Childhood Post-Infectious Autoimmune Encephalitis

PANDA Problems

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Disclosures

- None
Terms

- **PANDAS**
  Pediatric Autoimmune Neuropsychiatric Disorders Associated with Strep
- **PANS**
  Pediatric Autoimmune Neuropsychiatric Syndrome
- **CPAE**
  Childhood Post-Infectious Autoimmune Encephalopathy

Course Objectives

Discuss postinfectious autoimmune problems including PANDAS
  - Pathophysiology
  - Diagnosis
  - Treatment

Talk about establishing a CPAE clinic
  - Resources
  - Institutional support
  - Community support
Immunology, description, and definitions

• Many common infections have antigens that are similar to human antigens
• This may represent molecular mimicry and an attempt to evade immunity or may be incidental
• Strep is an excellent example of this with induction of autoantibodies against cardiac and neurologic targets

Overview continued

Cross reactive antibodies to carbohydrate antigens on strep lead to rheumatic fever and Sydenham’s chorea

Many other examples of molecular mimicry possibly leading to autoimmune disease
• Antiphospholipid antibody syndrome
• Autoimmune thrombocytopenic purpura
• Celiac disease
• Dermatomyositis
• Crohn’s disease
• Guillain-Barre syndrome
• Type-1 diabetes
• Multiple sclerosis
Just a sore throat?

- Rheumatic fever
- Sydenham’s Chorea

Epidemiology of strep and movement, mood, and behavior

- Prospective community cohort study: 693 kids followed for 8 months, strep cultures, movement, behavior assessments
- 3 months post-strep
  - 3x as likely to have movement problems
  - 2x as likely to have behavior problems
  - Kids with more strep infections had greater symptoms
- Retrospective: Denmark, all kids getting throat cultures-presumed strep if given abx in 2 weeks, presumed not strep if not, compared to historical controls
  - OCD increased 51% in presumed strep, 28% in not strep group
  - Tics increased 35% in presumed strep, 25% in not strep group
Pathophysiology

- Two Hits! Autoantibodies and disruption of blood-brain barrier
  - Commercial test for specific autoantibodies had at best moderate specificity and sensitivity making it an imperfect way to make a diagnosis
  - Animal models show the importance of Th17 cells in disrupting blood brain barrier, so antibodies alone may not be enough
- PET scanning looking for inflammation shows increased signal in basal ganglia in PANDAS (also in Tourette syndrome)
- Transfer of GABHS to rats causes movement/behavior changes associated with antibodies produced against dopamine receptors
- Transfer of IgG from these rats to other rats recreates the same disease

Pathophysiology- Basal Ganglia
Etiology of disease

- Postinfectious autoimmune encephalopathy
- Idiopathic psychiatric illness (OCD, anxiety)
- Neurological Conditions (tics, chorea)
- Genetics
- Family stress and trauma

Clinical Presentation

- Postinfectious autoimmune encephalopathy
- Idiopathic psychiatric illness (OCD, anxiety)
- Neurological Conditions (tics, chorea)
- Genetics
- Family stress and trauma
Personalized Medicine and Disease Specific Treatments

Family stress and trauma

Postinfectious autoimmune encephalopathy

Neurological Conditions (tics, chorea)

Genetics

Idiopathic Psychiatric illness (OCD, anxiety)

Diagnosis

- Dramatic onset of OCD/severely restricted food intake
- Presence of at least 2 of the following:
  - Anxiety
  - Emotional lability and/or depression
  - Irritability, aggression, oppositional behavior
  - Behavioral/Developmental regression
  - Deterioration in school performance (ADHD, memory, cognition)
  - Sensory or motor abnormalities (tics, chorea)
  - Somatic signs and symptoms (sleep, enuresis, urinary frequency)
- Symptoms are not better explained by known neurologic or medical disorder such as SC

Obsessive-Compulsive Disorder
Clinic experience

• 13 year old girl burns her clothing if someone touches her
• 10 year old boy can’t tolerate staying in an exam room during clinic
• 6 year old girl obsessed with germs in her food
• 12 year old boy obsessed that he will choke on his food

Somatic (Physical) Changes

• Tics
• Chorea
• Handwriting changes
• Changes in urination
• Sleep
Motor Tics

Phonic Tics
Chorea

Handwriting
Handwriting (Flare)

Comparison
Urinary Symptoms

• Urinary frequency
• Nocturnal enuresis

Sleep

• Nightmares
• Fearful of sleeping alone
What we ask our immune system to do every day

Bacteria
Viruses
Parasites
Fungi

Keys
Locks
100,000 different possible house keys

1,000,000 different possible car keys

1,000,000,000,000-10,000,000,000,000,000 different possible antibodies

Sometimes one key fits two locks
If we can’t change the lock, can we stop the key?  
(Lock=infection, key=antibody reaction)

Why is this so hard?

- The bacteria that are triggering the autoimmune reaction are everywhere
- Other types of infections can trigger the same immune cross reaction issues
- The antibodies can last months, but the cells that produce them can live for decades
- Late recognition and delayed treatment can lead to damage and persistent defects
- Fighting 100 million years of evolution. The immune system tends to keep doing what its been doing
Treatment

• It is critical to pursue all clinically relevant neurologic, psychiatric, and behavioral diagnoses that may be causing, or may be part of, the symptoms being.
• While medical treatment is being pursued for PANDAS, it is important to continue behavioral, psychological, and psychiatric treatment as appropriate (depending on the needs of the patient/family and the available resources).
• Try to use objective data to measure responses to treatments.

Theory: Reduce inflammation

Tiered treatment:
• Antibiotics
• Nonsteroidal medications (ibuprofen, naprosyn)
• Less common, Prednisone
• Much less common, Intravenous immune globulin
**IVIG**

- **Drawbacks**
  - Human blood product
  - Can’t be synthesized. Irreducibly complex
  - Expensive
  - Finite resource. 4-5g/liter of plasma
  - Expensive and insurance challenges
  - Difficult to administer. IV, Premedication, hydration
  - Risk of reactions (most severe reactions are less common)
    - Allergy to components
    - Anaphylactoid reactions
    - Headaches, aseptic meningitis
    - Thrombosis
  - Complex mechanisms of action

**Authorization Required**

- Met with state Medicaid director. Discussed the language of the state Medicaid laws related to IVIG and its status (experimental v/s therapeutic)
- Re-wrote our letters directly addressing the Medicaid language, referenced articles supporting use of IVIG in these conditions
- Still often denied, but eventually get to peer-to-peer
- Offer a trial of IVIG with objective, validated pre- and post-IVIG testing, if no benefit to treatment will stop
- About 90% approval rate
Mechanisms of immunomodulation by IVIG

- Antibodies to pathogens, superantigens
- Inhibition of complement activation
- Blocking pathological antibodies (anti-idiotypic antibodies)
- Saturating FC receptors with IgG but no antigen shuts off microglia, macrophages, and other antigen presenting cells
- Non-antibody components of IVIG

Banner CPAE Clinic

Present: Neurology, DBP, Immunology, Psychiatry, Psychology, Sleep, GI
Pending: Alternative-complementary medicine

Plan over time:
- We prefer phone calls from primary physicians rather than waiting for a clinic visit.
  - Travel is difficult for these families.
  - This is not medically complex.
- Managing patients through PCP in Canada, Mexico City, Bangkok, 22 states.
Research

- Registry
- IVIG trial with 3 other sites
- Collaboration with 14 sites and the NIMH to share data
- Biomarkers, genotypes

History of the Center

- Approached by families and asked to start a COE in 1 year
- Worked with NIMH and other sites to learn and develop the center
- Started seeing patients in May, 2016.
Banner Center of Excellence Team – Mesa

• Chris Spiekerman, D.O., F.A.A.P.
• Angela Riggs, NP
• Kathryn Schneck, RN
• Megan Robles, PCC

Banner Center of Excellence Team - Tucson

• Michael Daines, MD (Immunology)
• Sydney Rice (Developmental Pediatrics)
• Sejal Jain, MD (Pediatric Neurology)
• Peter Klinger, MD (Child Psychiatry)
• Andrew Gardner, PHD, BCBA (Behaviorist)
• Dan Combs, MD (Sleep Medicine)
• Fayez Ghishan, MD (Gastroenterology)
• Victoria Smith, RN
• Jessica West, RN
• Jennifer Andrews, PHD
• Maureen Galindo RN
• Georgette Mehalik, NP
• Linnette Mayate Ortiz, MPH
Goal: Education, not referral

• School nurses
• Pediatricians
• Family practitioners
• Urgent care providers
• ED providers and Hospitalist