PANS / PANDAS
Pediatric Acute-onset Neuropsychiatric Syndrome / Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

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J. Owen Hendley Memorial Lecture
• I have no financial disclosures to report
• Some off-label use of medications will be discussed
• My institution benefits financially from expensive, invasive, therapies
Case

• TG is a 10 yo boy who presented to ID clinic for evaluation for PANDAS

• Sxs started 1 year ago with viral URI followed by severe anxiety preventing him from attending school, restlessness, and fidgeting

• Sxs come and go, associated with monthly strep infections

• Currently taking Azithromycin q3d and Valtrex daily

• CBT hasn’t helped much
PANS / PANDAS: objectives

- Define PANS / PANDAS
- Outline the clinical manifestations of these entities
- Discuss possible etiologies / pathophysiology
- Provide a framework for treatment strategies
Sydenham’s Chorea: Physical and Psychological Symptoms of St Vitus Dance

Susan E. Swedo, MD; Henrietta L. Leonard, MD; Mark B. Schapiro, MD*; B. J. Casey, PhD; Glenn B. Mannheim, MD; Marge C. Lenane, MSW; and David C. Rettew

ABSTRACT. Eleven children with Sydenham's chorea (8 girls and 3 boys, mean age = 8.4 ± 2.2 [SD] years) underwent comprehensive physical, neuropsychologic, and psychiatric examination. The chorea was manifested as dysarthria, gait disturbances, and frequent adventitious movements of the face, neck, trunk, and extremities. Antineuronal antibodies were present in 10 of 11 children. All children exhibited concomitant psychologic dysfunction, specifically obsessive-compulsive symptomatology, increased emotional lability, motoric hyperactivity, irritability, distractibility, and age-regressed behavior. Obsessive-compulsive symptoms were observed in 9 (82%) children, 4 of whom met diagnostic criteria for obsessive-compulsive disorder. These behavioral symptoms began several days to weeks before the chorea was observed, and they waxed and waned in severity along with the motoric abnormalities. These results suggest that psychologic, particularly obsessive-compulsive, symptoms are accompanying manifestations of Sydenham's chorea which may require medical attention. Pediatrics 1993; 91:706-713; Sydenham's chorea, movement disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder, neuropsychology.

and it was suggested that Sydenham’s chorea might be a cause of schizophrenia or other nervous conditions.

Based on these historical anecdotes10 and our postulates of the relationship between childhood-onset obsessive-compulsive disorder and basal ganglia dysfunction,11 we hypothesized that Sydenham's chorea would be associated with increased obsessive-compulsive symptomatology and undertook a retrospective comparison of obsessionality in 23 Sydenham's chorea patients and 14 rheumatic fever patients without chorea.12 As hypothesized, significantly increased obsessionality was demonstrated in the choreic patients, with three such patients meeting diagnostic criteria for obsessive-compulsive disorder (OCD) only while affected with the movement disorder.12

The present investigation was designed to supplement and verify those retrospective findings, as well as to examine systematically other psychologic and physical symptoms of Sydenham’s chorea. To our knowledge, this study is the first such prospective...
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

A review of clinical observations and literature reports leads to the hypothesis that, via a process analogous to Sydenham’s chorea, infections with group A β-hemolytic streptococci, among others, may trigger autoimmune responses that cause or exacerbate some cases of childhood-onset obsessive-compulsive disorder (OCD) or tic disorders (including Tourette’s syndrome). If this hypothesis is correct, then immunological treatments should lead to decreased symptoms in some cases. Four cases with abrupt, severe onset or worsening of OCD or tics are presented from an open treatment study. All were boys aged 10 to 14 years. One had OCD, one had Tourette’s syndrome, and two had both OCD and Tourette’s syndrome. Clinically and on standardized rating scales, their symptoms were in the moderate to very severe range. Two had evidence of recent group A β-hemolytic streptococci infections, and the others had histories of recent viral illnesses. Two were treated with plasmapheresis, one with intravenous immunoglobulin, and one with immunosuppressive doses of prednisone. All had a clinically significant response immediately after treatment. Diagnostic criteria are provided that describe these cases of pediatric, infection-triggered, autoimmune neuropsychiatric disorders (PITANDs). Suggestions are made regarding the evaluation and management of patients who may have this condition. J. Am. Acad. Child Adolesc. Psychiatry, 1995, 34, 3:307–311. Key Words: autoimmune, obsessive-compulsive disorder, tic disorders, streptococcal infections, viral infections, Tourette’s syndrome.
50 pediatric patients who met 5 criteria (not clear how they derived these criteria)

- Presence of OCD and/or tic disorders
- Pre-pubertal symptoms onset (mean age 6.3 years)
- Episodic course of symptom severity
- “Association” with Group A Strep
- “Association” with neurological abnormalities (tics, choreiform movements but only in some)

- Symptoms were acute and dramatic, relapsing and remitting
- “Associated” with increase in ASO antibody titers
- 31% of neuropsych episodes associated with documented Strep infection, 42% with pharyngitis or URI (no culture), and 4% with Strep exposure
PANDAS unpacking: the diagnostic definition

- Pediatric onset (between 3 years and onset of puberty)
- “Temporal relation” between group A strep (GAS) infection and onset and/or exacerbation (days to months)
- Obsessive compulsive disorder (OCD) and/or tic disorder essential
- “Specific” neurologic abnormalities (helpful, not essential)
- *Abrupt* onset and episodic course of symptoms (episodic not essential)

- No inclusion of autoimmune criteria in the definition
- Anxiety or depression are NOT sufficient!
PANDAS unpacking: evidence of group A strep infection

- **Temporal relation** should exist between group A strep (GAS) infection and onset and/or exacerbation
  - GAS within 9 months of illness onset or within 4 weeks of clinical exacerbation\(^1\) (suggested definition)
  - Rapid strep or culture positive or...
- Antibodies:
  - **ASO** (positive in 20-50% of PANDAS cases), peaks at 3-5 weeks\(^2\)
  - **Anti-DNase B** (positive in 80% of PANDAS cases), peaks at 6-8 weeks\(^2\)

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PANDAS unpacking: clinical manifestations

- Obsessive compulsive disorder (OCD) and/or tic disorder meeting DSM V criteria is essential
  - Obsessions, compulsions, or both
  - Motor or vocal tics or both
- **Specific** movement abnormalities support the Dx
  - Motoric hyperactivity
  - Choreiform movements with stressed postures
- May become moody or irritable, experience anxiety attacks, or show concerns about separating from parents or loved ones, but these are **not sufficient** to meet diagnostic criteria
PANDAS unpacking: clinical manifestations

- **Abrupt** onset and **episodic** course of symptoms:
  - “Explosion” of symptoms within 24-48 hours of associated GAS infection
  - Gradual resolution over weeks to months may be seen
  - Saw-tooth pattern may be seen
  - Subsequent study suggests that about 50% will have a second episode

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The PANDAS Controversy

**PANDAS**
- Is a very common entity
- Is caused by gas (even if CX --)
- Is autoimmune
- Requires aggressive immune blockade
- May or may not ever remit
- Is previously under-diagnosed and under-treated by American physicians

**PANDAS**
- Is not even real
- Is not caused by gas
- Is not autoimmune
- Is not treatable using ABX or immunomodulation
- Is not an actual public health problem
- Is not previously under-diagnosed and under-treated by American physicians

*Can there be a middle ground in this argument?*
Can we even admit that we don’t know?
PANDAS: pathophysiology?

- Autoimmune plausibility
  - GAS and acute rheumatic fever/Sydenham chorea
    - Molecular mimicry leading to
      - Transient arthritis due to the formation of immune complexes
      - Chorea due to binding of antibody to basal ganglia
      - Carditis due to antibody binding and infiltration of T cells
      - Most patients with SD have behavioral changes
  - GAS and post-strep glomerulonephritis
    - Deposition of nephritogenic strep antigens in the kidney leads to
      - Immune complex deposition
      - Triggers complement activation and inflammation
Hypothesized Pathophysiology

- Based on clinical similarities with Sydenham chorea, perhaps GAS can cause neurologic changes?
- Abnormal immune response in a susceptible host?
- Antibodies against strep cross-react with neurons (antineuronal antibodies)?
- Repeated exposure stimulates immune memory?
PANDAS: pathophysiology

- Kurlan, et al: case-control, prospective, blinded study of 40 patients who met criteria for PANDAS and 40 patients who had OCD or a tic disorder but whose symptoms were not related to GAS infection at the time of diagnosis
- Followed subjects over 2 years
  - Throat cultures once per month
  - Anti-strep antibodies measured every 3 months
  - Testing for GAS performed during exacerbations of OCD / tic symptoms
- Control group had 25 exacerbations, none temporally related to GAS
- Cases had more exacerbations than controls (40), but only 5 exacerbations occurred within 4 weeks of GAS infection
- 87.5% of exacerbations in PANDAS group were not related to GAS
- May be autoimmune, but GAS cannot be the sole trigger

PANS?

• **Pediatric Acute-Onset Neuropsychiatric Syndrome**

• **May include other infectious triggers**
  • Mycoplasma, flu, EBV, Lyme disease

• **Definition:**
  • 1. Abrupt, dramatic onset of OCD or severe restricted food intake
  • 2. Concurrent neuropsychiatric symptoms
    • (2/7) anxiety, emotional lability/depression, aggression/oppositional behaviors, regression, decreased school performance, sensory or motor abnormalities, somatic signs (sleep, stooling, or voiding disturbances)
  • 3. Symptoms not better explained by another disorder such as Sydenham Chorea
Pathophysiology – PANDAS/PANS

• *In my opinion*, the lack of a well-defined, *unique* clinical syndrome makes determination of pathophysiology difficult and decisions about treatment particularly troublesome. Particularly troubling is lack of consistent association with GAS

• Research Consortium 2017
  • “Because the criteria define a broad spectrum of neuropsychiatric conditions, the syndrome is presumed to result from a variety of disease mechanisms and to have multiple etiologies, ranging from psychological trauma or underlying neurological, endocrine, and metabolic disorders to post-infectious autoimmune and neuroinflammatory disorders such as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), cerebral vasculitis, neuropsychiatric lupus, and others.” ¹

Is there truly a temporal relationship to GAS infection?
Denmark
- Population based cohort study using data from children who received a strep test from 1996-2013
- >1 million children
- +Strep test → increased risk of any mental disorder, RR 1.18, P<0.001
  - OCD: RR 1.51, P<0.001
  - Tic disorder: RR 1.35, P<0.001
- Nonstreptococcal throat infection
  - Increased risk of any mental disorder, RR 1.08, P<0.001
  - Increased risk of tic disorder RR 1.25, P<0.001
- Conclusion:
  - Streptococcal throat infection associated with increased risk of mental disorders, particularly OCD and tic disorders
  - Nonstrep throat infections associated with increased risk of mental disorders, although less so than with strep
• 3 studies, 82 patients with PANDAS compared to 127 controls with OCD or tic disorder

• Evidence is NOT significant for higher rates of temporally associated strep infections with neuropsychiatric symptoms in patient who met criteria for PANDAS
The Autoimmune Hypothesis
If autoimmune....

- Timing would be consistent with other autoimmune disorders
- Symptoms would wane with diminishing antibody titers
- Should be like other post-GAS syndromes, which characteristically improve over time without immune modulation therapy
- Symptoms could return with repeated colonization by GAS
- Permanent sequelae would be unlikely
- Treating/eradicating GAS would be the mainstay of therapy
- Note that optimal treatment of Sydenham chorea is still unclear
- Why do some PANDAS thought leaders invoke SLE, AE as models to support immuno-modulation therapies?
Enrolled 30 Johns Hopkins patients with PANDAS; 30 patients with Tourette Syndrome

• ELISA performed for anti-glial and anti-neuronal antibodies (anti-GFAP, anti-MAP2)
• Immunofluorescence and EIA reactivity did NOT correlate with tic severity nor elevated antistreptococcal antibody titers
• These data do not support, but do not rule out the autoimmune hypothesis for PANDAS (or Tourette Syndrome)
Prospective blind study of 12 Baltimore children with PANDAS
ELISA to measure antineuronal antibodies before, during, and after clinical exacerbation
6 patients had an exacerbation with an associated strep infection
6 patients had an exacerbation without an associated strep infection
There was no difference in antibody levels with or without an exacerbation
Conclusion: Immune markers **failed to correlate** with clinical exacerbations
Obtained serum from 5 Yale pediatric patients with well-characterized PANDAS and 5 matched controls
Infused serum into the striatum of mice
Antibodies from children with PANDAS bound to 80% of cholinergic neurons vs. ~50% in controls
Elevated binding resolved following treatment with IVIG
The mice did not demonstrate behavioral changes
Antigens shared between mice and men?
Neuroanatomical features and its usefulness in classification of patients with PANDAS.

Cabrera B¹, Romero-Rebollar C², Jiménez-Ángeles L³, Genis-Mendoza AD¹,⁴, Flores J¹, Lanzagorta N⁵, Arroyo M¹, de la Fuente-Sandoval C⁶, Santana D⁵, Medina-Bañuelos V², Sacristán E², Nicolini H¹,⁵.

Mannose-Binding Lectin 2 Gene Polymorphism in PANDAS Patients.

Çelik GG¹, Taş DA², Tahiroğlu AY¹, Erken E², Seydaoğlu G³, Ray PC¹, Avci A¹.


Quagliariello A¹, Del Chierico F¹, Russo A¹, Reddel S¹, Conte G², Lopetuso LR³, Ianiro G³, Dallapiccola B⁴, Cardona F², Gasbarrini A³, Putignani L¹,⁵.
PANS / PANDAS: treatment

• 2017 PANS / PANDAS Research Consortium published a 3 part treatment guideline based on expert opinion from treating collectively over 1000 patients with PANS / PANDAS

  • **Part I: psychiatric and behavioral interventions**¹ (This makes total sense)
    • Intervene early with psychotherapy – cognitive behavioral therapy, exposure response prevention, parent management training
    • Add SSRI if indicated (as would consider for any child presenting with anxiety, depression, OCD). May need to start low and go slow as these patients seem particularly prone to experiencing adverse effects of medications (which can mimic presenting symptoms)
    • Can also consider anti-psychotics (aggressive behaviors), alpha-2 adrenergic agonists (tics), benzodiazepines (would potentially address anxiety, agitation, aggression, insomnia and could be used prn)
    • School accommodations – 504 or IEP. May have provisions based on poor handwriting skills, urinary frequency, OCD symptoms, etc
    • Safety plan in place

PANS / PANDAS: treatment

- 2017 PANS / PANDAS Research Consortium
  - Part II: Use of immunomodulatory therapies
    - Rationale for using immunomodulatory therapy
      - PANDAS is autoimmune (?)
    - Perform diagnostic work-up before starting immunomodulatory therapy:
      - History and physical
      - CBC, CRP, ESR, CMP
      - LP, EEG, MRI, sleep study, evaluate for immunodeficiency, screen for tuberculosis (infectious diseases evaluation)
    - NSAIDS → corticosteroids (burst or long-term) → high dose IVIG → TPE → DMARDs (holy cow)

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PANS / PANDAS treatment

• Current evidence for immune mechanism for PANS specifically is lacking, and even for PANDAS (in absence of choreiform movements) this is plausible rather than well defined, for example
  • Recent crossover, blinded RCT of IVIG (17 children): no difference between IVIG and control groups at 6 weeks, then allowed open label and showed improvement with IVIG¹
  • Transfer of sera from PANDAS pts to naïve rodents did not induce behavioral changes in the rats²
  • Lack of clear association with GAS is strong evidence against the autoimmune hypothesis

Effects of immunomodulation

- IVIG – “…some side effects, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury (TRALI), are serious.” Front Immunol. 2018; 9: 1299.


PANS / PANDAS: treatment

• 2017 PANS / PANDAS Research Consortium
  • Part III: Treatment and prevention of infections¹
    • Identify and treat GAS infections (throat, impetigo, perianal)
      • Amoxicillin 50 mg / kg daily x 10 days, max 1 gram
      • Azithromycin (resistance rates of 5-10%) 12 mg / kg x 5 days, max 500 mg
      • Consider follow up swab 2-7 days after treatment completion and re-treat if still positive
      • Consortium recommends treating all new diagnosis of PANS for GAS even if evidence of infection is lacking
    • “Currently insufficient evidence to support long-term streptococcal prophylaxis for children with PANDAS” but members of the Consortium “commonly” do this
    • Onset and exacerbations of PANS frequently associated with URIs and sinusitis
      • Treat with antibiotics only if clinically indicated by disease
      • Consider: influenza, mycoplasma
    • Vitamin D (involved in immune regulation)
    • No evidence for adenotonsillectomy
    • No role for probiotics
    • Continue to get routine vaccines

Retrospective treatment study of 371 children, 345 with PANDAS, 26 with PANS

Results

- ASO and anti-DNAse antibody titers were positive in all PANDAS subjects, negative in PANS
- All PANDAS patients were treated with **Augmentin** for 10-21 days at diagnosis
- All patients were treated with **penicillin** prophylaxis for at least 5 years
- 75% of PANDAS patients have shown improvement in neurologic symptoms
- Both groups had relapses

Conclusion

- There may be benefit to long-term antibiotic prophylaxis in PANDAS (and PANS)
PANS / PANDAS treatment at UVA

• First, do no harm
  • Current evidence does not support long-term antibiotic prophylaxis
    • In prospective case-control study of 40 PANDAs patients, majority of exacerbations of neuropsychiatric symptoms were not associated with GAS infection\(^1\)
    • Equal number of GAS infections in antibiotic prophylaxis and placebo groups for 37 patients with PANDAS\(^2\)
  
• Side effects of long-term antibiotics are real
• But....If patient is a GAS carrier, may be better to eradicate if you can

PANS / PANDAS treatment at UVA

• If you meet specific clinical criteria for PANS / PANDAS, I will discuss with families:
  • Treatment with 5 days of azithromycin to eradicate carriage state for GAS if history of recurrent GAS infection
  • If chronic pain or hyperesthesia, naproxen bid x 4-6 weeks
  • Supplement with vitamin D if low
  • Low dose SSRI (prefer for PCP to start / manage)

• If patients experience improvement but have a recurrence, suggest repeat above after testing for GAS (would not re-treat with antibiotics unless proven new infection)

• Connect with needed referrals
  • Psychotherapy and psychiatry
  • Neurology for tic management
  • Teen Health for eating disorders / food restrictions
PANS / PANDAS treatment at UVA

- No crisis management
- I do not do extensive laboratory work up unless there are concerns on exam or history
  - Specifically, concerns for encephalitis, delirium, hallucinations, seizures would be referred to neurology / ED
PANS / PANDAS: areas of future research

• Better define a unique clinical syndrome to delineate pathophysiology
• Identify sensitive and specific diagnostic markers
• Conduct large, high-quality treatment studies – blinded, randomized, placebo controlled – particularly of those treatments associated with higher risk (e.g. immunomodulatory therapies, antibiotic prophylaxis); then publish even if the results are negative!
PANS / PANDAS

Referrals to UVA Pediatric Infectious Diseases / Diagnostic Clinic  434.243.5500

Dr. Sarah Boggs, Pediatric Infectious Diseases specialist

PANS / PANDAS referral letter:

Thank you for contacting the Pediatric Diagnostic Clinic at the University of Virginia. One common referral that we see in this clinic is for children whose families or primary care physicians are concerned about a possible diagnosis of PANS / PANDAS (Pediatric Acute-onset Neuropsychiatric Syndrome / Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections).

There is no specific test to tell whether or not someone has this diagnosis; instead, the diagnosis is based on a group of symptoms. There is also no definite answer about what causes this group of symptoms. Although the word “autoimmune” is in the title of these disorders, definitive scientific evidence that proves that PANS / PANDAS is caused by an autoimmune process is lacking.

In the Diagnostic Clinic we can review your child’s symptoms and discuss whether testing for any underlying cause would be helpful. Based on the current scientific evidence and the balance of benefit versus risk we do not recommend any immune-modulatory therapies including steroids, immune globulin (IVIG), or plasmapheresis.
Susan Swedo, MD
National Institutes of Health

• PANDAS is most definitely real
• PANDAS is autoimmune in nature
• Immunomodulation and antibiotic treatment are the mainstays of therapy
• PANDAS is not what we think
• Children with tics, OCD and behavioral abnormalities should be treated symptomatically
• By ascribing PANDAS we are missing opportunities to treat the real causes
• Some PANDAS therapies offer more risk than benefit
• PANDAS is real but rare and of obscure cause
• Medical history is filled with surprise and discovery
• Group A strep infections cause autoimmune phenomena and can even cause behavioral abnormalities
• GAS sequelae may occur in the absence of clinical signs of infection, and even serology is ambiguous
• If a patient meets diagnostic criteria, culture for GAS (even if no pharyngitis)
• Cognitive behavioral therapy is of proven benefit and little risk
• Immunomodulation is not indicated
Case

- TG is a 10 yo boy who presented to ID clinic for evaluation for PANDAS
- Sxs started 1 year ago with viral URI followed by severe anxiety preventing him from attending school, restlessness, and fidgeting
- Sxs come and go, associated with monthly strep infections
- Currently taking Azithromycin q3d and Valtrex daily
- CBT hasn’t helped much
I don’t know’ has become ‘I don’t know yet’.

Bill Gates

In the meantime, we will do the very best we can for your child.