Are Contamination Fears Justified in Obsessive Compulsive Disorder and PANDAS?

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Objectives of the Presentation
- Identify the five criteria for the PANDAS subgroup.
- Differentiate between PANDAS and other cases of childhood onset OCD.
- Describe the etiologic model for PANDAS, and the etiological role of group A streptococcal infections.
- Discuss the diagnostic criteria for PANS, and the relationship to PANDAS.
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

Obsessive Compulsive Disorder in DSM-5

- Presence of OBSESSIONS – repetitive, intrusive thoughts or concerns; and COMPULSIONS – mental or physical rituals performed repetitively in response to anxiety or compulsive urge
- Symptoms are seen as senseless, excessive, or unreasonable
- Symptoms cause marked distress, are time-consuming, and/or significantly interfere with normal routine, work/school functioning, and/or social relationships

fMRI scan of the Orbitofrontal-Striatal-Thalamocortical Circuit

Casey et al., 2002
Sydenham Chorea & OCD

- Historical reports suggested a link
- Retrospective study showed that obsessions and compulsions occurred in 2/3 children with SC
- Symptoms started 2–4 weeks before chorea began
- OC symptoms followed their own timecourse
- Other behavioral symptoms previously described in SC – emotional lability in 95% and irritability and/or aggressiveness in 80-90%

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 a post-streptococcal illness. (Gilbert 2009)
- Etiologic mechanism is unknown but postulated to be related to molecular mimicry.
Model of Etiopathogenesis for Rheumatic Fever (Sydenham Chorea)

- Group A Streptococci
- Genetically Susceptible Host
- Molecular Mimicry
- Abnormal Immune Response
- Carditis
- Polyarthritis
- E. Marginatum
- Subcut. nodules
- Chorea (SC)

Pediatric Autoimmune Neuropsychiatric Disorders Associated with 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
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

PANDAS - Clinical Manifestations

- Extremely abrupt onset – differed greatly from typical gradual onset of OCD
- Relapsing-remitting symptom 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 common (65%)
- Other comorbid symptoms occur frequently

Comorbid Dx’s and Symptoms in NIMH Sample

<table>
<thead>
<tr>
<th>COMORBID DIAGNOSES</th>
<th>SYMPTOMS DURING EXACERBATIONS</th>
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<tbody>
<tr>
<td>ADHD – 40%</td>
<td>Choreiform movements – 95%</td>
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<tr>
<td>ODD – 40%</td>
<td>Emotional lability – 66%</td>
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<tr>
<td>Depression – 36%</td>
<td>School changes – 60%</td>
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<tr>
<td>Dysthymia – 12%</td>
<td>Personality change – 54%</td>
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<tr>
<td>Sep. Anxiety – 20%</td>
<td>Bedtime fears – 50%</td>
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<tr>
<td>Overanxious – 28%</td>
<td>Fidgetiness – 50%</td>
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<tr>
<td>Enuresis – 20%</td>
<td>Separation fears – 40%</td>
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<tr>
<td></td>
<td>Sensory defensiveness – 40%</td>
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<tr>
<td></td>
<td>Irritability – 40%</td>
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<td>Impulsivity /distraction – 38%</td>
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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 talk, tantrums
- Inability to concentrate 87%
- Hyperactivity, inattentiveness 71%
- Aggressiveness 62%
- Learning difficulties 62%
- Eating disorder 17%
- Hallucinations 9%
- Terror-striken look (mydriasis) or Hyper-alert appearance 83%
- Urinary frequency, urgency, enuresis (night and daytime) 88%
- Deterioration in handwriting 89%
- Tics 72%
- Short-term memory problems 62%
- Sensory hypersensitivity or insensitivity 39%

Episodic Course is Associated with Adventitious Movements (Tics & Others)

Handwriting changes correlated with increase in neuropsychiatric symptoms

BEFORE ACUTE ONSET OF TICS

AFTER ONSET OF TICS

Difficulties with GAS in PANDAS

- Strep is common and “temporal association” is a true/true/unrelated finding
  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, but became clinical norm
    Treating titers
  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
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
  - HIN1

Prototype Disorder: Sydenham Chorea

Group A streptococci (PANDAS)

Infectious Trigger (PITANDS)

Other Microbes

Non-Infectious Trigger

Environmental factors

Mood disorders

Obsessive compulsive disorder

Susan E. Swedo, M.D.
DRAFT Diagnostic 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**

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

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**Using PANDAS as a Model of Etiology & Pathogenesis**

Strep. Bacteria → Genetically Susceptible Host → Abnormal Immune Response → PANDAS OCD/Tics

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**PANDAS – From Model to Data**

ANTIBIOTIC PROPHYLAXIS → Strep. Bacteria → Genetically Susceptible Host → Abnormal Immune Response → PANDAS OCD/Tics
Documentation of Etiologic Role for GAS in Rheumatic Fever

- **Direct Evidence**
  - GAS infection prior to rheumatic fever symptoms
  - Identification of “rheumatogenic” strains of GAS

- **Indirect Evidence**
  - Epidemiologic studies showed temporal relationship
  - Penicillin prophylaxis prevents recurrences
  - Rheumatic fever rates declined after antibiotic treatment of GAS pharyngitis became routine

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.

  Murphy et al, Biol Psychiatry 2007
**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*

**Antibiotics Prophylaxis in PANDAS**

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

*THEN*
- 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) Pilot Data

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: 0.78/subject

*SAME RATE AS KURLAN et al., 2010

*T > 5.25; p < 0.01 for both

Snider et al, 2002

Other Research & Opportunities

- Group A Streptococci as trigger
  - Ongoing research by Madeleine Cunningham
  - Others
- Mycoplasma
- Lyme
- Other etiologic triggers?
  - Vaccines
  - Impact of Reye syndrome and Aspirin ban?

Snider et al, 2002
PANDAS – Abnormal Immune Response

- Local
  - Identification of antineuronal antibodies
- Regional
  - Pathological reports from Sydenham chorea
  - MRI - Volumetric changes in basal ganglia
- Systemic
  - Serum Cytokine abnormalities
  - Effectiveness of immunomodulatory therapies

MRI Evidence of Regional Inflammation

Giedd et al, 2000

Deficits of Executive Functions

BJ Casey et al, 2002
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
- 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 from other patients with tic disorders.
- Cunningham et al. – Acute vs convalescent sera from PANDAS and SC pts

Kirvan & Cunningham: Cross-Reactive Antibodies

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Anti-Lyso-Ganglioside Antibodies in PANDAS Decrease in Convalescence

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Induced CaM kinase II Activity

Transfer of Antibodies Produces PANDAS-like Symptoms

Production of symptoms by passive transfer is the last of Koch’s Postulates.

The other five have also been met -- sufficient evidence to conclude that GAS plays an etiologic role in PANDAS.

Immunomodulatory Treatment Trial
Plasma Exchange vs. IVIG vs. Placebo
Handwriting Changes

BEFORE IVIG RX

AFTER IVIG RX

June 2006
Ongoing Research at NIMH

- Natural history study of PANDAS/PANS
- EEG – partial or other focal slowing
- Polysomnography – abnormalities of REM sleep
- Natural history study of acute-onset anorexia
- Treatment trial extension
- To refer patients: Rebecca Hommer or Precilla D’Souza at 301/496-5323

With Appreciation to Our Colleagues & Collaborators

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- Univ Oklahoma: M Cunningham
- Univ S Florida: T Murphy
- USC: P Levitt
- Yale University: H Grantz, R King, J Leckman

RESOURCES & REFERENCES

- NIMH Website – “PANDAS”
- International OCD Foundation (IOCDF) and PANDASnetwork.org