The PANDAS Subtype of Childhood-onset Obsessive Compulsive Disorder: Continued Controversy? Or Case Closed?

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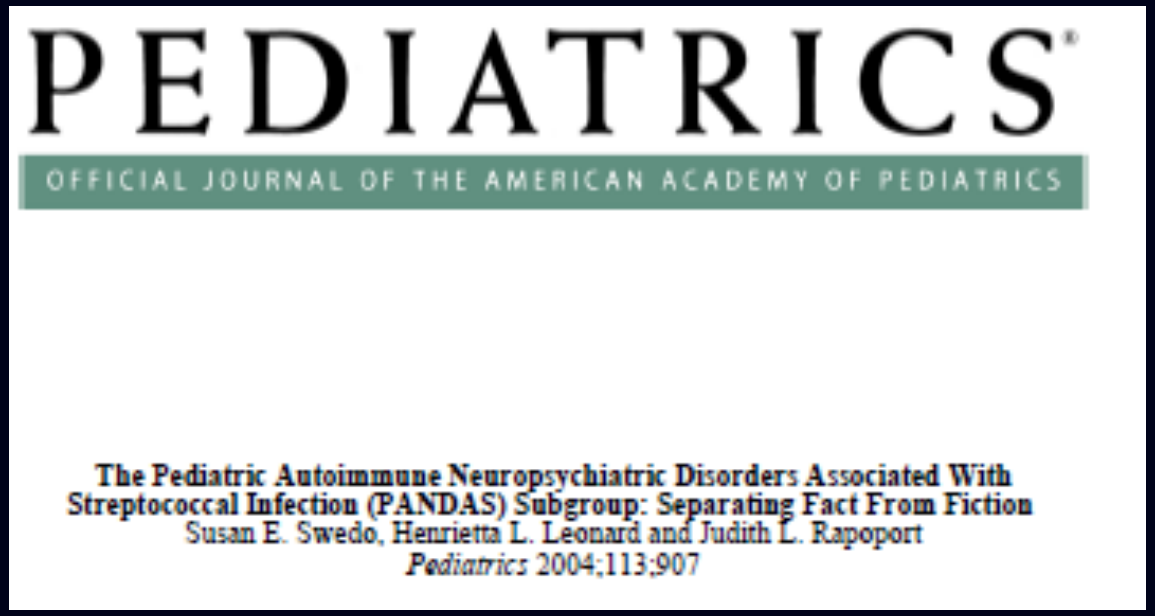
Nothing to declare or disclose.

NOTE: Grifols Therapeutics is providing the IVIG for Yale-NIMH trial described in presentation.

The Controversy Begins



The Controversy Continues

Pediatrics

INFECTIOUS DISEASES IN CHILDREN

PANDAS to CANS: Evolution of a controversial disorder

Little consensus exists on role of group A streptococcal infection in autoimmune/neurological phenomenon.

Infectious Diseases in Children, October 2012

The Need to Move beyond PANDAS

The concept of PANDAS has been the topic of intense debate and controversy for many years.[2-8] Historically, several re-

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MEDICAL PROGRESS

Moving from PANDAS to CANS

Harvey S. Singer, MD[1], Donald L. Gilbert, MD[2], David S. Wolf, MD, PhD[1], Jonathan W. Mink, MD, PhD[3], and Roger Kurlan, MD[4]

Swedo et al., Pediatr Therapeut 2012, 2:
http://dx.doi.org/10.4172/2161-0665.100011

Pediatrics & Therapeutics

Research Article Open Access

From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

Susan E. Swedo[1*], James F. Leckman[2] and Noel R. Rose[3]

Outline of Talk

- What is PANDAS?
  - Historical and clinical background
  - Clinical features & sources of "controversy"
- Evolution to PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)
- Lessons learned from PANDAS
  - Recognition and case management
  - Etiopathogenesis of post-streptococcal disorder
  - Identification of unique clinical cohort

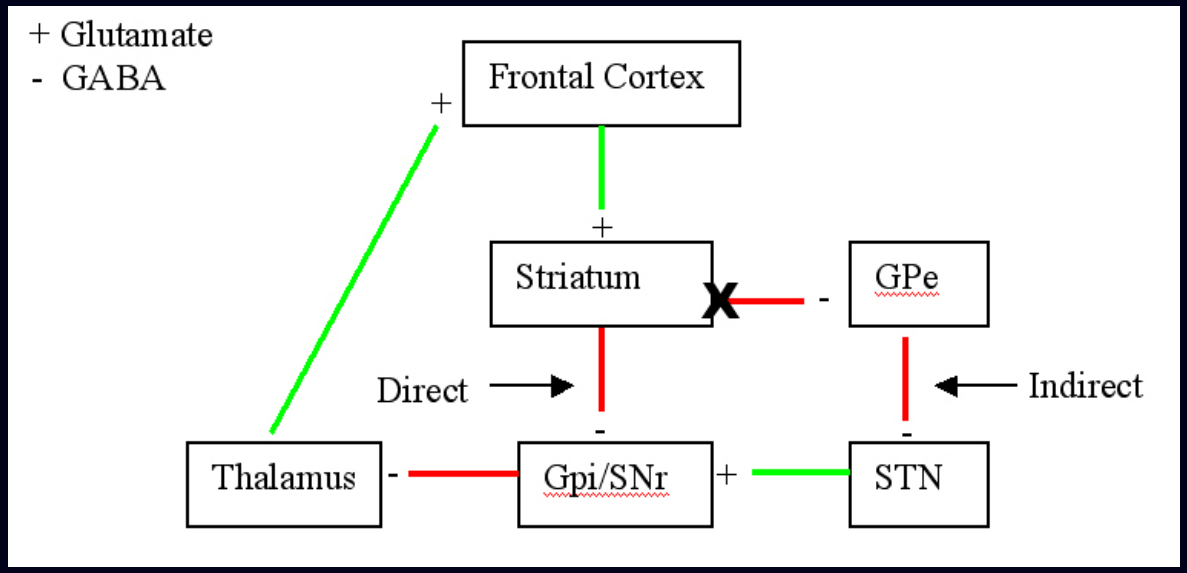
Context for Discovery of PANDAS Subgroup

Mid-1980's

- OCD was conceived to be result of "punitive toilet training and other harsh parenting practices"
- Search for medical model – Judy Rapoport (NIMH); Michael Rutter (London) and others for adult OCD.

  Orbital-frontal cortex(OFC)→basal ganglia→thalamus →OFC

  Sydenham chorea as best example for pediatric cases.



Sydenham chorea as a model of OCD/Tics

SYDENHAM CHOREA (SC)

- 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
- Choreiform movements present in 1/3 of children with OCD
- Episodic course, abrupt onset in some children with OCD
- Kiessling – Tic patients have antineuronal antibodies
- Young children with OCD/tic disorders exacerbate after streptococcal infections

The First Case of "PANDAS"

QR

- 8 y.o. male referred for Sydenham chorea
- Flailing arm movements and "dysarthria"
- Family history positive for rheumatic fever and Tourette disorder (older sibling – interesting hx)
- NIMH interview revealed handwashing; refusal to swallow his saliva; hoarding and other OC sx's
- Neurological exam – no chorea. Arm movements were repetitive - complex tic vs. compulsion.
- GAS positive at NIMH. Antibiotics and "Tincture of Time" reduced symptoms

PANDAS - Clinical Manifestations

- Extremely abrupt onset – differed greatly from typical gradual onset of OCD
- Relapsing-remitting symptom course
- Young age at onset

  6.5 $\pm$3.0 years for tics

  7.4 $\pm$2.7 years for OCD
- Boys outnumber girls - 2.6:1
- Comorbid tics and OCD common (65%)
- Other comorbid symptoms occur frequently

Comorbid Dx's and Symptoms in NIMH Sample

COMORBID DIAGNOSES

- ADHD – 40%
- ODD – 40%
- Depression – 36%
- Dysthymia – 12%
- Sep. Anxiety – 20%
- Overanxious – 28%
- Enuresis – 20%

SYMPTOMS DURING EXACERBATIONS

- Choreiform movements - 95%
- Emotional lability – 66%
- School changes – 60%
- Personality change – 54%
- Bedtime fears – 50%
- Fidgetiness – 50%
- Separation fears – 40%
- Sensory defensiveness – 40%
- Irritability – 40%
- Impulsivity /distraction – 38%

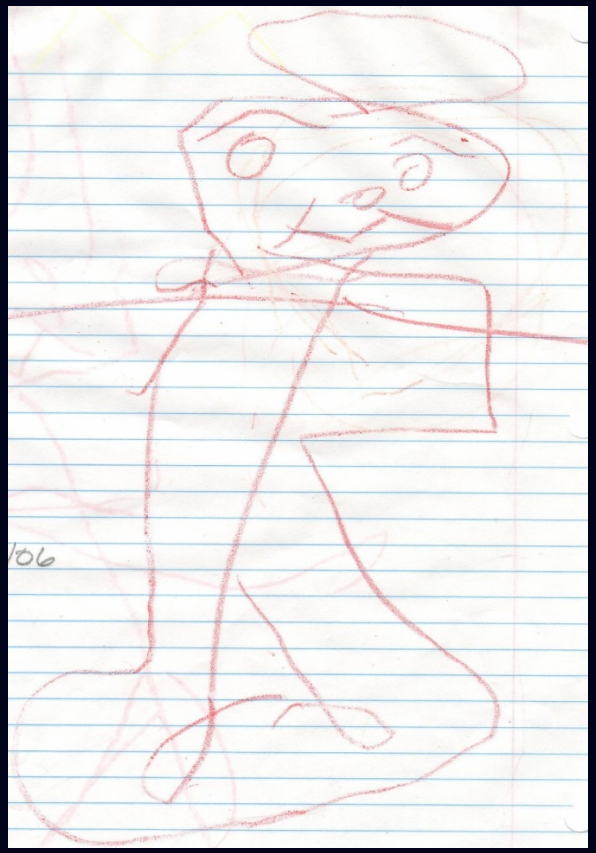
Am J Psychiatry 155:2 Feb 1998

Comorbid Symptoms of 108 Patients with PANDAS (from Miro Kovacevic, Hinsdale IL)

- Sleep disorders 84%
  Insomnia, night terrors, refusal to sleep alone
- Behavioral regression
  Separation anxiety (98%), baby tal k, tantrums
- Inability to concentrate 87%
- Hyperactivity, inattentiveness71%
- Aggressiveness 62%
- Learning difficulties 62%
- Eating disorder 17%
- Hallucinations 9%
- Terror stricken look (mydriasis) or Hyper-alert appearance 83%
- Urinary frequency, urgency, enuresis (night and daytime) 88%
- Deterioration in handwriting 89%
- Tics 72%
- Short-term memory problems62%
- Sensory hypersensitivity or insensitivity 39%

Behavioral Regression

Acute Illness



Convalescence

Criteria for PANDAS

I. Presence of OCD and/or Tic Disorder

II. Prepubertal onset

III. Acute (dramatic, abrupt) onset and episodic course (relapsing-remitting)

IV. Association with neurological abnormalities (choreiform movements)

V. Temporal relationship between symptom exacerbations and streptococcal infections

*Sources of controversy

Am J Psychiatry 155:2 Feb 1998

Basis for: *OCD and/or Tic Disorder*

- 2/3 patients had both OCD and tics
- Frequency of solitary tic disorders was same as that for OCD alone . However, OCD was generally more severe and impairing than tics.
- Problem: Overlap between tics and OCD.
- Problem: Difference in diagnostic work-up in neurologic and psychiatric clinics. (Also different patient populations)
- Problem: Overlap of tics with chorea, dystonia and other "movement disorders"

Basis for: *Prepubertal onset*

- Mean age at onset = 6.7 yrs
- Different presentations for boys with prepubertal onset of OCD (comorbity with tics & ADHD) vs. girls with peripubertal onset (comorbidity with depression & anxiety dx's)
- Epidemiologic evidence for GAS "resistance" by age 12 yrs in 98% of population
- Maximal homogeneity of subjects
- Problem: Post-pubertal cases "disproved" PANDAS hypothesis.

Basis for: *Acute onset and exacerbations*

- *Acute onset* – From first symptom to peak severity is generally less than 1- 2 days
  - Onset is "overnight", "sudden", "explosive"; exact date of onset is recalled
  - Exacerbations are equally sudden and dramatic
- *Episodic course* – Symptoms are relapsing and remitting, not waxing and waning.

- Problem: Acute onset was not included in AJP list of criteria
- Problem: Tourette syndrome also has an "episodic course" with numerous triggers for symptom exacerbations.

Basis for: *Association with neurological abnormalities (Choreiform movements)*

- **Choreiform movements present in 98% of pts during acute exacerbations and less often during remissions**
- **Patients did not demonstrate chorea. Tics could be easily separated from choreiform movements.**

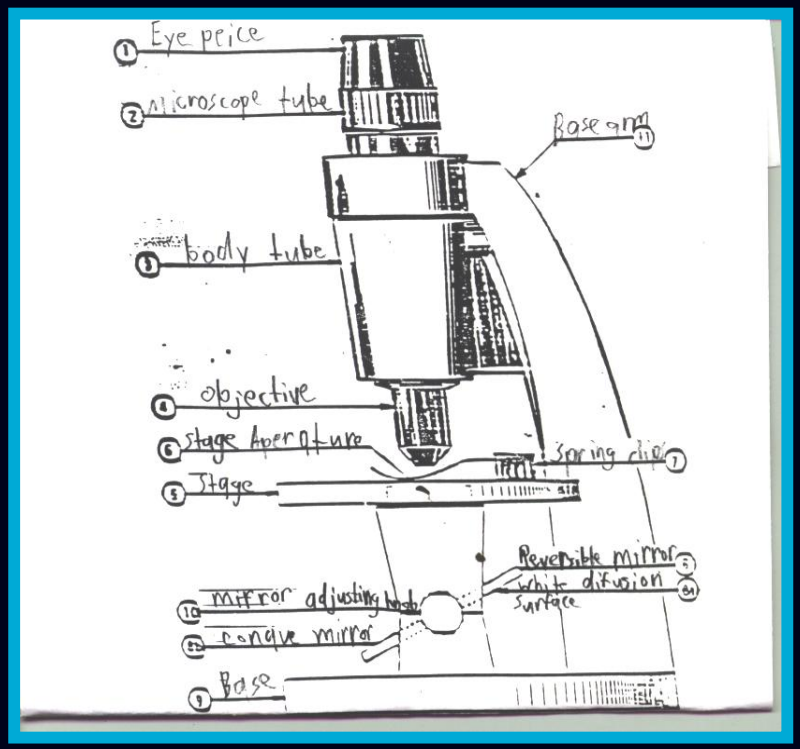
CONCLUSION: **Requiring presence of choreiform movements improves specificity without compromising sensitivity.**

PROBLEM: **Confusion of choreiform movements for chorea ("minimal chorea" defined in 2010).**

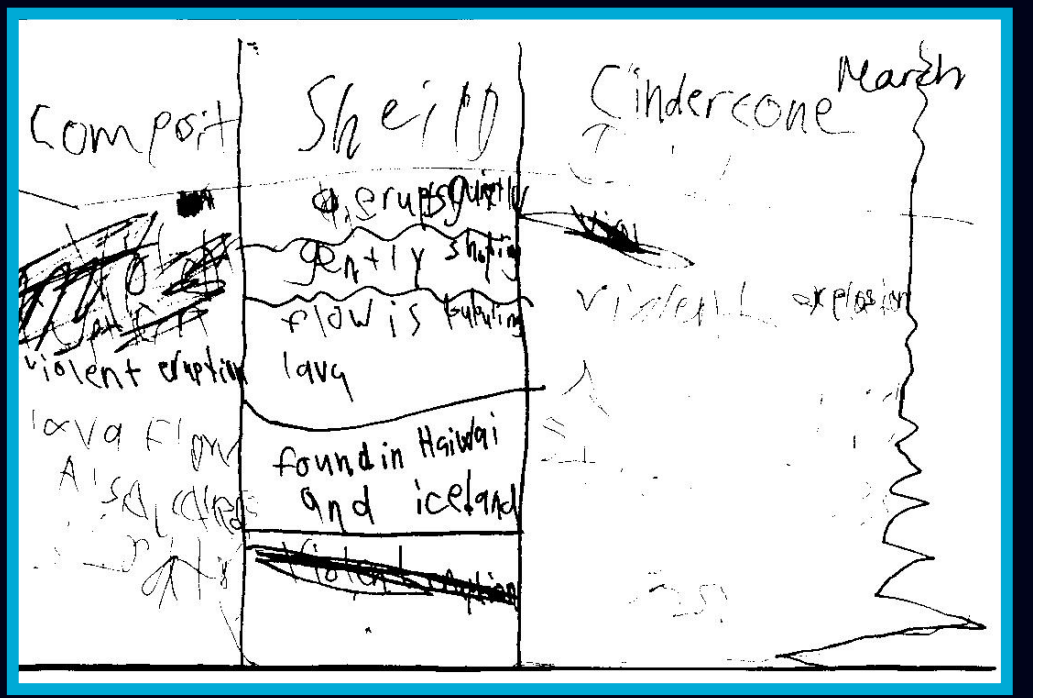
Association with neurological abnormalities

Handwriting changes correlated with increase in neuropsychiatric symptoms

BEFORE ACUTE ONSET OF TICS



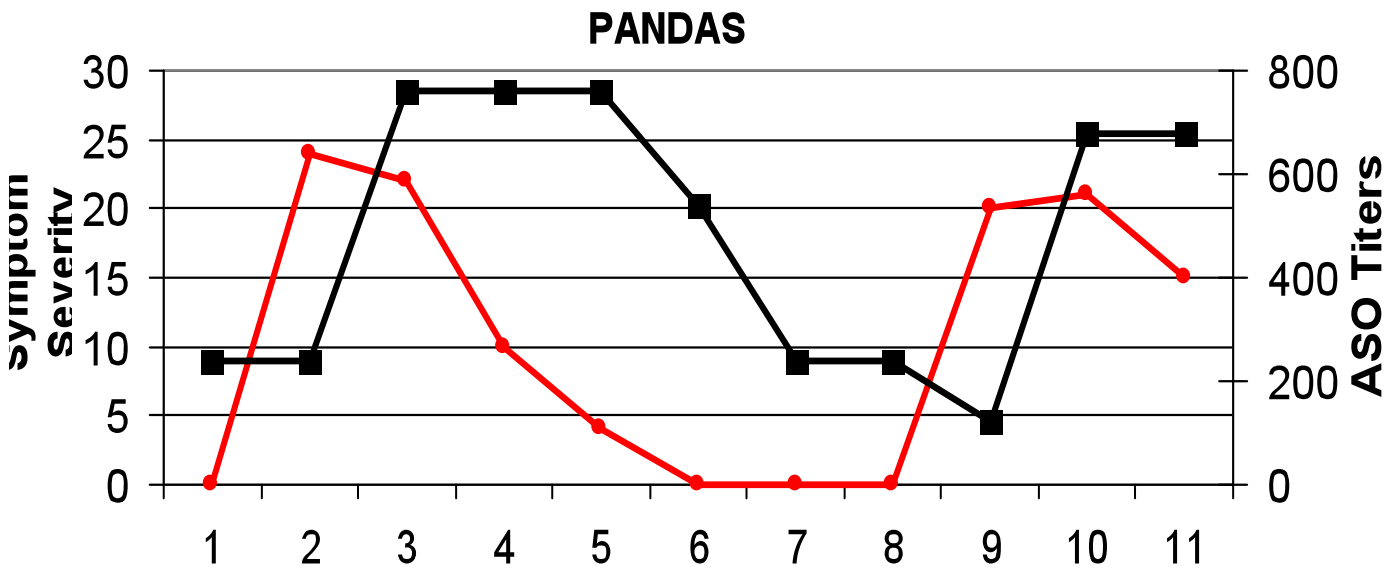
AFTER ONSET OF TICS



Basis for: *Temporal relationship between exacerbations and streptococcal infections*

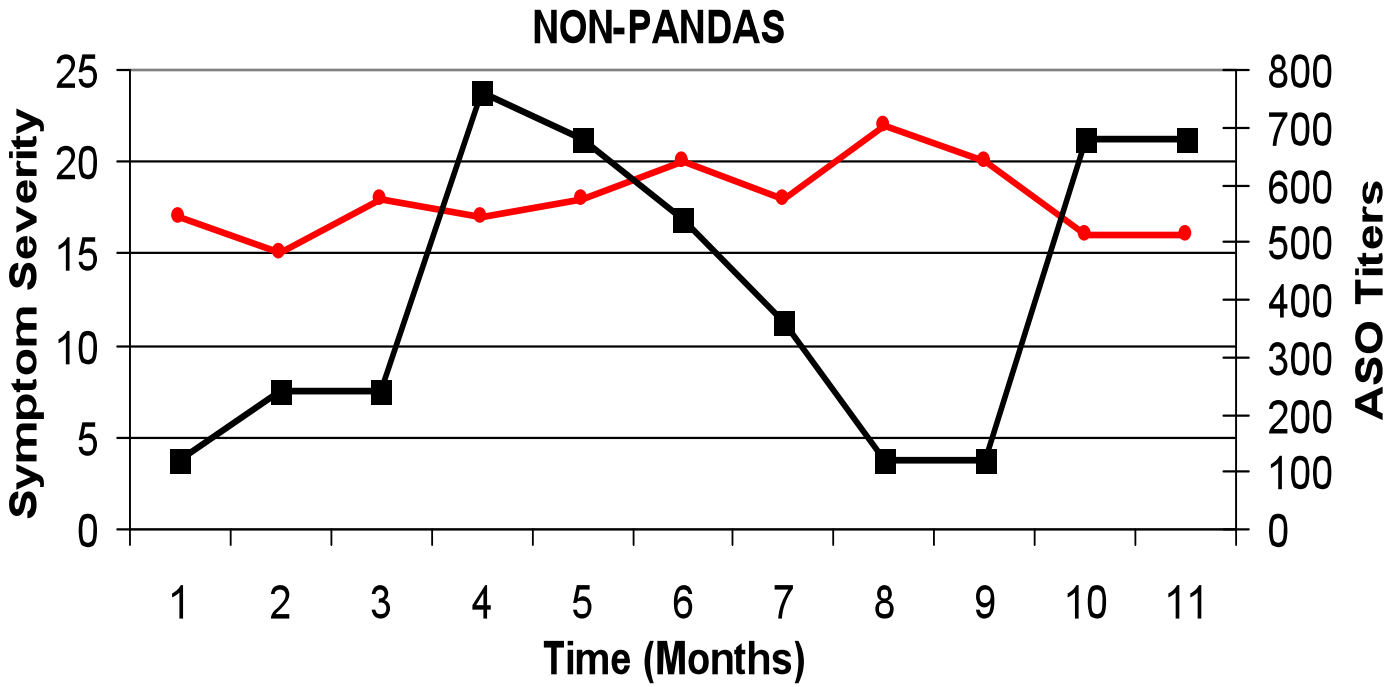
- **Sydenham chorea lags behind inciting GAS infection by 5-9 months; less for recurrences. No data for PANDAS, so criteria didn't specify timing**
- **Subsequent experience revealed GAS closely linked to exacerbations (as in index case)**
- **M. Murphy et al – resolution of OCD w/ Rx of GAS**

CONCLUSION: GAS+ (throat culture) at onset or exacerbations identifies unique subgroup of patients with target for intervention.



ASO TITER --

Y-BOCS ---



ASO TITER ---Y-BOCS ---

"Prospective Identification and Treatment of Children with PANDAS" *M. Murphy & M. Pichichero*

- 12 patients identified over 3 years period
- 7 boys & 5 girls presented with neuropsychiatric symptoms related to GABHS infections
  - 100% with OCD (3/4's were germ-related) and emotional lability
  - 58% (7/12) with urinary frequency or enuresis
  - 42% (5/12) with acute separation anxiety
  - 33% (4/12) with tics or handwriting changes
- Antibiotic treatment of GABHS infections reduced symptom severity in 5 – 21 days

Arch Ped Adolesc Med 2002;156:356-361

"Associated with Streptococcal infections"

Difficulties in establishing GAS – OCD association

- *Frequency of GAS infections confounds relationship*
  - GAS infections occur in 65-70% of grade-school aged children during school year
  - "Normal" titers = 440 for grade-school aged children
    - However, 440 is still a positive titer
    - Requirement for demonstrating two-fold titer rise needs to be met
    - Random titer measurements are useless – never a focus of treatment
- *Positive throat cultures in association with symptom exacerbation are spurious*
  - Carrier states "common" with rates as high as 15% cited. Actually, carriers are uncommon – 4-6%
  - "Asymptomatic" strep infections are common
- *Negative studies of two types:*
  - Failure to identify PANDAS cases accurately
  - Failure to assess relationship of GAS to OCD/tics

(e.g. Schrag et al, 2010)

Failure to Accurately Identify PANDAS Cases

1) **Prospective, longitudinal multi-site study of "PANDAS"**
   - Neurologic subjects followed prospectively for 2 years with monthly evaluations, including GAS cultures.
   - "No relationship between GAS infections and symptom exacerbations"
- HOWEVER:
   - "Published AJP 1998 criteria were used" without regard for acuity of onset and 90% had Tourette syndrome (chronic symptoms)
   - GAS infections were reported to LMD's (who then treated them)
   - Results actually showed a direct correlation between GAS infections and symptom exacerbations – but also saw exacerbations following viral infections and psychosocial stress

Kurlan, Johnson, Kaplan Pediatrics 2008

Leckman, King, …Kurlan JAACAP 2011

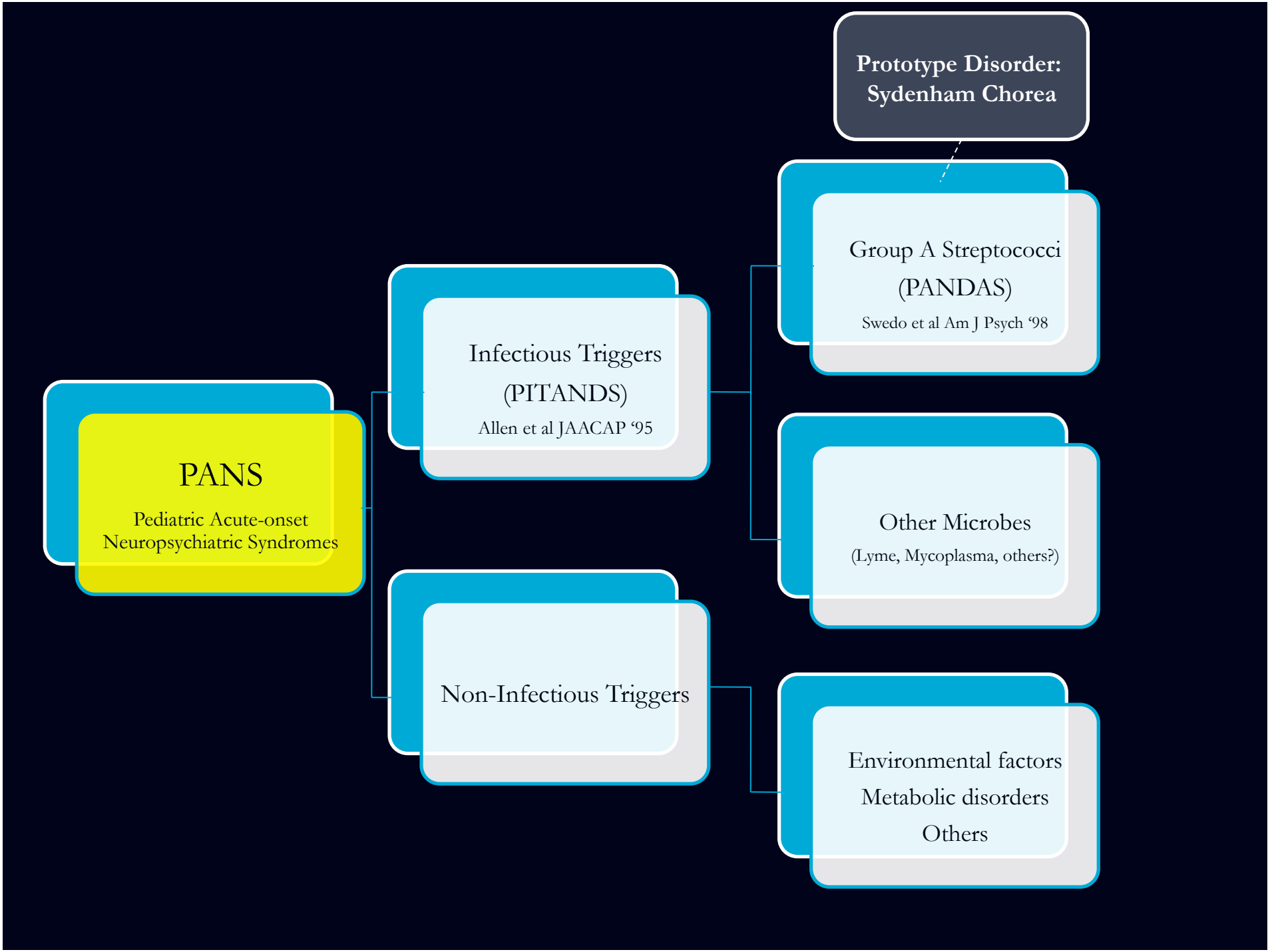
Failure to Accurately Identify GAS

2) "Streptococcal infection, Tourette syndrome and OCD: Is there a connection?"

"Results argue against a strong causal relationship between group A SIs and clinical symptoms of tics or OCD" Schrag et al, Neurology 2009

HOWEVER: Throat cultures and titers couldn't be used and the "cases" met only 1 of 5 PANDAS criteria: Subjects had OCD or tics.

- Pts were not pre-pubertal -- Age range: 2-25 years
- No mention of onset acuity or nature of clinical course
- "Temporal relationship" was set at **2 years** prior to OCD or tics
- "SIs" included **all** throat codes: e.g., "healthy tonsils", Staph, Viral & "Non-Strep" pharyngitis, as well as all pyodermas, including chancriform lesions.


PANS
Pediatric Acute-onset Neuropsychiatric Syndromes
Infectious Triggers (PITANDS)
Allen et al JAACAP '95
Non-Infectious Triggers
Prototype Disorder: Sydenham Chorea
Group A Streptococci (PANDAS)
Swedo et al Am J Psych '98
Other Microbes
(Lyme, Mycoplasma, others?)
Environmental factors
Metabolic disorders
Others

PITANDS

Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders

- Series of cases with:
  - Acute, dramatic onset
  - Significant comorbidity
  - Preceding infections
    - Group A streptococci
    - Influenza A
    - Varicella (chickenpox)
- Subsequent reports of OCD associated with:
  - Mycoplasma
  - Lyme disease
  - H1N1


Case Study: A New Infection-Triggered, Autoimmune Subtype of Pediatric OCD and Tourette's Syndrome

ALBERT J. ALLEN, M.D., PH.D., HENRIETTA L. LEONARD, M.D., AND SUSAN E. SWEDO, M.D.

ABSTRACT

DRAFT Criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

I.	Abrupt, dramatic onset or recurrence of obsessive-compulsive disorder (Eating disorders may be an alternate manifestation of OCD and are counted here)
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly acute onset, from at least two of the following seven categories (see text for full description):
	1. Anxiety
	2. Sensory or motor abnormalities
	3. Behavioral (developmental) regression
	4. Deterioration in school performance
	5. Emotional lability and/or depression
	6. Urinary symptoms
	7. Sleep disturbances
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. Note: The diagnostic work-up for PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

PANS – Expected Presentation

- Acute symptom onset – "foudroyant"
- OCD (or Eating Disorder) **PLUS**
  - Separation anxiety, panic, other anxiety sx's
  - Emotional lability and irritability
  - Behavioral regression
  - Urinary frequency, urgency, secondary enuresis
  - Academic difficulties – memory, concentration, hyperactivity
  - Motoric and/or sensory abnormalities

PANDAS/PANS Eating Disorders

- Classic anorexia is rare, but does occur (SC pts)
- More commonly, restricted eating is secondary to OCD sx's. Once weight loss exceeds 10-15% of body weight, body dysmorphia may develop
- Obsessional fears linked to eating restrictions:
  - Contamination fears – poison, fats, excess calories
  - Fear of choking, vomiting, others
  - Guilt/scruplosity – "don't deserve to eat"
- **SWALLOWING STUDY MAY BE INDICATED.**

PANS Diagnostic Instrument

- Collaboration between NIMH and Yale Child Study Center
- Parent Questionnaire/Clinician Interview
  - Acuity of onset/potential triggers
  - OCD (or eating disorder) (0-25)
  - Additional neuropsychiatric symptoms (0-25)
  - Degree of impairment (0-50)
- Rate severity of symptoms for
  - Week prior to PANS onset
  - Week of onset (and currently)

PANS/PANDAS Medical Work-Up

- Physical examination for occult infections (adenoids and tonsils, sinuses, urethra, anus)
- Look for choreiform movements and rule-out rheumatic fever
- Test for GAS infections
  - Only detectable with adequate swab and culture
  - Gold standard: throat culture plated for 48 hours
  - Rapid strep test from separate (adequate) swab
  - Nasopharyngeal culture may be necessary

PANS/PANDAS Lab Tests

- Obtain blood for anti-strep titers if onset <1 week (will need second set in 4-6 weeks)
  - ASO
  - Anti-strep DNAse B
  - ACHO
- Antinuclear antibody titers (+ in 56% of pts)
- Others – e.g., Madeleine Cunningham titers

PANS/PANDAS Crisis Management

- Treatment with antibiotics for 3-4 weeks?
  - If so, use narrowest spectrum possible
  - Trial underway at Harvard & Univ South FL - Tampa
- Psychotropic medications - **START LOW & GO SLOW!**
  - SSRI's
  - Major tranquilizers/antipsychotics
  - Anxiolytics?
  - Melatonin or soporific agents?