Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS): An Inflammatory Hypothesis for Pediatric Obsessive Compulsive Disorder

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Disclosures

- I have received research support from the non-profit foundation PANDAS Network to conduct a neuroimaging study in PANDAS patients.
- I will discuss the off-label use of Intravenous Immunoglobulin (IVIG), Non-steroidal anti-inflammatory (NSAID) medications, and antibiotic medications in the treatment of PANDAS.
• William Osler, M.D., publishes “On Chorea and Choreiform Affectations”

• Recognizes that chorea is associated with “rheumatism” and may follow infections

• Sydenham’s Chorea
Behavioral Descriptions in Sydenham’s Chorea

“Odd and meaningless acts...”
Fast Forward 125 years....

• Obsessive Compulsive Disorder is now recognized as a major neuropsychiatric manifestation of Sydenham’s Chorea

• Cohort studies suggest that as many as 70% of patients with SC either meet criteria for OCD or have prominent OCD symptoms

Punukollu et al., 2015
Sydenham’s Chorea Pathogenesis

• Hypothesized to be a autoimmune disorder induced by a Group A Streptococcal infection

• Either antibodies, or inflammation, lead to abnormal basal ganglia function
From Sydenham’s to PANDAS

• Sue Swedo and Judith Rappaport, 1990’s

• Conducting a study of Sydenham’s Chorea as a model of “acquired” OCD

• Many children don’t meet criteria for Sydenham’s….
Symptoms may be triggered by any infectious agent (Bacteria/Virus)
PANDAS Diagnostic Criteria

• 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)
Clinical Case-PANDAS

Prior to symptom onset

3 months following onset
• Is the onset of PANDAS reliably associated with streptococcal infections?
• Do these children present with unique symptoms or respond uniquely to treatment?
• Are the symptoms of PANDAS produced by autoimmunity or inflammation?
Population-Based Studies
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.

Orlovská et al., JAMA Psych, 2017
• 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

Orlovská et al., JAMA Psych, 2017
Patient-Based/Clinical Studies
Can we separate the Children with PANDAS from Children with OCD based on clinical symptoms?

- Two small cohort studies (Murphy et al 2012¹, Bernstein et al 2010²):
  - Dramatic onset of OCD symptoms + GAS infection + periods of symptom remission provided the greatest discrimination between PANDAS and OCD¹
  - PANDAS cohort showed significantly increased rates of increased urinary frequency, new-onset separation anxiety, and hand-writing deterioration compared to those with OCD²
Fine Motor Control/Visual Motor Integration

- In PANDAS patients, we see an acute decline from reported baseline function with symptom onset.
- Fine motor control at baseline evaluation has been shown to predict future OCD and tic severity\(^1,2\) in patients with OCD and tic disorders.

Colvin et al., manuscript in preparation
Serological Measures

• No systematic analyses of cytokines/inflammatory markers in PANDAS
• In our clinic, we see a high rate of Immunoglobulin A (IgA) Deficiency (~15%)
• Using the Partners Research Patient Data Repository (RPDR) we conducted an analysis of IgA levels in children with OCD compared to those with autism, ADHD, and anxiety disorders
• Celiac Disease was used as a comparison population
• Pediatric OCD patients display significantly lower IgA levels than children with ASD, anxiety disorders

• Higher rate of IgA deficiency in Pediatric OCD compared to children with ASD, anxiety disorders, Adult OCD

Williams et al., submitted
MRI Studies

• 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

Treatment Studies
PANDAS Treatment

• Immunomodulatory treatments
  • Hypothesis: If PANDAS is an autoimmune disorder, can the symptoms of PANDAS be treated through immunomodulatory therapies?

• Intravenous Immunoglobulin (IVIG)
• Plasma Exchange Therapy (PEX)
IVIG vs. Plasma Exchange vs. Placebo

- IVIG group (1 month):
  - 45% decrease in obsessive compulsive symptoms
  - 19% decrease in tic severity

- PEX Group (1 month):
  - 58% decrease in obsessive compulsive symptoms
  - 49% decrease in tic severity

- Placebo Group (1 month):
  - 3% decrease in obsessive compulsive symptoms
  - 12% decrease in tic severity

Perlmutter et al., Lancet, 1999
IVIG Trial in PANDAS

• 36 children who met PANDAS criteria
  • Screened from >1100 referrals

• 18 Received Saline
• 17 Received IVIG (2gm/kg), blinded (1 child withdrew)
• Assessed for OCD severity at baseline and 6 weeks following infusion

• Following the 6 week time-point, those subjects who did not achieve a 30% reduction in OCD severity were offered an open label IVIG infusion
  • OCD severity assessed 6 weeks following open-label infusion

Williams, et al., JAACAP, 2016
- No significant observed effect of IVIG vs placebo in the blinded phase.
- 10% Mean decrease in OCD severity for placebo group.
- 23% Mean decrease in OCD severity for IVIG group.
Conclusions from IVIG Trial

• No significant IVIG effect in the blinded phase
• Significant effect in the open label phase for all subjects receiving treatment
• 80% of subjects had a >50% reduction in OCD symptom from baseline to study termination
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 Immunity 2018
One last thing….

- PET study investigating neuroinflammation in adults with OCD compared to healthy controls

- Significantly higher levels of inflammation found in adult OCD patients in the orbital frontal cortex, basal ganglia, thalamus

Attwells et al., JAMA Psych, 2017
Conclusions

• Epidemiological studies suggest an association between streptococcal infections and new-onset OCD and tic diagnoses

• Clinical studies have yet to find replicated clinical or serological markers that differentiate between PANDAS and OCD

• Mechanistic/animal based studies suggest that:
  • PANDAS patients may generate antibodies capable of binding basal ganglia neurons
  • Streptococcal infections/immunizations in mice produce blood brain barrier disruption, behavioral abnormalities, and immune cell migration/deposition into the CNS
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Questions?