PANDAS (and PANS): Are Contamination Fears Justified in Pediatric OCD?

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Nothing to declare or disclose.
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections

Perhaps a better name? Post-streptococcal autoimmune encephalitis (of the basal ganglia)
The Need to Move beyond PANDAS

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

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

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Moving from PANDAS to CANS

Harvey S. Singer, MD1, Donald L. Gilbert, MD2, David S. Wolf, MD, PhD1, Jonathan W. Mink, MD, PhD3, and Roger Kurlan, MD4
PANS (CANS)
Pediatric (Childhood)
Acute-onset Neuropsychiatric Syndromes

Infectious Triggers (PITANDS)
Allen et al JAACAP ’95

Group A Streptococci (PANDAS)

Other Microbes
(Lyme, Mycoplasma, others?)

Non-Infectious Triggers

Environmental factors
Metabolic disorders
Others

Prototype Disorder: Sydenham Chorea
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
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) and Michael Rutter (London); Others for adult OCD.

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

Sydenham chorea as best example for pediatric cases.
Sydenham Chorea

- Sydenham chorea (SC) is the neurologic manifestation of ARF.
  - Lag-time between inciting GAS infection and symptom onset is 3 – 9 months for SC
  - 45-70% of SC patients do NOT have carditis
- Acute rheumatic fever (ARF) is accepted as a post-GAS illness and requires anti-GAS prophylaxis
- Etiologic mechanism is unknown but postulated to be related to molecular mimicry.
SYDENHAM CHOREA

Adventitious, choreoathetoid involuntary movements (often released by voluntary actions)

Muscle weakness (can proceed to chorea molle)

Failure to sustain tetanic contractions (milkmaid’s grip and snakelike tongue)
Model of Etiopathogenesis for Rheumatic Fever (Sydenham Chorea)

Group A Streptococci → Genetically Susceptible Host → (Misdirected) Autoimmune Response → Molecular Mimicry → Carditis, Polyarthritis, E. Marginatum, Subcut. nodules, Chorea (SC)
Relationship of Sydenham Chorea to Obsessive-Compulsive Disorder

- 1894 -- Sir William Osler described “perseverativeness” of behavior in choreic children; parents reported “changed child”
- 1950’s & 60’s -- Increased “obsessional neurosis” among children with SC and adults with hx of SC during childhood
- 1989 –SC pts, (but not carditis pts) have OC symptoms (12/23 vs 0/14) with three SC pts meeting criteria for OCD
- 1994 & 2002 – Two prospective NIMH studies revealed OC symptoms in 75% of acutely ill pts with SC
- 1998 & 2005 – Brazil – 25-65% of SC pts had OC symptoms at initial episode (none in RF carditis). Follow-up revealed that 100% of children with multiple episodes had OCD.

In all SC cases: Obsessive-compulsive symptoms started 2-4 weeks BEFORE chorea began.
PANDAS – Clinical Presentation

Observations in 25% of 125 childhood-onset OCD and 50 children with “acute onset” OCD

- Extremely abrupt onset – differed greatly from typical onset of OCD
- Relapsing-remitting (not waxing-waning) course
- Young age at onset
  - 6.5 ±3.0 years for tics
  - 7.4 ±2.7 years for OCD
- Boys outnumber girls - 2.6:1
- Comorbid tics and OCD in 65% and always had additional comorbidity

(Am J Psych 98)
Criteria for PANDAS

I. Presence of OCD and/or Tic Disorder
II. Prepubertal onset
III. Acute onset and episodic course (relapsing-remitting, not waxing & waning)
IV. Association with neurological abnormalities (choreiform movements)
V. Temporal relationship between symptom exacerbations and GABHS infections

Am J Psychiatry, 1998
Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

- Acute symptom onset – “foudroyant”
- OCD (or Eating Disorder – 20%?) 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 with body image distortions and/or

- Restricted Eating secondary to OCD symptoms:
  - Contamination fears – poison, fats, excess calories
  - Fear of choking, vomiting, others
  - Guilt/scruplosity – “don’t deserve to eat”
  - Once weight loss exceeds 10-15% of body weight, body dysmorphia may develop

- SWALLOWING STUDY for dysphagia
PANDAS/PANS Comorbid Symptomatology
(200+ PANDAS Pts – NIMH & M. Kovacevic)

- Sleep disorders 80%
  - Insomnia, night terrors, refusal to sleep alone
- Behavioral regression
  - Separation anxiety (98%), baby talk, tantrums
- Inability to concentrate 90%
- Hyperactivity, inattentiveness 70%
- Aggressiveness 60%
- Learning difficulties 60%
- Eating disorder 20%
- Hallucinations 10%

- Terror stricken look (mydriasis) or Hyper-alert appearance 80%
- Urinary frequency, urgency, enuresis (night & daytime) 90%
- Handwriting deterioration 90%
- Tics 70%
- Short-term memory loss 60%
- Sensory hypersensitivity or insensitivity 40%
Handwriting changes correlate with increase in neuropsychiatric symptoms (& GAS infections)

BEFORE ACUTE ONSET OF TICS

AFTER ONSET OF TICS
Behavioral Regression

Acute Illness

Convalescence
PANDAS Model of Etiopathogenesis

Group A Streptococci → Genetically Susceptible Host

Molecular Mimicry

(Misdirected) Autoimmune Response → PANDAS OCD/Tics
Evidence that GAS is Etiologically Associated with PANDAS

- Clinical observations and epidemiologic studies
- Treatment of GAS reduces OCD/tic exacerbations
- Prevention of OCD/tics with antibiotics prophylaxis
- Cross-reactive Antibodies Correlate with OCD/tics
- Animal models
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Point Prevalences for Tics & Behavioral Problems in an Elementary School Population
GAS Infections Correlate with Abnormal Movements and Hyperactivity

- Tanya Murphy and colleagues at Univ FL
- In-person observations among 693 elementary school children revealed:
  - Direct correlation between + GAS throat cultures and
  - Presence of tics, adventitious movements and problem behaviors
  - Recurrence of GAS infections increased the risk.

  TK Murphy et al, Biol Psychiatry 2007
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Group A Streptococci
“Prospective Identification and Treatment of Children with PANDAS” M. Murphy & M. Pichichero, 2002

- 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

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Group A Streptococci
Antibiotics Prophylaxis in PANDAS

**IF**

- OCD/Tics are sequelae of GABHS infections (similar to Sydenham chorea)

**THEN**

- Prevention of GAS (antibiotics prophylaxis) should be effective in reducing exacerbations of OCD/Tics
Azithromycin vs. Penicillin Trial

- Double-blind, parallel-design study of azithromycin (500 mg q week) and penicillin (250 mg po bid)
- 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
Penicillin (PCN) vs. Azithromycin (Zith) Double-blind Controlled Trial

N = 22

- **Streptococcal Infections***
  - Year Prior to Study: 2.0/ subject
  - Study Year: 0.0/ subject

- **Exacerbations***
  - Year Prior to Study: 2.0/ subject
  - Study Year: .78/ subject
  *SAME RATE AS Kurlan, Gilbert et al., 2010

*T >5.25; p< 0.01 for both

Snider et al, 2002
Evidence that GAS is Etiologically Associated with PANDAS

- Clinical observations and epidemiologic studies
- Treatment of GAS reduces OCD/tic exacerbations
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Group A Streptococci
Model of Pathogenesis for PANDAS

- GABHS

  Susceptible Host

  Susceptibility Markers (e.g. D8/17)

- Abnormal Immune Response

  Clinical Manifestations
Host Susceptibility

In ARF/SC, 1 in 20 families vulnerable. In PANDAS, dual vulnerability to OCD/tic disorders and ARF
Questions Needing Answers

- **Neurologic**
  - Why the basal ganglia?
  - What is the brain antigen that is recognized?

- **Developmental – Why 4 – 8 years?**
  - Number and type of infectious exposures?
  - Unique aspect of brain during neurodevelopment?

- **Genetic – HLA subtyping underway**
  - Association w/ both OCD and RF for PANDAS
  - Relationship to autoimmune disorders
  - Other immune dysfunction?
Model of Pathogenesis for PANDAS

GABHS → Susceptible Host → Molecular Mimicry → (Misdirected) Autoimmune Response → Clinical Manifestations
PANDAS – Evidence for Autoimmunity

- **Local**
  - Identification of cross-reactive anti-streptococcal/antineuronal antibodies

- **Regional**
  - (Pathological reports from Sydenham chorea)
  - MRI - Volumetric changes in basal ganglia
  - PET evidence of caudate inflammation (Chugani)
  - Neuropsychological abnormalities

- **Systemic**
  - Serum Cytokine abnormalities
  - Effectiveness of immunomodulatory therapies
  - Animal models
MRI Evidence of Regional Inflammation

Giedd et al, 2000
Deficits of Executive Functions

BJ Casey et al, 2002
Antineuronal Antibodies in OCD/Tics

- Husby et al. – SC (not SLE) + anti-strep: antineuronal Abs
- 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 (tic patients).
- Hallett et al. – Serum from patients induces stereotypies in rats infused in basal ganglia
- Morshed et al. – Antibodies against striatum among patients; “control” sera also induces stereotypies
- Kirvan et al. – Cross-reactive antibodies found in sera of acutely ill PANDAS patients
- Singer et al. – Cross-reactive antibodies don’t distinguish “PANDAS” patients (Kurlan’s cohort) from other patients with tic disorders.
- Cunningham et al. – Acute vs convalescent sera from PANDAS and SC pts
CSF from Sydenham Chorea (SC) and PANDAS
Cross-Reactivity of GAS Antibodies
with Human Caudate Putamen Tissue

Anti-Lysoganglioside Antibodies in PANDAS Decrease in Convalescence

Subject 1

Subject 2

Subject 3

Lysoganglioside Titer

Lysoganglioside acute (A)
Lysoganglioside convalescent (C)
Induced CaM kinase II Activity

CaM Kinase II activation (% above basal rate)

SC PANDAS Non-PANDAS
Anti-Dopamine D2 Receptor Antibodies in PANDAS and Sydenham chorea

PANDAS  Sydenham chorea  TS/OCD  ADHD  Normal Controls
N=16  N=6  N=38  N=8  N=19

Titer

P=.036
P=.005
Antibodies (IgG) in Sydenham chorea, PANDAS and TS/OCD are Specific for the D2 Receptor Compared to the D1 Receptor.
Passive Transfer of Antibodies Produces PANDAS-like Symptoms

Production of symptoms by passive transfer fulfills the last of Witebsky’s criteria for establishing a disorder as “autoimmune”
Immunomodulatory Treatment Trial

IVIG vs. Placebo vs. Plasmapheresis

RANDOMIZATION

IVIG
N = 9

SHAM IVIG
N = 10

Plasmapheresis
N = 10
Change in OCD Severity 1 Month Following Treatment With IVIG, Placebo, or Plasma Exchange
Caudate Size in 14 y.o. Patient with OCD

BEFORE TREATMENT

AFTER TREATMENT

SWEDO & GIEDD, 1992
So...What does this mean for MY patients with OCD?
HISTORY IS KEY!

Child with PANDAS
1. Presence of OCD and/or Tic Disorder
2. Prepubertal onset
3. Acute onset and episodic course (relapsing-remitting)
4. Association with neurological abnormalities (choreiform movements)
5. Temporal relationship between symptom exacerbations and GABHS infections
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 (carditis, chorea, arthritis)
- 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

- Only useful to find “rising titers” which document recent GAS infection:
  - Obtain blood for anti-strep titers if onset <1 week (will need second set in 6-8 weeks)
    - ASO
    - Anti-strep DNase B
    - ACHO
- Antinuclear antibody titers (+ in 56% of pts)
- Others – e.g., Moleculara lab assay for cross-reactive titers and CAM II Kinase activity
PANS/PANDAS Medical Work-Up

- Swallowing study if obsessional symptoms re. vomiting, choking, etc or food restrictions
- Polysomnography for sleep disturbances
  - Failure to establish atony during REM sleep
  - Disruptions of sleep-wake architecture
- Electroencephalogram (EEG) to R/O encephalopathy – regional slowing
- Lumbar puncture to obtain CSF for lab assays, including assessment of antineuronal antibodies
PANS/PANDAS Acute Management

- Eradicate infection (3-4 weeks of antibiotics)
  - Cefdinir study completed by T. Murphy with + results
  - Azithromycin study underway
  - “Augmentin addicts” (dopaminergic and glutamatergic effects of clavulinic acid)

- Consider immunomodulatory therapy
  - Steroid burst (may also serve as diagnostic test)
  - Intravenous immunoglobulin (IVIG) for moderate-severe symptoms – single course of therapy often sufficient
  - Plasmapheresis for severe, life-threatening symptoms
PANS/PANDAS Case Management

- Cognitive behavior therapy (exposure w/ response prevention) – may not tolerate during acute illness
- Psychotropic medications - START LOW & GO SLOW!
  - SSRI’s
  - Major tranquilizers/antipsychotics
  - Anxiolytics (benzodiazepines?)
  - Melatonin or stronger sedative agents
  - Role for stimulants or antipsychotics??
- Antibiotics prophylaxis for PANDAS cases
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