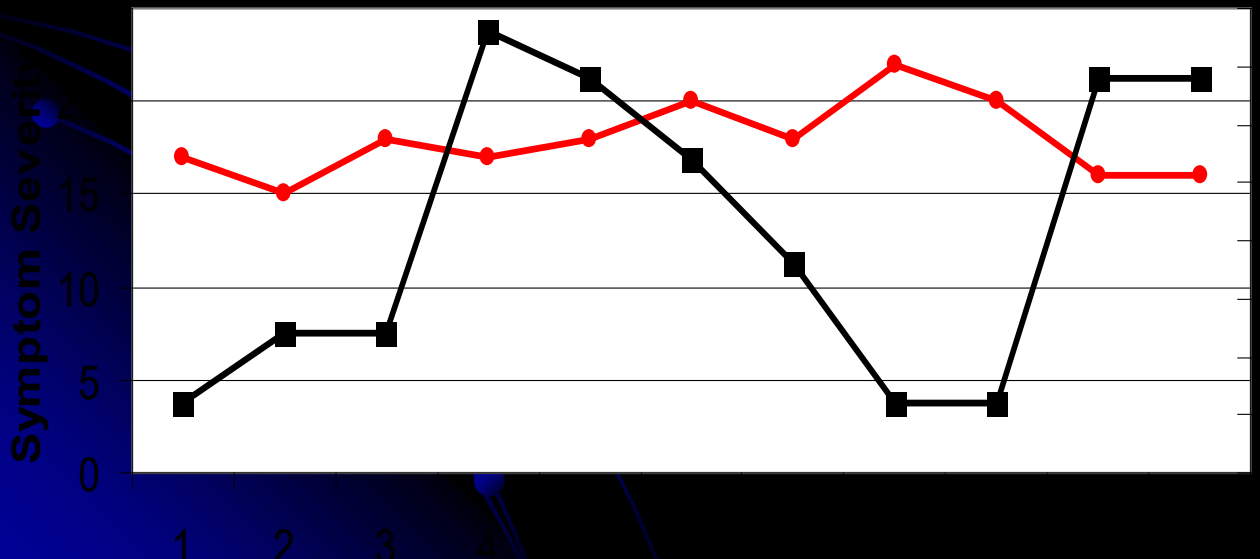
Carapetis, JR, A Beaton, MW Cunningham *et al.* (2015) Acute rheumatic fever and rheumatic heart disease Nature Reviews: Disease Primers doi:10.1038/nrdp.2015.84



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.

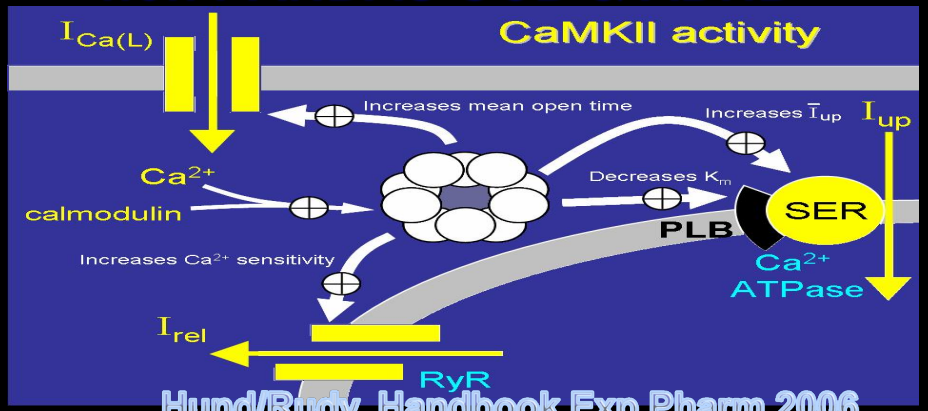
Anti-neuronal Antibodies in a Heterogeneous Group of Children & Young Adults with TICS & OCD.

- 1. 311 patients, aged 4-27 years 66% Male with neuropsychiatric disease with confirmed history of Gr A Strep infection.
- 2. 222 [71%] had evidence of Gr. A Strep assoc. with OCD &/or TICS [p=0.0083]
- 3. Serum antibodies were determined against basal ganglion tissue [Cunningham Panel].
- 4. Sera from 261 with TICS &/or OCD were positive against lysoganglioside, tubulin, D1 and D2, and had elevated activity with CAM Kinase II assay. p<0.0001] with I, D1 & CAM KII
- 5. Patients with TICs and OCD had higher activation profiles [p=0.033] than if only TICs or OCD alone.
- Cox, Chang, Cunningham. J. Chil.d Adol.Psychophram. 2015; 25:76/

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 [but anti-capsular Ab]**
- **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**



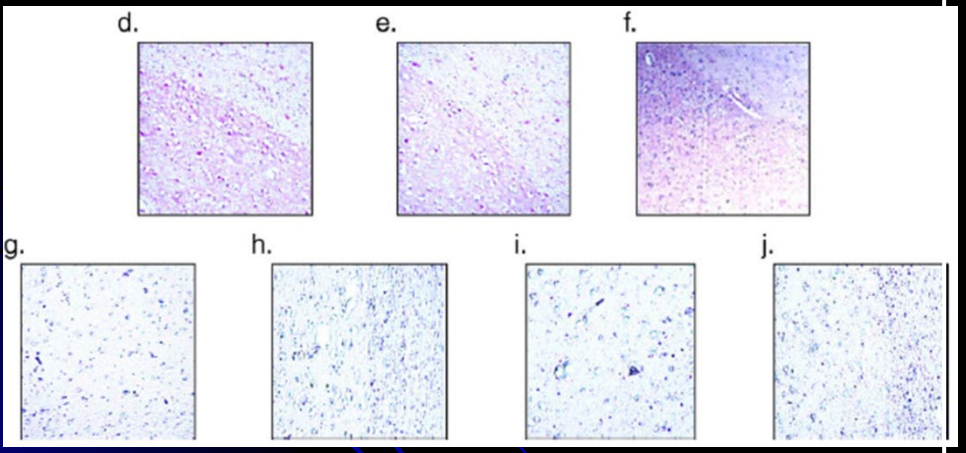
Autoantibody Binding Effect on Neuronal Cell Signaling

Binding of cerebral spinal fluid antibodies to Human Brain Caudate-Putamen in Children with Movement Disorders

Journal of Neuroimmunology

Antibody-Mediated Neuronal Cell Signaling in Behavior and Movement Disorders

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



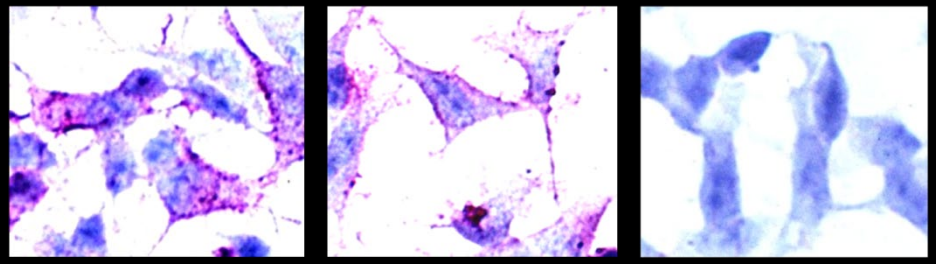
Control Control Control Control

Sydenham Chorea Autoantibodies to Human Neurononal Cells Bind and Stimulate calmodulin-dependent protein kinase (CaMKII)

nature medicine

Mimicry and Autoantibody-Mediated Neuronal Cell Signaling on Sydenham Chorea

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



VOLUME 9 | NUMBER 7 | JULY 2003 NATURE MEDICINE

Published research supports antibody mediated disruption of neuronal cell signaling and connection to behavior and movement disorders

Courtesy of Dr. C. Shimasaki

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]
- 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
- Alleviated by D2 blocker [halo-peridol] & SSRI [paroxetine]

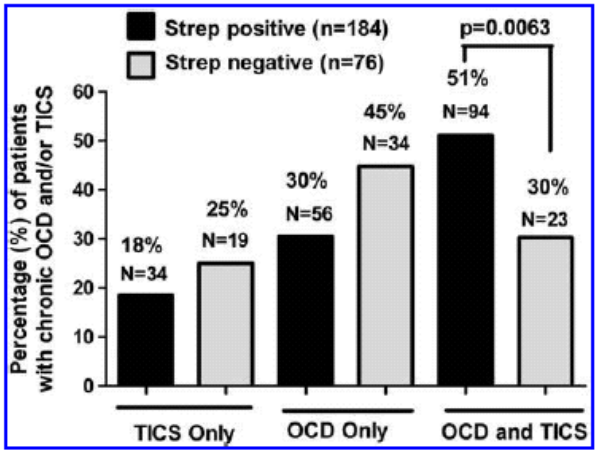
Antineuronal Antibodies in Children with Motor Tics and OCD

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015

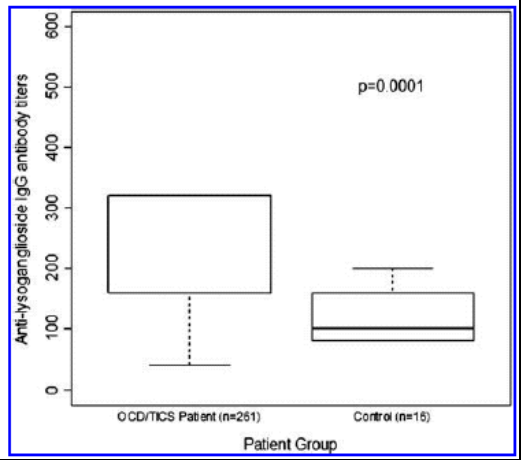
Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and Obsessive-Compulsive Disorder

Carol J. Cox, PhD,[1*] Amir J. Zuccolo, PhD,[1*] Erica V. Edwards, BS,[1] Adita Mascaro-Blanco, BS,[1] Kathy Alvarez, BS,[1] Julie Stoner, PhD,[2] Kiki Chang, MD,[3] and Madeleine W. Cunningham, PhD[1]

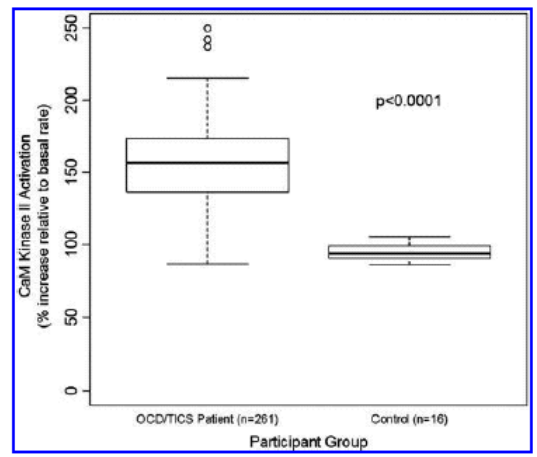
OCD + Tics Association with Strep



OCD + Tics > Anti-Lysoganglioside



OCD + Tics Association with CaMKII



OCD / motor tics are associated with the presence of antineuronal antibodies post a strep infection and correlation with CaMKII activity

Courtesy of Dr. C. Shimasaki

Treatment for PANS

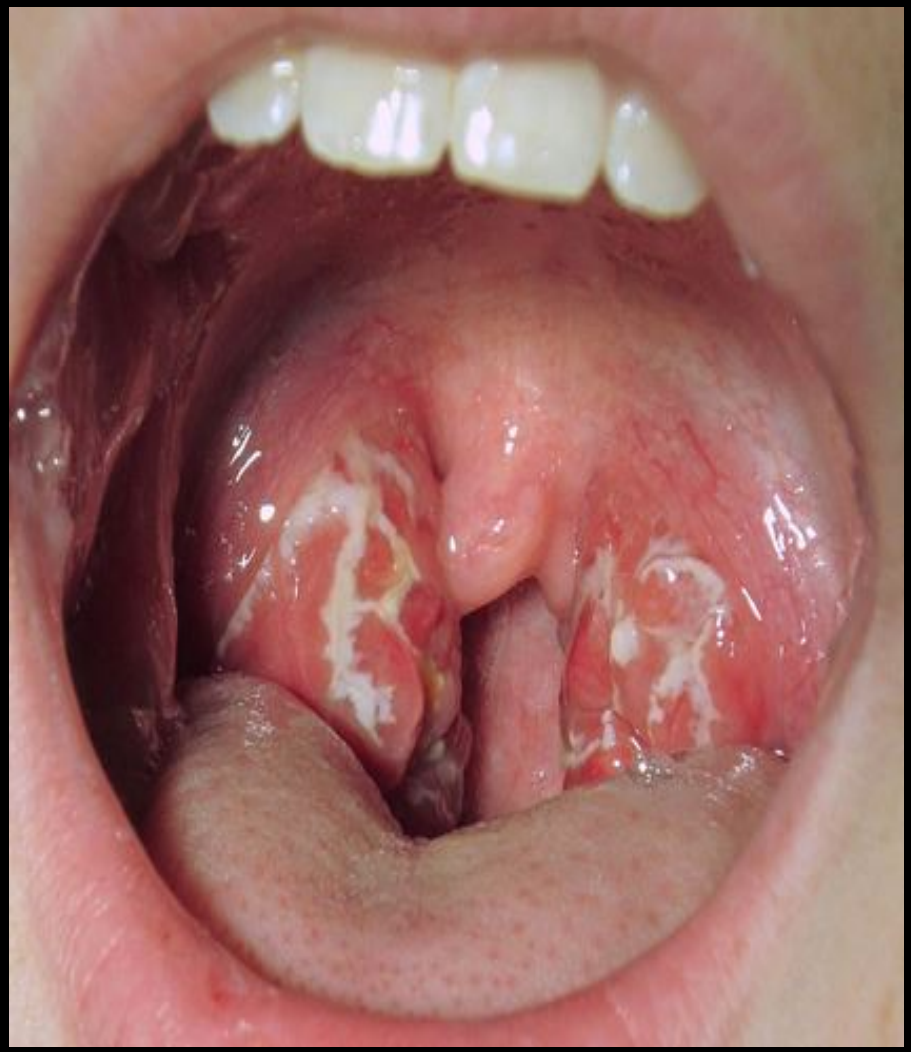
- Antibiotics: beta-lactams/Macrolides: anti-infective, anti- inflammatory, immune-modulatory, up-regulation of neurotransmitters?
- Anti-inflammatory:NSAIDS steroids.
- Anti-inflammatory & Immune Modulators: IVIG, plasmaphoresis, mycophenolate, rituximab et al.
- Psychiatric Medications: SSRI's, anti-D receptor
- Surgical Intervention: tonsillectomy/adnoidectomy, sinus surgery.

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
- Anti-anxiety medications
- Anti-depressive medications
- 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]

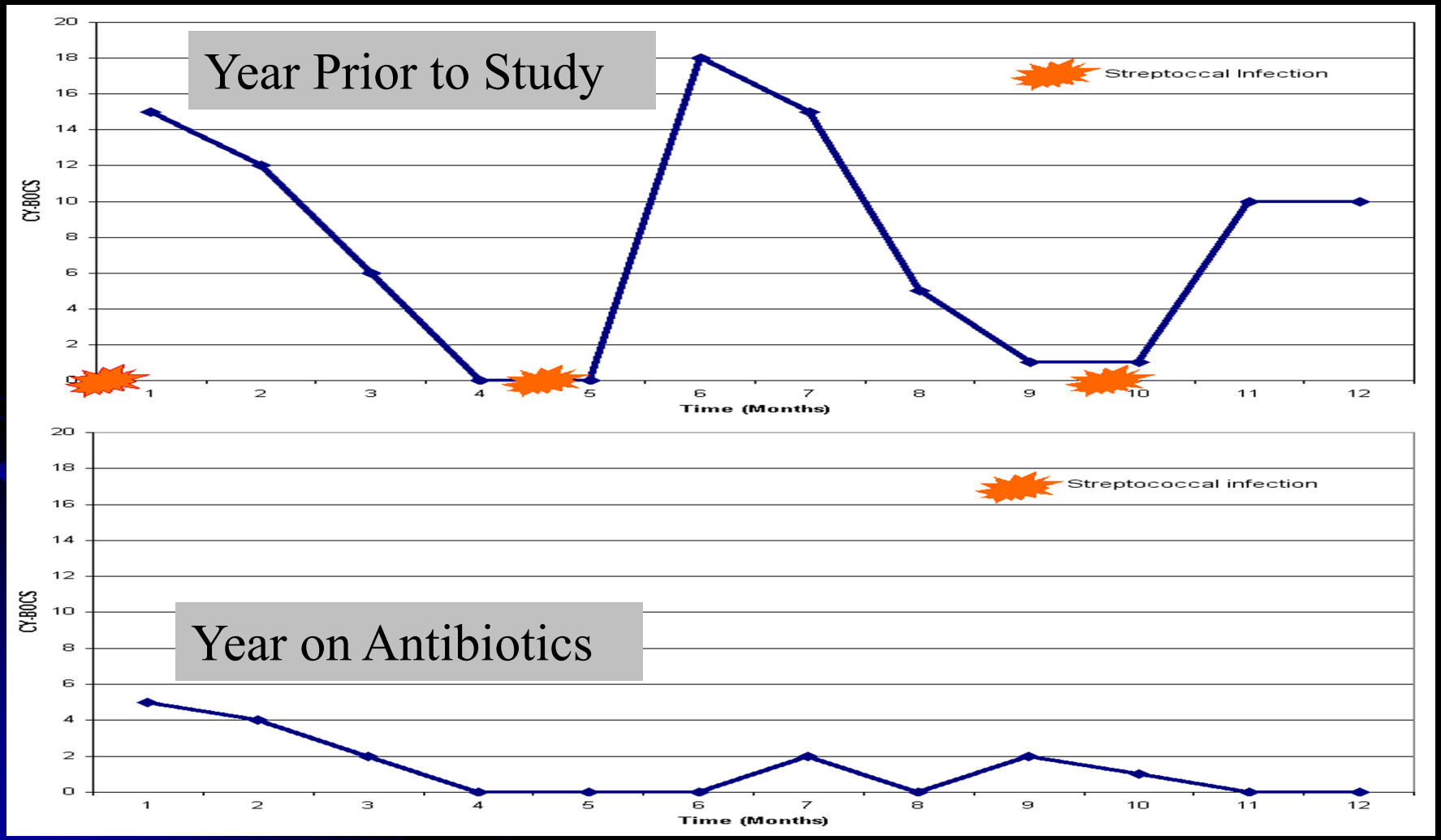


Antibiotic Choices

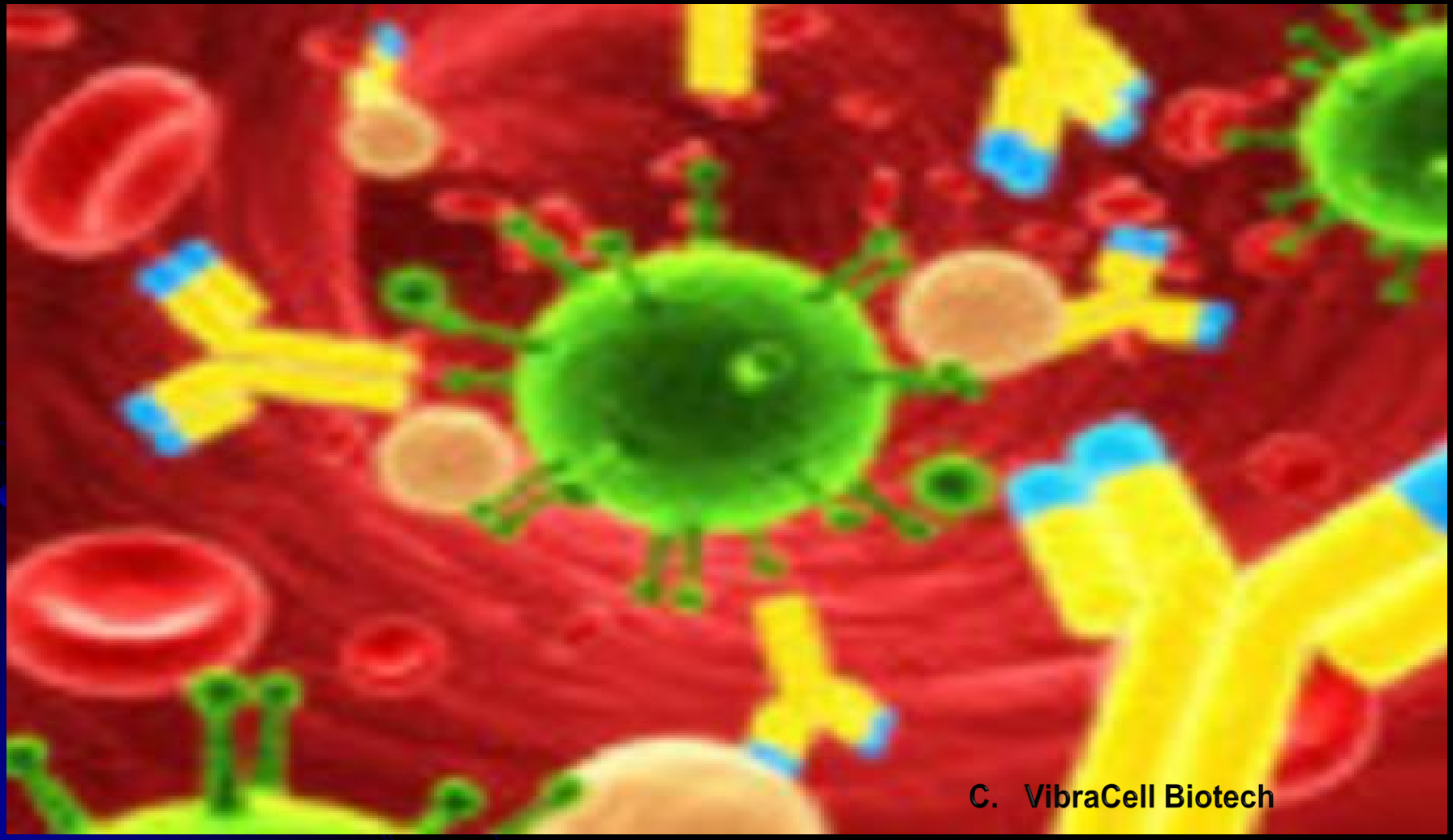
- Beta-lactam antibiotics might be particularly useful: found to promote glutamate transporter GLT1 which may have a neuro-protective role.
- Augmentin: clavulinic acid crosses BBB has has anxiolytic & anti-depressive properties in rodents and non-human primates.
- Macrolides: anti-inflammatory effects well-demonstrated but resistant strains of GrA strep; but does not cross BBB.
- Minocycline & doxycycline have immunomodulatory effects

- Responses often dramatic, within days but more typically within 2 weeks.
- Some centers recommend changing to another antibiotic if not responsive [Stanford].
- Patients often respond better to one antibiotic better than another.
- Length of treatment unknown, but often more than one year.
- Some patients completely cured
- However, many are improved but still have symptoms

Effectiveness of Antibiotic Prophylaxis **



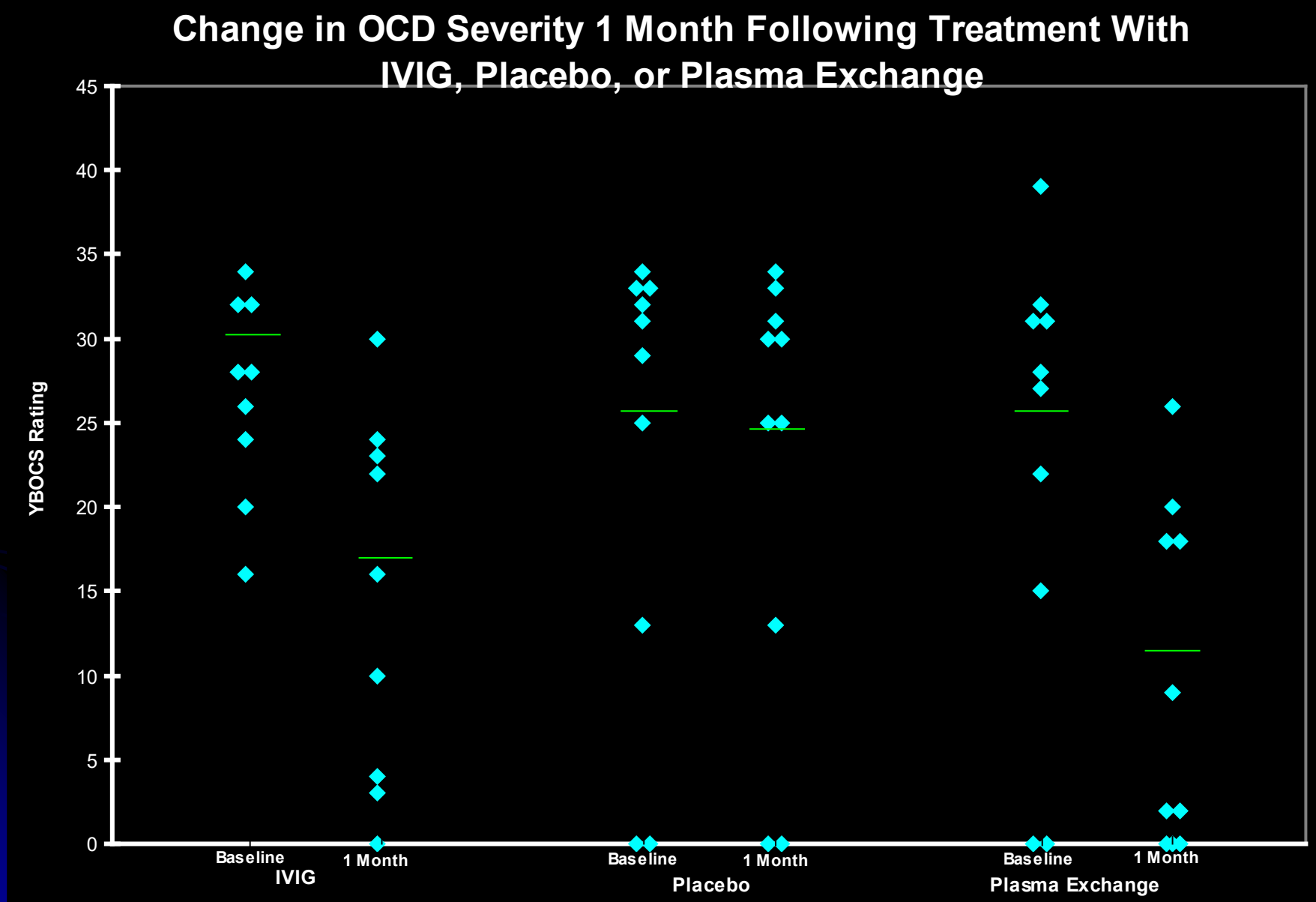
Can Immunomodulatory Therapy Reduce Clinical Symptoms?



Group A Streptococcus Intranasal Infection promotes CNSInfiltration by Strep-specific Th17

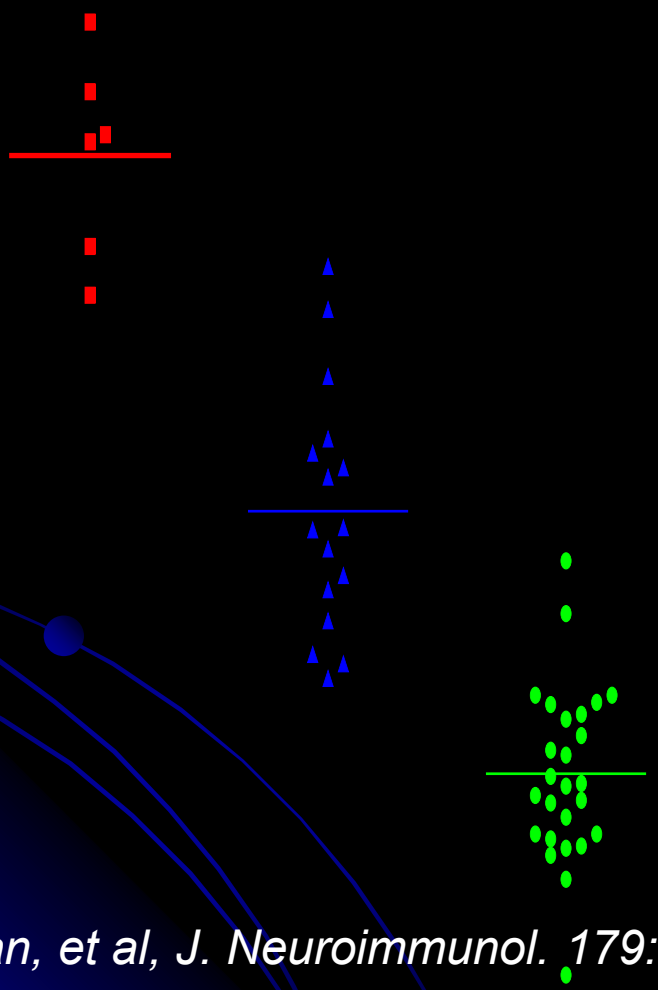
Dilepan T et al J. Clin Investigation 126: 303-317

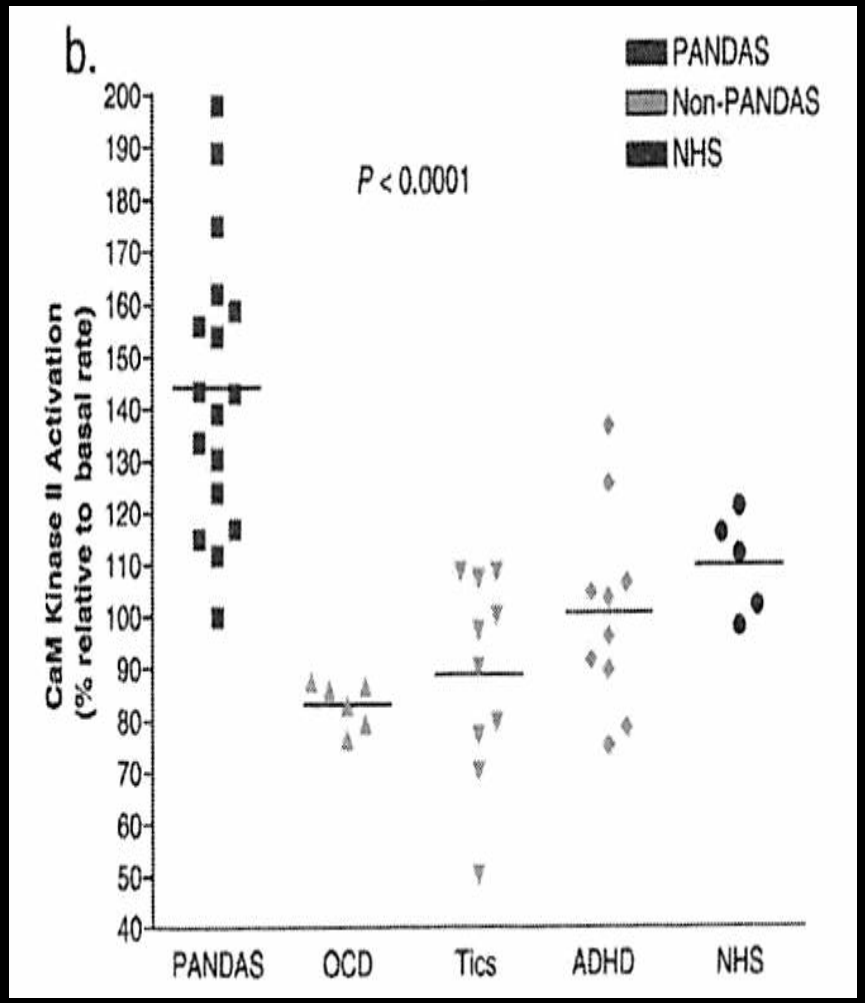
- Previous demonstration of brisk TH17 response in NALT tissue in mouse models nasally infected with Group A strep
- Identified GAS specific TH17 cells in tonsillar tissues and then used a mouse model.
- Nasal innoculated mouse model repeatedly demonstrated migration of GAS-specific TH 17 cells into the brain, BBB breakdown, IgG deposition, microglial activation and no evidence of bacteria in tissue.



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

CAM Kinase II Activity

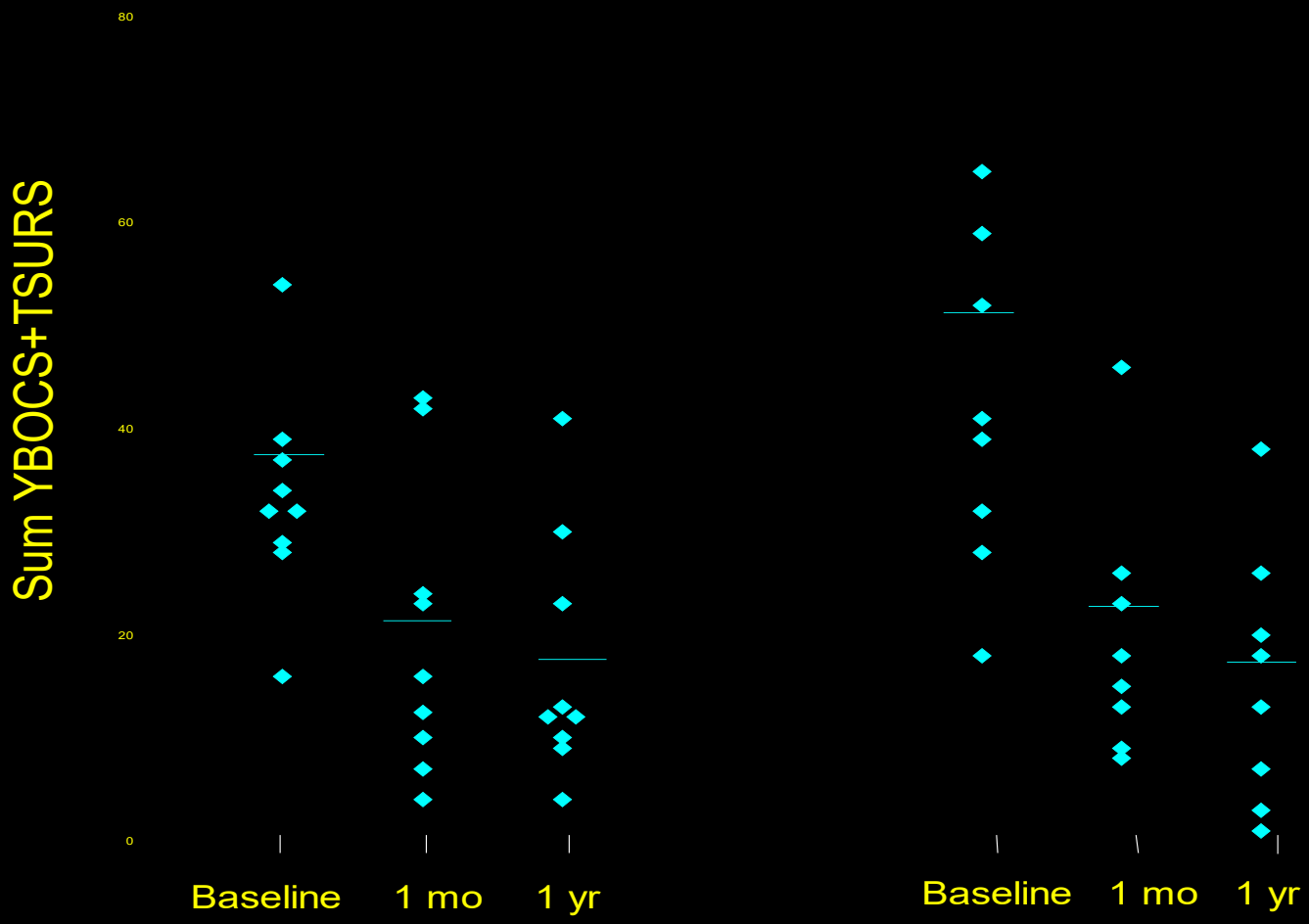




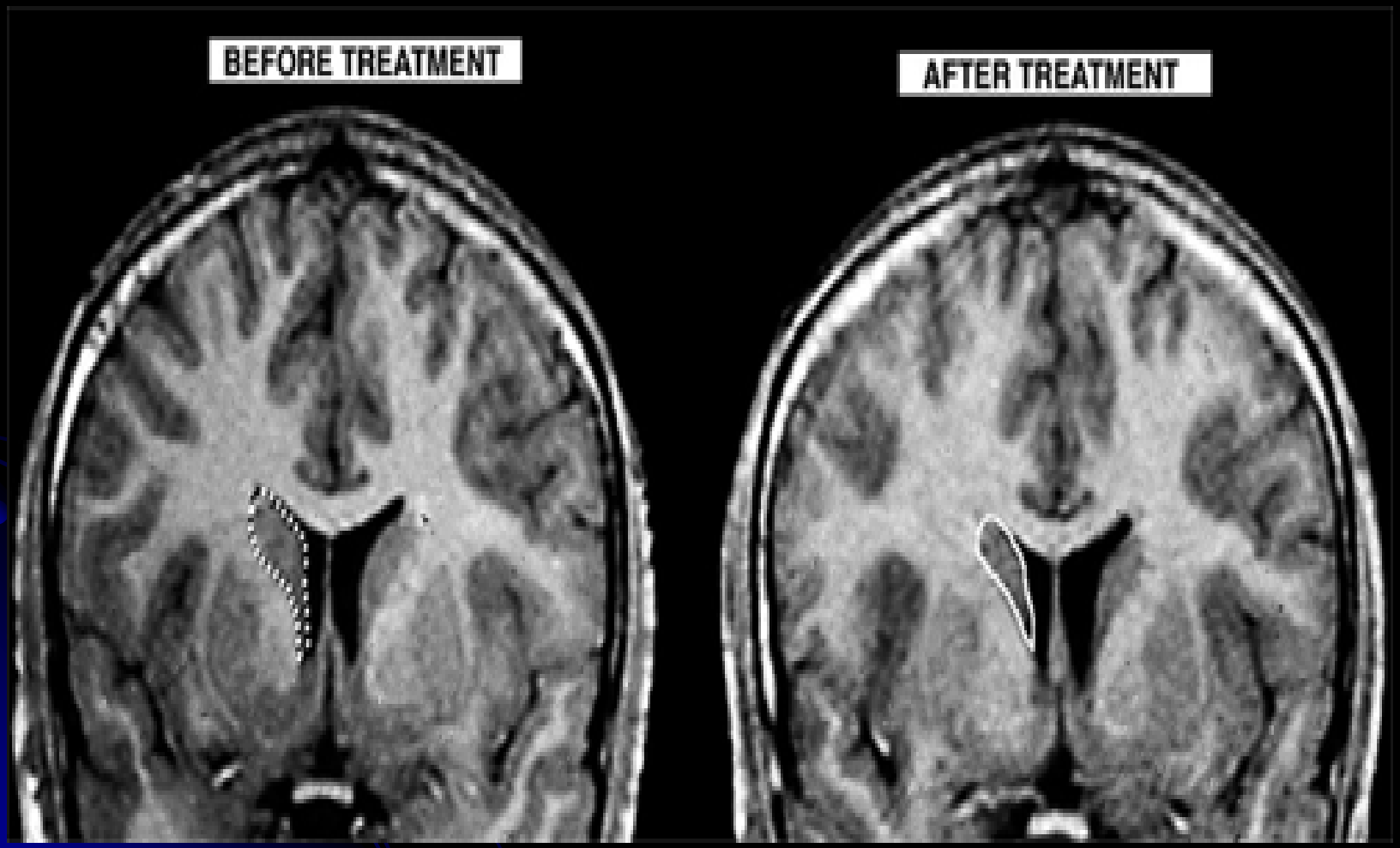
Kirvan, et al, J. Neuroimmunol. 179: 173-179

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

Small Study Suggesting Prolonged Effect



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.*



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

Other Immune Modulatory Measures

- High dose IV Steroids
- Plasmaphoresis
- Cell Cept
- Rituximab
- Sinus Surgery/T&A

- Journal of Child and Adolescent PsychopharmacologyVol. 27, No. 7 Guidelines
- **Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies**
- Frankovich Jennifer
- , Swedo Susan
- , Murphy Tanya
- , Dale Russell C.
- Hornig Mady
- , Chugani Harry
- , Sanger Terence
- , Muscal Eyal
- , Pasternack Mark
- , Cooperstock Michael
- , Gans Hayley
- , Zhang Yujuan
- , Cunningham Madeleine

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; auto-immunity?
- What is the role of tonsillectomy/adenoidectomy?
- Are there Biofilms and could it be driving an inflammatory response?
- Grant to study IVIG on biomar-kers; correlate with psychometric and clinical measurements?

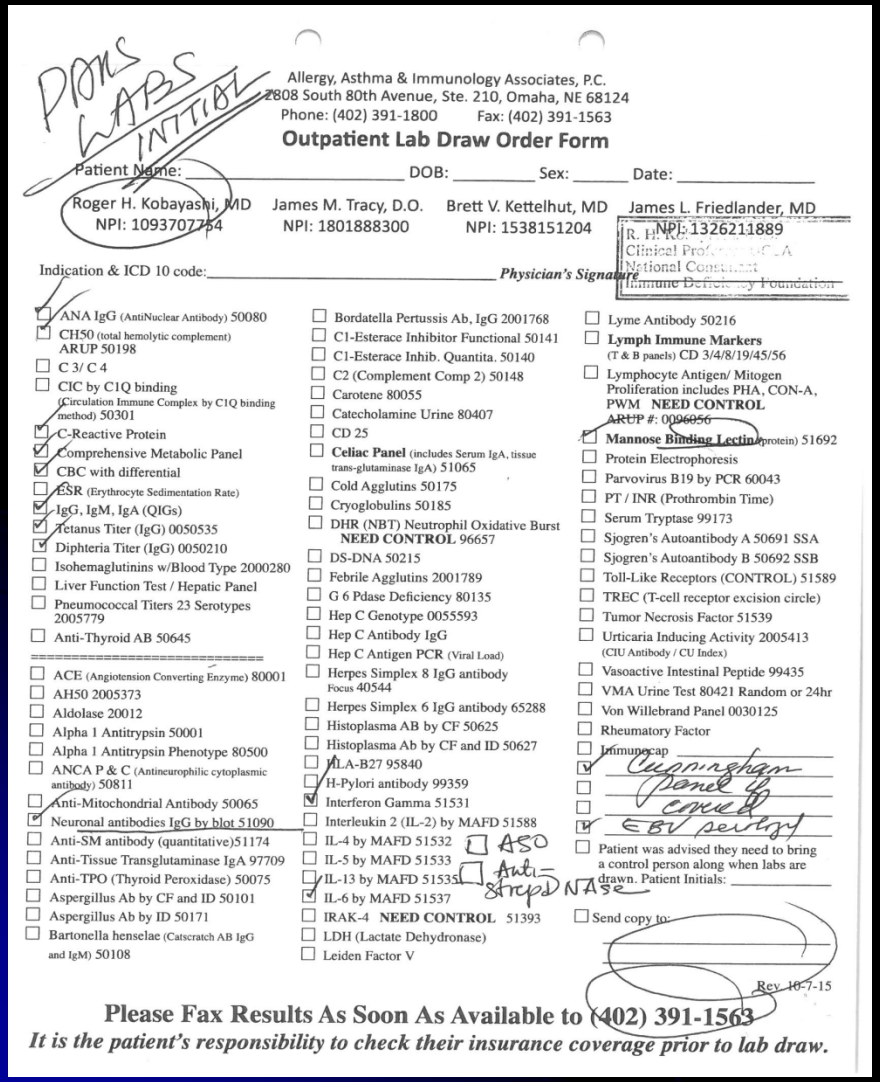
- **Why Would We Want to See These Children?**
- **The answer is quite simple really: "Kodomo no tame ni"**

What We Try to Do

- Have records and labs sent before you see.
- Evaluate carefully from and immune/ auto-immune/infection 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?]

Laboratory Studies & Follow Up Questionnaire



PANS LABS INITIAL

Allergy, Asthma & Immunology Associates, P.C.
2808 South 80th Avenue, Ste. 210, Omaha, NE 68124
Phone: (402) 391-1800 Fax: (402) 391-1563

Outpatient Lab Draw Order Form

Patient Name: _____ DOB: _____ Sex: _____ Date: _____

Roger H. Kobayashi, MD NPI: 1093707754 | James M. Tracy, D.O. NPI: 1801888300 | Brett V. Kettelhut, MD NPI: 1538151204 | James L. Friedlander, MD NPI: 1326211889

R. H. Kobayashi, MD, FACAAI, FAAAAI
Clinical Professor, UCLA
National Consultant
Immune Deficiency Foundation

Indication & ICD 10 code: _____ *Physician's Signature*

- ☐ ANA IgG (AntiNuclear Antibody) 50080
- ☑ CH50 (total hemolytic complement) ARUP 50198
- ☐ C 3/ C 4
- ☐ CIC by C1Q binding (Circulation Immune Complex by C1Q binding method) 50301
- ☑ C-Reactive Protein
- ☑ Comprehensive Metabolic Panel
- ☑ CBC with differential
- ☐ ESR (Erythrocyte Sedimentation Rate)
- ☑ IgG, IgM, IgA (QIGs)
- ☑ Tetanus Titer (IgG) 0050535
- ☑ Diphteria Titer (IgG) 0050210
- ☐ Isohemaglutinins w/Blood Type 2000280
- ☐ Liver Function Test / Hepatic Panel
- ☐ Pneumococcal Titers 23 Serotypes 2005779
- ☐ Anti-Thyroid AB 50645

==========

- ☐ ACE (Angiotension Converting Enzyme) 80001
- ☐ AH50 2005373
- ☐ Aldolase 20012
- ☐ Alpha 1 Antitrypsin 50001
- ☐ Alpha 1 Antitrypsin Phenotype 80500
- ☐ ANCA P & C (Antineurophilic cytoplasmic antibody) 50811
- ☐ Anti-Mitochondrial Antibody 50065
- ☑ Neuronal antibodies IgG by blot 51090
- ☐ Anti-SM antibody (quantitative)51174
- ☐ Anti-Tissue Transglutaminase IgA 97709
- ☐ Anti-TPO (Thyroid Peroxidase) 50075
- ☐ Aspergillus Ab by CF and ID 50101
- ☐ Aspergillus Ab by ID 50171
- ☐ Bartonella henselae (Catscratch AB IgG and IgM) 50108
- ☐ Bordatella Pertussis Ab, IgG 2001768
- ☐ C1-Esterace Inhibitor Functional 50141
- ☐ C1-Esterace Inhib. Quantita. 50140
- ☐ C2 (Complement Comp 2) 50148
- ☐ Carotene 80055
- ☐ Catecholamine Urine 80407
- ☐ CD 25
- ☐ **Celiac Panel** (includes Serum IgA, tissue trans-glutaminase IgA) 51065
- ☐ Cold Agglutins 50175
- ☐ Cryoglobulins 50185
- ☐ DHR (NBT) Neutrophil Oxidative Burst **NEED CONTROL** 96657
- ☐ DS-DNA 50215
- ☐ Febrile Agglutins 2001789
- ☐ G 6 Pdase Deficiency 80135
- ☐ Hep C Genotype 0055593
- ☐ Hep C Antibody IgG
- ☐ Hep C Antigen PCR (Viral Load)
- ☐ Herpes Simplex 8 IgG antibody Focus 40544
- ☐ Herpes Simplex 6 IgG antibody 65288
- ☐ Histoplasma AB by CF 50625
- ☐ Histoplasma Ab by CF and ID 50627
- ☐ HLA-B27 95840
- ☐ H-Pylori antibody 99359
- ☑ Interferon Gamma 51531
- ☐ Interleukin 2 (IL-2) by MAFD 51588
- ☐ IL-4 by MAFD 51532 ☐ ASO
- ☐ IL-5 by MAFD 51533 ☐ Anti-Strep DNase
- ☐ IL-13 by MAFD 51535
- ☑ IL-6 by MAFD 51537
- ☐ IRAK-4 **NEED CONTROL** 51393
- ☐ LDH (Lactate Dehydronase)
- ☐ Leiden Factor V
- ☐ Lyme Antibody 50216
- ☐ **Lymph Immune Markers** (T & B panels) CD 3/4/8/19/45/56
- ☐ Lymphocyte Antigen/ Mitogen Proliferation includes PHA, CON-A, PWM **NEED CONTROL** ARUP #: 0096056
- ☑ **Mannose Binding Lectin** (protein) 51692
- ☐ Protein Electrophoresis
- ☐ Parvovirus B19 by PCR 60043
- ☐ PT / INR (Prothrombin Time)
- ☐ Serum Tryptase 99173
- ☐ Sjogren's Autoantibody A 50691 SSA
- ☐ Sjogren's Autoantibody B 50692 SSB
- ☐ Toll-Like Receptors (CONTROL) 51589
- ☐ TREC (T-cell receptor excision circle)
- ☐ Tumor Necrosis Factor 51539
- ☐ Urticaria Inducing Activity 2005413 (CIU Antibody / CU Index)
- ☐ Vasoactive Intestinal Peptide 99435
- ☐ VMA Urine Test 80421 Random or 24hr
- ☐ Von Willebrand Panel 0030125
- ☐ Rheumatory Factor
- ☐ Immunocap _____
- ☑ Cytomegalovirus
- ☐ Panel B
- ☐ Covid
- ☑ EBV serology

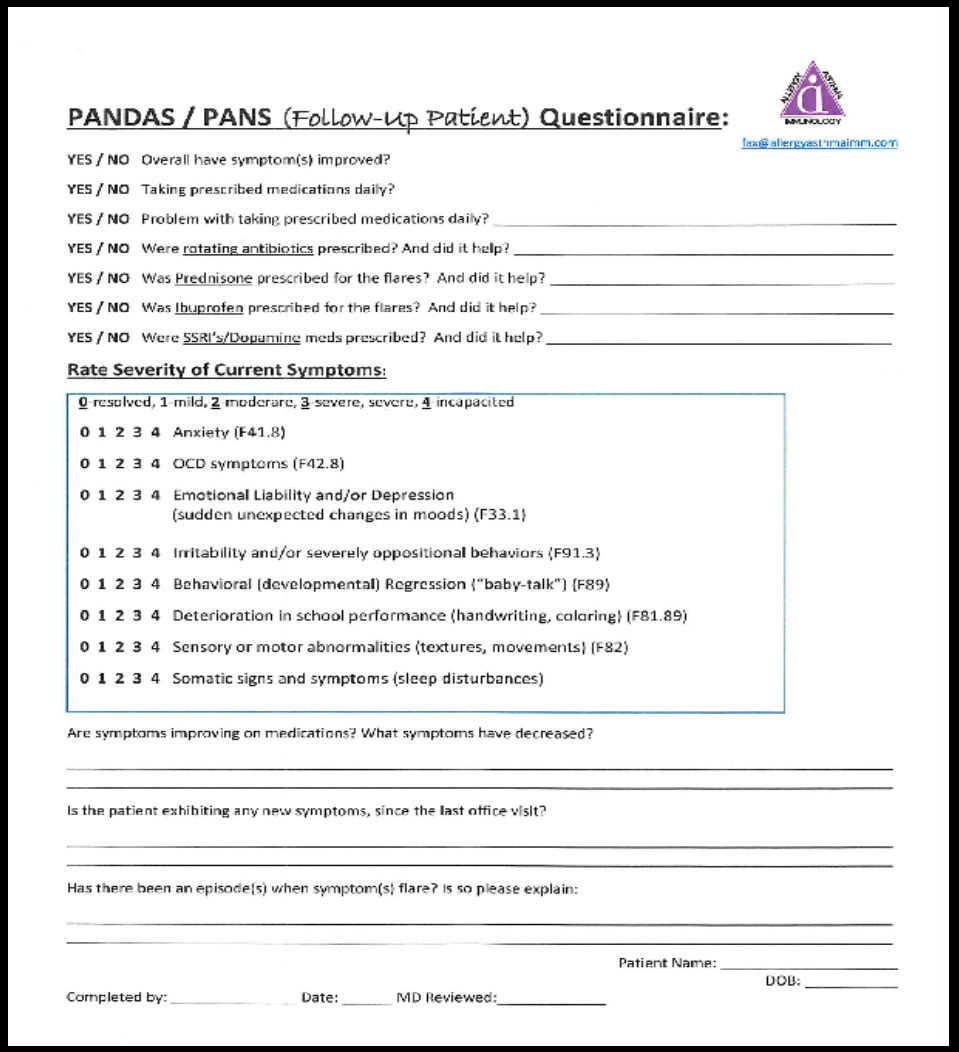
☐ Patient was advised they need to bring a control person along when labs are drawn. Patient Initials: _____

☐ Send copy to: _____

Rev. 10-7-15

Please Fax Results As Soon As Available to (402) 391-1563

It is the patient's responsibility to check their insurance coverage prior to lab draw.



PANDAS / PANS (Follow-Up Patient) Questionnaire:

fax@allergyasthmaimm.com

YES / NO Overall have symptom(s) improved?

YES / NO Taking prescribed medications daily?

YES / NO Problem with taking prescribed medications daily? _____

YES / NO Were rotating antibiotics prescribed? And did it help? _____

YES / NO Was Prednisone prescribed for the flares? And did it help? _____

YES / NO Was Ibuprofen prescribed for the flares? And did it help? _____

YES / NO Were SSRI's/Dopamine meds prescribed? And did it help? _____

Rate Severity of Current Symptoms:

0 resolved, 1 mild, 2 moderate, 3 severe, severe, 4 incapacited

- 0 1 2 3 4 Anxiety (F41.8)
- 0 1 2 3 4 OCD symptoms (F42.8)
- 0 1 2 3 4 Emotional Liability and/or Depression (sudden unexpected changes in moods) (F33.1)
- 0 1 2 3 4 Irritability and/or severely oppositional behaviors (F91.3)
- 0 1 2 3 4 Behavioral (developmental) Regression ("baby-talk") (F89)
- 0 1 2 3 4 Deterioration in school performance (handwriting, coloring) (F81.89)
- 0 1 2 3 4 Sensory or motor abnormalities (textures, movements) (F82)
- 0 1 2 3 4 Somatic signs and symptoms (sleep disturbances)

Are symptoms improving on medications? What symptoms have decreased?

_____

_____

Is the patient exhibiting any new symptoms, since the last office visit?

_____

_____

Has there been an episode(s) when symptom(s) flare? Is so please explain:

_____

_____

Patient Name: _____

DOB: _____

Completed by: _____ Date: _____ MD Reviewed: _____

moleculera labs

Cunningham Panel™ Testing Results

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

PATIENT REPORT

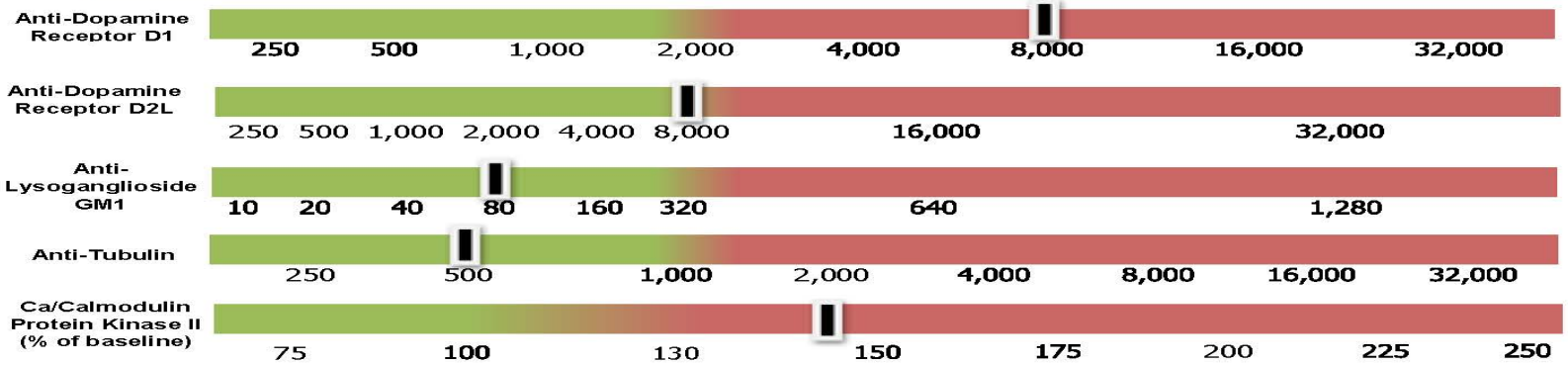
Submitting Prescriber: Doctor Name, MD
Date of Collection: MM/DD/YYYY
Date of Receipt: MM/DD/YYYY

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**

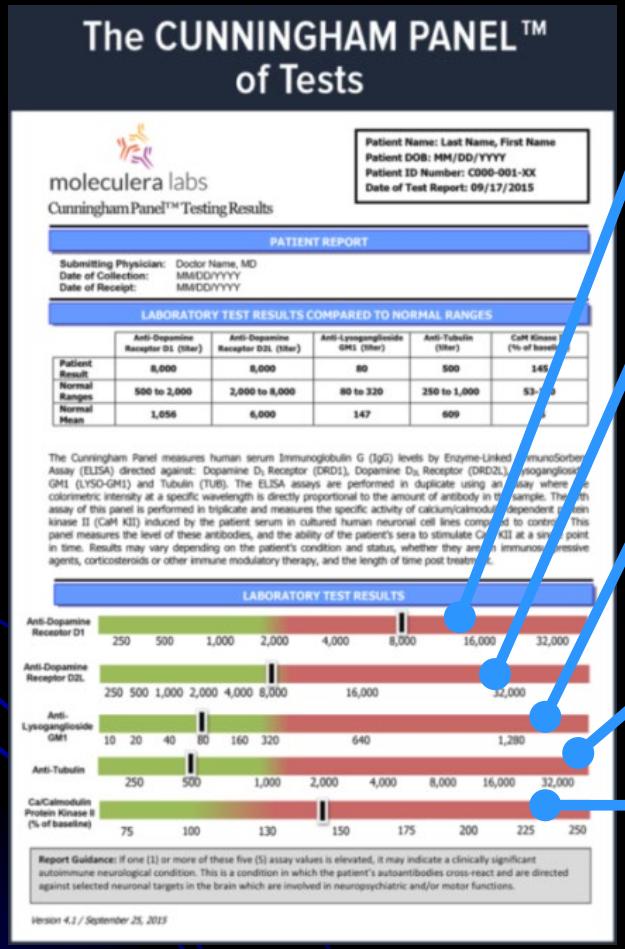
***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved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

The Cunningham Panel™ Test Results



The CUNNINGHAM PANEL™ of Tests

moleculera labs

Cunningham Panel™ Testing Results

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Version 4.1 / September 25, 2015

1) Anti-Dopamine D1

2) Anti-Dopamine D2L receptor

3) Anti-Lysoganglioside GM1

4) Anti-Tubulin

5) CaM KII Activity

Ref: (1) Reported by Dr. [illegible] 112 patients studied

Courtesy of Dr. C. Shimasaki

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

RESOURCES FOR PANS/PANDAS SUPPORT

- **NIH:** 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/**

- **State Groups:**
- NE:pandasnebraska@cox.net
- IA:iowapandas411@yahoo.com
- KS:kcareapandas@gmail.com
- MO:kristenmarsh1@hotmail.com

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

- Parents want their child to be well NOW
- Physicians need to consider that autoimmunity may cause psychiatric disease
- Who should treat PANS?
- Multi-specialty Approach Might Be Best
- Research must be done to delineate PANS and Determine Best Treatment
- Third Party Payers Need to Be Convinced That This Is A Real Disease
- “Ho’okahu ka ‘ilau like ana”

“That’s All Folks!"