PANS-PANDAS
An Update on Research and Clinical Management

Kyle Williams, MD PhD
Director, Pediatric Neuropsychiatry and Immunology Program
Massachusetts General Hospital
Clinical Case-PANDAS

• 10 y.o. male with no previous history of psychiatric illness, no family hx of OCD/Tics
  – Independent, A student, socially well adjusted

• Feb: School letter advising 6 “Strep throat” infections in pt’s classroom

• Feb: Pt ill with sore-throat, high fever, throat swab positive for *Streptococcus pyogenes* (Group A Strep)
  – Treated with antibiotics; full recovery
Clinical Case-PANDAS

- March-April: Mother notices severe stuttering not present the day prior, shortly after:
  - Pt expresses fear over not pronouncing words “exactly”
  - New onset frequent hand-washing and showering rituals
  - Extreme avoidance of door-knobs and “dirty surfaces”
  - Pt’s blinking more pronounced, new “grunting” noise
- March-April: Symptoms become disabling, severe disruption at home/school, school performance declines to C’s/D’s
- Acute deterioration in handwriting
Clinical Case-PANDAS
Clinical Case-PANDAS

• Neurology evaluation: MRI normal, EEG normal
  – Diagnosed with Tic disorder
  – Started on Guanfacine for tic disorder

• Child Psychiatry evaluation:
  – Diagnosed with Obsessive Compulsive Disorder
  – Started on Sertraline
  – Cognitive Behavioral Therapy referral

• 12 weeks later, medications have minimal effect; symptoms remain severe, meds discontinued for excessive sedation

• Referral to NIMH
Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS)

• 1. Presence of a tic and/or Obsessive Compulsive Disorder
• 2. Pediatric onset
• 3. Abrupt symptom onset and an episodic course of symptom severity
• 4. Association with Group A Streptococcal infection
• 5. Neurological abnormalities (“choreiform” movements, hyperactivity, psychomotor agitation)
PANDAS

• Rapid, new onset of Obsessive-Compulsive and/or tic symptoms in previously healthy child

• Symptom onset temporally associated with Group A Streptococcal (GAS) infection
  – Hypothesized to be an autoimmune disorder induced by a GAS infection
  – Autoimmune cells cross-react with CNS proteins
PANDAS

• “All kids get Strep throat”

• OCD is a common psychiatric disorder in children

• 1+1=3?
  – Why OCD and not depression, psychosis, etc?
  – Why GAS and not influenza, staphylococcus, etc?
PANDAS-Historical Context

• GAS infections are associated with a variety of autoimmune disorders

• Sydenham’s Chorea (St. Vitus’s Dance):
  – Acute onset movement disorder in children
  – Follows a GAS infection
  – Patients also have significant, new-onset OCD symptoms
  – Hypothesized to be the result of autoimmune antibodies against the basal ganglia
Dr. Susan Swedo and colleagues at NIMH investigating Sydenham’s chorea and OCD in the 1990s

- Described a subset of children who did not meet criteria for Sydenham’s Chorea but showed:
  - Rapid onset OCD behaviors following GAS infections
  - New-onset tics (as opposed to chorea)
  - Relapsing-remitting course of illness
Symptoms may be triggered by any infectious agent (Bacteria/Virus)

Symptoms triggered by Group A Streptococcal infections (*Streptococcus pyogenes*)
**PANS** ➔ **PITANSDS** ➔ **PANDAS**

- **PANS**
  - Pediatric Acute Onset Neuropsychiatric Syndrome
  - Swedo, Leckman, Rose, Pediatric & Therapeutics, 2012

- **PITANSDS**
  - Infectious Triggers (PITANSDS)

- **PANDAS**
  - (Streptococcal Triggered)

- **Non-infectious Triggers**

- **Other Microbes** (Lyme, Mycoplasma, etc)

- **Environmental Factors, Metabolic Disorders**
PANS Diagnostic Criteria

• Pediatric Acute Onset Neuropsychiatric Syndrome:
  – Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
  – Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories:
    • Anxiety
    • Emotional lability and/or depression
    • Irritability, aggression, and/or severely oppositional behaviors
    • Behavioral (developmental) regression
    • Deterioration in school performance (related to attention-deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)
    • Sensory or motor abnormalities
    • Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency
  – Symptoms are not better explained by a known neurologic or medical disorder
First 50 Cases-Swedo et al., 1998 (Am J Psych)

- Mean age of onset 7.4 (±2.7)
  - Boys > girls at earlier ages of onset

- OCD Symptoms:
  - Contamination most prevalent obsession (50%)
  - Washing/cleaning most prevalent compulsion (42%)

- ADHD (40%), MDD (36%), Separation Anxiety (20%)

- ~6 week time difference between GAS infection and symptom onset/exacerbation
Evidence for Streptococcal Infections as a trigger for OCD/Tics

- Danish Health Registry Study analyzing >1 million children in Denmark, followed for up to 17 years
- Analyzed the incidence of new psychiatric diagnoses following testing for Group A Streptococcal infections
  - Positive streptococcal test was inferred from the filling of an antibiotic prescription in the 8 days following a streptococcal test

Orlovska et al., *JAMA Psych*, 2017
• Children with a positive streptococcal test had an 18% increased rate for any psychiatric disorder.

• Children with a negative test had a 28% and 25% increased risk for OCD and tics, respectively.
Evidence for Streptococcal Infections as a trigger for OCD/Tics

- Children with a positive streptococcal test had an 51% increased rate for an OCD diagnosis
- Children with a positive streptococcal test had an 35% increased rate for a tic disorder diagnosis
- Sibling pair analysis showed a 94% increased risk for OCD with a positive streptococcal result

Orlovska et al., JAMA Psych, 2017
Translational Evidence for PANDAS?

- 34 PANDAS subjects vs. 82 healthy controls
  - 8% increased caudate volume
  - 7% increase pallidal volume
  - 5% increased putaminal volume
- No difference in thalamic volume or total brain volume

Diagnosis and Treatment
Diagnosis

• How do we separate children with OCD/Tic Disorders and those with PANDAS/PANS?
  – No defined temporal criteria between the time of infection and onset of symptoms
  – PANDAS Diagnostic criteria are difficult to operationalize in clinical practice
Diagnosis

• Step 1: Stick to the diagnostic criteria
  – General principles: Rapid onset (24-48h) is crucial
    • Should be the “first episode” of either OCD/Tics
    • Evidence of GAS infections in the preceding 6-8 weeks (as a general guideline)
      – Minimally elevated GAS titers (ASO/DNAseB not very useful)

• Look for the presence of potential ancillary symptoms
Diagnosis

• Ancillary symptoms:
  – Acute handwriting deterioration
  – New onset separation anxiety
  – Urinary frequency/bedwetting
  – Anorexia
  – Sleep disturbance
  – Emotional lability/impulsive aggression
  – Developmental regression
  – Concentration difficulty
Diagnosis

- Pilot studies suggest that
  - Separation anxiety
  - Urinary frequency
  - ODD
  - Inattention/Hyperactivity
  - Choreiform movements
  - Handwriting deterioration
  - Decline in school performance

- May distinguish PANDAS from Peds OCD

Bernstein et al., JAACAP, 2010
Diagnosis

• Pilot studies also show the following symptoms differentiate PANDAS vs. Peds OCD:
  – Sudden onset
  – Definite periods of symptom remission
  – Remission during antibiotic therapy
  – Clumsiness

• The most discriminating characteristics:
  – Rising GAS titers/culture+dramatic onset (Risk Ratio: 3.5)
  – Rising GAS titers/culture+remissions (Risk Ratio 2.2)
  – Rising GAS titers+dramatic onset+remissions (Risk Ratio:4.5)

Murphy et al., J. Pediatrics, 2012
Treatment
A word on antibiotics...

• 2 pilot studies of prophylactic antibiotic therapy in PANDAS:
  – Garvey et al., Biol Psych, 1999
    • Penicillin therapy failed to present GAS infections in PANDAS patients; failed study
  – Snider et al., Biol Psych, 2005
    • 33 Subjects with PANDAS randomized to azithromycin vs. penicillin for 12 months
    • Both antibiotics significantly decreased GAS infections in the study period compared to previous year
    • Both antibiotics significantly decreased symptom exacerbations in the study period compared to the previous year
Immune Modulating Therapy

• 2 types have been studied:
  – Intravenous Immunoglobulin (IVIG)
  – Therapeutic Plasma Exchange (PEX)

• One randomized trial (Perlmutter et al., Lancet, 1999)
  – PANDAS subjects assigned to
    • IVIG
    • PEX
    • Placebo
Williams et al., JAACAP 2016

- 35 PANDAS Subjects, blinded, randomized, multicenter trial between the NIMH and Yale Child Study Center
  - 1200+ Potential patients screened
    - 18 Randomized to Placebo
    - 17 Randomized to IVIG
Williams et al., JAACAP 2016

Williams et al., JAACAP, 2016
No significant observed effect of IVIG vs placebo in the blinded phase

- 10% Mean decrease in CYBOCS score for placebo group
- 23% Mean decrease in CYBOCS score for IVIG group

Williams et al., JAACAP, 2016
Conclusions

• Intriguing evidence for PANDAS as a unique diagnostic entity
  – No “smoking gun”
  – No definitive biological tests available
• No clear treatment guidelines exist
  – Unclear objective evidence on antibiotic effectiveness
  – Immunomodulatory benefit unclear
Autoreactive Antibodies in PANDAS?

When serum from PANDAS patients is infused into mouse brain, binding to Cholinergic Acetyl Transferase Neurons (ChAT) is observed.

Frick, Williams, Pittenger, et al, *Brain Behavior and Immunity, 2018*
Treatment

• Special Issue on PANS/PANDAS Treatment Consensus Guidelines: *Journal of Child and Adolescent Psychopharmacology*, Sept., 2017
• Psychiatric Management: Part 1
• Immunomodulatory Therapies: Part 2
• Treatment and Prevention of Infections: Part 3
You’ve made the diagnosis, now what?

- Do they have an active GAS infection?
  - Pharyngeal
  - Skin
  - Anal/Vaginal

- Rule out Sydenham’s Chorea
  - Echocardiogram/referral to Infectious Disease
Treatment

• Labwork:
  – If multiple instances of infection, look for evidence of immune deficiency
    • IgA, IgG, IgM immunoglobulins
    • CBC
    • ANA
    • ESR/CRP
Treatment

• Moderate Symptoms
  – CBT or SSRI
  – CBT/SSRI
  – Anti-inflammatories
    • NSAIDs/Short Course Steroids
  – Antibiotics?
Treatment

- Severe symptoms:
- CBT/SSRIs/Antibiotics/Anti-Inflammatories
- IVIG?
- Prophylactic antibiotic management may be warranted in children with immune deficiencies or repeated infections
Resources

• www.ocdinkids.org
  – International Obsessive Compulsive Disorder Foundation

  – Special Issues on Pediatric Acute Onset Neuropsychiatric Syndrome (PANS)/PANDAS
Thank You!

Questions