What is PANDAS

Fact or Fiction

Michael E. Pichichero, MD
Director
Rochester General Hospital
Research Institute and Legacy Pediatrics
Rochester, New York

**Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A Streptococci**

**Signs and Symptoms of PANDAS**

- Presence of obsessive-compulsive disorder (OCD) and/or tic disorder
- May include neurologic abnormalities (motor hyperactivity, subtle choreiform movements)
- Autoimmunity to basal ganglia of brain in longstanding cases (similar to Sydenham's chorea)
- Association with GAS infections
- Abrupt onset and episodic course of symptoms
Historical Perspective

1989: Sue Swedo describes high prevalence of OCD in kids with Sydenham’s chorea

1992: Swedo presents an abstract at Am Soc Psychiatry meetings linking OCD, tics, and GAS.

1993: Outbreak of GAS tonsillitis in Rhode Island associated with 10 fold increase in kids with tics - concept of post-strep tics is born

1994: Swedo links Sydenham’s to autoimmune neuropsychiatric disorders (OCD, tic disorder)

1997: Swedo describes the 1st 50 cases of a new syndrome she calls PANDAS

National Institute of Mental Health (NIMH) Hypothesis [Swedo]

- Significant overlap of symptoms between patients with Sydenham’s chorea (SC), childhood onset OCD (OCD) and Tourette’s syndrome (TS)
- Similarities in regional brain localization among these three disease entities (i.e. SC, OCD and TS)
- Cases of acute childhood onset OCD and tic disorders immediately preceded by streptococcal infection
Comorbid Symptoms

- Emotional liability (66%)
- Separation anxiety (46%)
- Night-time fears and bedtime rituals (50%)
- Cognitive deficits
  - Deterioration in school performance (60%)
  - Deterioration in math skills (26%)
- Night Oppositional behaviors (32%)
- Motor hyperactivity (50%)

Symptoms

Always started abruptly, began at the same time as OCD symptoms or tics, began or worsened and were also associated with elevated antistreptococcal antibody titers.
Predisposition to PANDAS

- 20% of patients with post-GAS tics have a family history of 1st or 2nd degree relatives with post-GAS autoimmune disorders.
- In patients with PANDAS there is a family history of psychiatric or movement disorders in up to 39% of 1st degree relatives.
- Pre-existing ADHD predisposes kids to PANDAS.

Neuroimaging in PANDAS

- Volumetric MEI shows specific enlargement of the caudate and putamen of the basal ganglia during the acute phase of Sydenham’s chorea and PANDAS.
- The enlargement resolves during remission.
Anti-Neuronal Antibodies

- Anti-neuronal antibodies directed to basal ganglia identified in 46% of Sydenham’s chorea vs 14% in ARF vs 2% in controls. Antibody disappears when chorea remits.
- 93% to 100% of patients with acute Sydenham’s vs 0% to 13% of controls have autoantibodies to basal ganglia proteins of 40, 45, and 60 kDa.
- Passive transfer of IgG from Tourette’s syndrome patients produced Tourette’s in a rat model.

Autoimmune Etiology in Pathogenesis

- Autoantibody in patients with Sydenham’s chorea, Tourette’s syndrome and PANDAS cross reacts with lysoganglioside GM1 (a neuronal cell surface molecule), resulting in altered neuronal cell signaling.
- Molecular mimicry antigen on GABHS identified as N-acetyl-beta-D-glucosamine (GlcNAc).
- Specific Pandogenic strains are M12 and M19.
- Autoantigen on basal ganglia cells identified as neuronal glycolytic enzymes involved in cell energy metabolism, cell signaling and synaptic neurotransmission.
- Cell surface signaling pathway involves calcium-calmodulin dependent protein (CaM) kinase II activity.

Treatment

- One randomized controlled trial compared intravenous immunoglobulin (IVIG) with plasma exchange and placebo found a significant reduction of obsessive-compulsive symptoms in the IVIG and plasma exchange groups and a significant reduction of tics in the plasma exchange group.
- Antibiotic prophylaxis with Penicillin or Azithromycin decreased neuropsychiatric exacerbations.

Case Control Study
West Coast HMO

- Children 4 to 12 years receiving their first Dx of OCD, Tourette’s syndrome (TS) or Tic, 1992-1999
- Odds Ratio (OR) for OCD, TS or Tic increases
  - 2.2 if GAS within 3 months prior to diagnosis
  - 3.1 if multiple GAS infections within 12 months OR for TS only
  - 13.6 if multiple GAS infections within 12 months
**Italian Case Control Study**

150 consecutive children presenting with Tics to Neuropsychiatric Clinic, 1996-98

<table>
<thead>
<tr>
<th>Frequent past URTIs</th>
<th>Patients N= 150</th>
<th>Controls N= 150</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65%</td>
<td>65%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Mean ASO titer (IU) | 434 +/- 338 | 155 +/- 126 | <0.001 |


**Case Report**

- AW a 5-year-old boy acutely developed obsessive, frequent daytime urination. He voided, then immediately felt the urge to void again; producing only drops of urine. There was no fever, dysuria, incontinence or symptoms during the night.
- This compulsive need to repeatedly urinate increased over 7 days until his mother was convinced he had a kidney infection.
- During the visit, the mother pinpointed the exact hour of onset of urinary frequency.
Case Report (cont.)

- Exam: Mild tonsillopharyngeal erythema, minimal cervical adenopathy, no fever or tonsillar enlargement. Rapid Strep test and Throat culture were positive for GAS. A cephalosporin was prescribed. 6 days later the compulsive need to urinate ended.
- A month later, AW returned with abrupt onset of compulsive urination and a mild sore throat. On exam, the pharynx was red, but there was no fever or adenopathy. Rapid test and culture were both negative. The parent was advised to return in 72 hours if symptoms did not improve.
- She did, when a repeat test was positive for GAS, a cephalosporin was prescribed and in 5 days his OCD behaviors were gone. Follow-up exam and culture were negative and the symptoms have not recurred in 7 years of follow-up.

Characterization of PANDAS Cases

<table>
<thead>
<tr>
<th>Case / Initials</th>
<th>Gender</th>
<th>Age</th>
<th>Month of OCD Onset</th>
<th>Sudden Onset OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. RS</td>
<td>M</td>
<td>10 11/12</td>
<td>April</td>
<td>5,</td>
</tr>
<tr>
<td>2. DS</td>
<td>M</td>
<td>5 1/3</td>
<td>October</td>
<td>5, tics</td>
</tr>
<tr>
<td>3. JB</td>
<td>F</td>
<td>10 5/12</td>
<td>September</td>
<td>2</td>
</tr>
<tr>
<td>4. TT</td>
<td>M</td>
<td>5 ½</td>
<td>October</td>
<td>2</td>
</tr>
<tr>
<td>5. BB</td>
<td>F</td>
<td>6 ½</td>
<td>October</td>
<td>1,2</td>
</tr>
<tr>
<td>6. HM</td>
<td>F</td>
<td>7 ¼</td>
<td>December</td>
<td>4,5</td>
</tr>
<tr>
<td>7. AW</td>
<td>M</td>
<td>5 1/3</td>
<td>February</td>
<td>2,5</td>
</tr>
<tr>
<td>8. AH</td>
<td>M</td>
<td>9 1/3</td>
<td>March</td>
<td>OCD Mimics ADD</td>
</tr>
<tr>
<td>9. KK</td>
<td>F</td>
<td>6 11/12</td>
<td>April</td>
<td>2</td>
</tr>
<tr>
<td>10. AP</td>
<td>M</td>
<td>5 ½</td>
<td>April</td>
<td>2, blinking tic</td>
</tr>
<tr>
<td>11. SM</td>
<td>M</td>
<td>5 5/6</td>
<td>November</td>
<td>Blinking tic</td>
</tr>
<tr>
<td>12. TM</td>
<td>F</td>
<td>6 ½</td>
<td>March</td>
<td>1,2,3,5</td>
</tr>
</tbody>
</table>

1) Germ related; 2) Urinary frequency, toilet hygiene; 3) Hand washing; 4) Hoarding germs; 5) Fear of harm to self or others/avoid separation
Primary Care physicians in a private practice setting may see 1 to 3 children/year with a first episode of PANDAS.

For the diagnosis you need:
1. Sudden onset of OCD or tics,
2. Recent tonsillopharyngitis and
3. Positive throat culture, rapid strep test or strep serology (ASO or anti DNase B)

Treatment with antibiotics directed at GAS (10 days of cephalosporin) at the first episode eradicates the GAS and should eliminate the OCD or tic behavior rapidly (7-14 days). A lack of response to antibiotics argues against PANDAS as a diagnosis.

If a recurrence of sudden onset OCD or tic occurs again with sore throat and a positive throat culture for GAS or rise in ASO or anti DNase B serology, antibiotics again should be prescribed, and the GAS and the OCD or tic should resolve.
The PANDAS Controversy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Unproved Hypothesis</th>
<th>Bona Fide Clinical Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>Whether or not clinical course of abrupt onset or dramatic exacerbation is specific to PANDAS remains to be established</td>
<td>Children with PANDAS have “an overnight explosion” of OCD symptoms; those with non-PANDAS OCD have a slow, gradual symptom onset</td>
</tr>
<tr>
<td>3.</td>
<td>Question temporal relationship of symptom onset or exacerbation and GAS infection</td>
<td>Only children with documented GAS infection in conjunction with neuropsychiatric symptoms and with + throat cultures and/or high anti-strep antibody titers in the PANDAS profile</td>
</tr>
<tr>
<td>3.</td>
<td>Patients in original cohort with “choreiform” movements may have actually been cases of Sydenham’s chorea</td>
<td>Choreiform movements in PANDAS children are fine piano-playing movements of fingers, not the writhing adventitious movements seen in Sydenham’s chorea</td>
</tr>
</tbody>
</table>

Studies reported by Breese, Disney, Pichichero et al., Rochester, NY

Studies reported by Kaplan et al., Minneapolis, MN/St. Paul, MN

GAS TONSILLOPHARYNGITIS PENICILLIN TREATMENT FAILURES OVER TIME

<table>
<thead>
<tr>
<th>Year</th>
<th>% Penicillin Treatment Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954-56</td>
<td>8</td>
</tr>
<tr>
<td>1964-65</td>
<td>6</td>
</tr>
<tr>
<td>1981</td>
<td>19</td>
</tr>
<tr>
<td>1984</td>
<td>21</td>
</tr>
<tr>
<td>1989</td>
<td>24</td>
</tr>
<tr>
<td>1996</td>
<td>26</td>
</tr>
<tr>
<td>2001</td>
<td>37</td>
</tr>
<tr>
<td>2003</td>
<td>38</td>
</tr>
</tbody>
</table>
Penicillin vs. Cephalosporins in Treatment of GABHS Pharyngitis

- 35 randomized trials
- 1970-2000
- 7,125 patients
- Bacterial failure 3x more frequently with penicillin than cephalosporins

Symptomatic Relapse of GAS Tonsillopharyngitis Legacy Pediatrics, Rochester, NY, 2004-2005

- Frequency of symptomatic relapses after antibiotic treatment
- 1080 Children
- Antibiotic treatment
  - Group 1 Penicillin
  - Group 2 Amoxicillin
  - Group 3 Cephalexin
  - Group 4 Broad Spectrum Antibiotics
    - Amoxicillin-clavulanate
    - Cefprozil
    - Cefuroxime
    - Cefdinir
    - Cefpodoxime

Symptomatic Relapse of GAS Tonsillopharyngitis Legacy Pediatrics, Rochester, NY, 2004-2005

1. p=0.03 for differences among the 4 treatment groups
2. p=0.005 for trend among the 4 treatment groups

---

Symptomatic Relapse of GAS Tonsillopharyngitis From 4 Pediatric Practices: Rochester NY, Houston TX, Spokane WA, Orange County, CA

1. P< 0.001 for differences among the 4 treatment groups for both treatment time intervals
Choice of antimicrobial therapy for the treatment of PANDAS is more complex now that penicillin and amoxicillin failures are more common.