INFLAMMATION AND AUTOIMMUNITY IN PEDIATRIC ANXIETY AND MOVEMENT DISORDERS

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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
OBSESSIVE COMPULSIVE DISORDER (OCD)

- Common psychiatric disorder in children worldwide (~2%)
- Characterized by repetitive anxious ideation and repeated behaviors to decrease the anxiety
- ~30% of patients fail to respond to standard treatments
- Despite demonstrated heritability, no genetic etiology has been identified
- Increased interest in autoimmunity and inflammation as an etiology for Obsessive Compulsive Disorder and Tourette Syndrome (TS)
OBSESSIVE COMPULSIVE DISORDER AND AUTOIMMUNITY?!?

- Hypothesis is derived from Sydenham Chorea (SC)
- SC is a post-streptococcal movement disorder
- Hypothesized to be an induced autoimmune disorder
- Antibodies/inflammation in the basal ganglia are thought to be pathogenic
- High rate of OCD (40-70%) of OCD
SYDENHAM CHOREA

• Serum antibodies from children with SC bind to human caudate (Husby, 1976)
• Cross-reactive antibodies between Streptococcus and caudate identified (Kirvan et al, 2003)
• Serum from SC children binds to SH-SY5Y cells, but not HEK cells (Brilot et al., 2011)
• Sydenham chorea responds to anti-autoimmune and anti-inflammatory therapies
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)

Symptoms triggered by Group A Streptococcal infections (Streptococcus pyogenes)
PANDAS?

- “All kids get Strep throat"
- OCD is a common psychiatric disorder in school age children (~2% pediatric population)
- $1 + 1 = 3$?
PRECLINICAL EVIDENCE FOR IMMUNE DYSFUNCTION IN OCD
ANIMAL MODELS OF IMMUNE DYSREGULATION AND OCD

- *Hoxb8*⁻/⁻ mice display a severe, repetitive grooming phenotype (Greer & Capecchi, 2002)
- This is the result of the lack of hematopoietic-derived microglia in the CNS (Chen *et al*, 2010), and abnormal corticostriatal synapses (Nagarajan, 2017)
- This phenotype can be reversed through chronic fluoxetine treatment (Nagarajan, 2017), or a bone-marrow transplant (Chen *et al*, 2010)
Progranulin (Grn \(^{-/-}\)) mice display a progressive obsessive-grooming phenotype with age (Lui et al, 2016) which is due to microglial activation.

Can be rescued with by crossing with a C1qa \(^{-/-}\) mouse OR a TNFα \(^{-/-}\) knockout mouse (Lui et al, 2016) (Krabbe et al., 2017).
**ARE MICROGLIA ABNORMAL IN HUMANS WITH OCD?**

- PET study investigating inflammation in adults with OCD compared to healthy controls.
- Significantly higher levels of TSPO binding in adult OCD patients in the orbital frontal cortex, basal ganglia, thalamus.

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Attwells et al., *JAMA Psych*, 2017
• PET study using TSPO in children with PANDAS and healthy adult controls
• Significantly higher TSPO binding in the caudate in PANDAS subjects compared to controls
• Caudate TSPO binding decreased in one subject treated with intravenous immunoglobulin (IVIG)

Kumar, Williams, and Chugani, J Child Neurology, 2014
• Immunomodulatory treatments
  • Hypothesis: If PANDAS is an autoimmune disorder, can the psychiatric symptoms of PANDAS be treated through immunomodulatory therapies?

• Intravenous Immunoglobulin (IVIG)
• Plasma Exchange Therapy (PEX)
IVIG TRIAL IN PANDAS

- 36 children who met PANDAS criteria, <1 year of illness
  - 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
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, in review
AUTOREACTIVE ANTIBODIES IN PANDAS?

**PV interneurons**

![Graph showing PV interneurons comparison between Control and PANDAS.](image)

**Control vs. PANDAS**

- **PV**
- **IgG**
- **Merge**

![Images showing PV, IgG, and Merge comparisons between Control and PANDAS.](image)

Frick, Williams, Pittenger, in review
AUTOREACTIVE ANTIBODIES IN PANDAS?

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**nNOS interneurons**

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**nNOS** | **IgG** | **Merge**

Control | PANDAS | Control | PANDAS | Control | PANDAS

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A) Baseline vs. Post-IVIG for CY-BOCS Total Score over visits.

B) Comparison of CY-BOCS Total Score change (Δ) for IgG binding to ChAT.

C) ΔCY-BOCS Score vs. ΔIgG binding to ChAT.

D) Immunofluorescence images showing ChAT, IgG, and Merge for Baseline (S1) and Post-IVIG (S3).

Frick, Williams, Pittenger, in review
INFLAMMATORY CHANGES IN TOURETTE SYNDROME

- Post-mortem analyses of brains from patients with TS show decreased ChAT neuronal number compared to controls in the basal ganglia (Kataoka et al., 2009)
- Post-mortem transcriptome analyses show greatly increased expression of microglia-related genes in TS
- Ablation of ChAT neurons in mice produces tic behaviors (Xu et al., 2015)

Kataoka et al., 2009
Lennington et al., 2016
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.

SEROLOGICAL MARKERS OF IMMUNE DYSREGULATION IN OCD

Williams et al., in review
SUMMARY

• Intriguing clinical and pre-clinical evidence to suggest that immune dysfunction may play an etiological role in OCD, Tourette syndrome
  - Autoimmune antibodies
  - Microglial dysfunction
• Significant challenge is detecting neuronal inflammation through non-invasive, repeatable means
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Questions?