Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS): Experience at a Tertiary Referral Center

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Abstract

Background: Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is an autoimmune disorder presenting with obsessive compulsive disorder and/or tics. Like Sydenham’s chorea, its presumed pathogenesis consists of autoantibodies cross-reacting with neurons in response to a group A beta-hemolytic streptococcal infection (GASI). There are currently no diagnostic laboratory findings and management ranges from antibiotic prophylaxis to intravenous immunoglobulin to plasmapheresis. The diagnosis remains controversial, resulting in inconsistent referrals and significant patient anxiety.

Methods: A retrospective study was performed on all patients referred to the Pediatric Infectious Disease Division with a pre-referral diagnosis of PANDAS. Patients were analyzed by demographics, medical history, co-morbidities, symptoms, prior treatment, laboratory tests, management strategies, and treatment outcomes.

Results: From 2003 to 2013, there were 21 patients with a pre-referral diagnosis of PANDAS. Only five met the diagnostic criteria. No patient at referral had an objective scale to monitor symptoms. Eight referrals had a major psychiatric disorder, and none fulfilled diagnostic criteria (p<0.01).

Discussion: The majority of the patients referred with a pre-diagnosis of PANDAS do not fulfill diagnostic criteria nor do they have objective criteria for symptom monitoring. Major psychiatric disorders do not seem to be associated with PANDAS, and better physician education may prevent misdiagnoses. Multidisciplinary management is recommended.

Keywords: PANDAS, over-diagnosis, management

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Introduction

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is a disorder that is believed to be caused by antibodies generated in response to a group A beta-hemolytic streptococcal infection (GASI) in genetically susceptible individuals. These antibodies are thought to negatively cross-react with specific, unidentified neuronal cells resulting in cellular dysfunction and subsequent neurological symptoms.1–5 The neurologic impairment most classically associated with PANDAS is obsessive compulsive disorder (OCD) and/or a tic disorder distinguishable from Tourette syndrome or a chronic tic disorder. This current, albeit controversial, proposed pathophysiology for PANDAS is similar to that observed with acute rheumatic fever presenting with Sydenham’s chorea; please note, it is not the intent of this study to either confirm or challenge this hypothesis.1–5 However, unlike Sydenham’s chorea, the diagnosis of PANDAS remains controversial, which results in inconsistent referral patterns and significant anxiety for the patients and their families.6,7 This familial anxiety frequently results in significant pressure being placed on referring physicians, who do not have sufficient evidence to combat internet-driven pressure, to take action.

Current diagnostic criteria for PANDAS include: 1) clinically diagnosed OCD and/or a tic disorder; 2) documentation of a temporal association of less than 6 weeks between a GASI and onset of symptoms; 3) multiple instances of episodic waxing and waning of symptoms in relation to GASI; and 4) acute onset of symptoms between 3 years of age and puberty, which was defined as 12 years of age in this study.1–12 Note that
while the original Swedo criteria were presented as five criteria, in this study the acute onset and onset before puberty criteria were combined into one category. The diagnostic criteria for PANDAS have changed over time, and further complicating the issue is the potential incorporation of Pediatric Acute-onset Neuro-psychiatric Syndrome and Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders, two new disorders in which an autoimmune response to an infection is linked to behavioral symptoms, which leads to additional confusion for potential diagnosticians. There is currently no laboratory findings diagnostic for PANDAS and proposed management strategies range from antibiotic treatment of each GAS to antibiotic prophylaxis against streptococcus to intravenous immunoglobulin (IVIG) to plasmapheresis to electroconvulsive therapy (ECT). To better understand PANDAS, we sought to assess both physician referral patterns in relation to the diagnostic criteria and the management of these patients.

Methods

After obtaining approval from the Institutional Review Board (IRB) of the University of Michigan Medical School, a retrospective chart study was performed by one of the authors (C.E.H.) on all patients referred to the Pediatric Infectious Disease Division at the University of Michigan with a pre-referral diagnosis of PANDAS (from 2003 to 2013). Patients were then analyzed by demographics (age, gender, race, etc.), medical and family history, co-morbidities, presenting symptoms, prior treatment, laboratory evaluation, and management strategies and treatment outcomes. Significance was tested by chi-square analysis, in which a subsection of the pre-referral diagnosis sample was compared with the sample as a whole.

Results

To date, 21 patients have been referred to the University of Michigan Division of Pediatric Infectious Diseases with a pre-referral diagnosis of PANDAS. Patients have been referred here by primary care physicians, psychiatrists, neurologists, and otolaryngologists. Of these 21 patients, only five (23.8%) actually met the diagnostic criteria for and were ultimately diagnosed with PANDAS. Sixty-two percent (n=13) of the patients met two or fewer of the four aforementioned requirements. Two referrals (9.5%), in fact, did not have either clinically diagnosed OCD or a tic disorder. In terms of not fulfilling other diagnostic requirements, 23.8% (n=5) of all referrals were under the age of 3 years or over the age of 12 years, 28.6% (n=6) did not have a documented GAS, 42.9% (n=9) had no temporal association between a GAS and symptom onset of less than 6 weeks, and 76.2% (n=16) did not display waxing/waning of symptoms associated with multiple GASIs. Interestingly, there were no patients without a final diagnosis of PANDAS who experienced episodic waxing and waning of symptoms in accordance with multiple GASIs.

Out of all the referrals, 38.1% (n=8) had a major psychiatric disorder: these included disorders in the autism spectrum, clinically diagnosed depression, and catatonia. However, none of the patients with a final diagnosis of PANDAS had a major psychiatric disorder (chi-square, p<0.01). Interestingly, hallucinations were observed in 19% (n=4) of the patients irrespective of the final diagnosis of PANDAS; hallucinations are documented as a condition associated with PANDAS. Attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) is documented to be a common co-morbidity among PANDAS patients; this is confirmed by our data with 40% (n=2) of the PANDAS patients having an ADD/ADHD diagnosis.1,3,5,7,9

Discussion

Complicating diagnostic factors

Four of the five patients with a final diagnosis of PANDAS had at least one documented instance of elevated anti-streptococcal titers: Antistreptolysin O titer, anti-DNase B, and/or streptozyme. The patient without elevated titers is assumed to now have elevated titers due to a recently documented GAS. However, 56.25% (n=9) of the patients who were not diagnosed with PANDAS had documented elevation in anti-streptococcal titers as well. This is not surprising due to the nature of the titers (indication of a past GAS) coupled with the extremely common nature of GASIs in pediatric patients. In fact, it is the overall prevalence of streptococcus that makes establishing a causal relationship between GAS and PANDAS so difficult and the diagnosis so controversial.7,8 Additionally, we do not routinely follow anti-streptococcal titers since they have not been shown to correlate with disease activity.

The emerging prevalence of disorders related to PANDAS, similar disorders with non-GAS etiologies, increases ambiguity, making it more difficult to establish diagnostic certainty. Childhood acute-onset neuropsychiatric symptoms (CANS) presents with OCD or a tic disorder but does not require a recent infection to precede the sudden onset of symptoms. An additional broad-spectrum diagnosis, Pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND), is defined as an acute onset of symptoms preceded by an infection other than GAS. These new disorders, which are also not clearly defined, have not garnered the same amount of attention as PANDAS, resulting in confusion and misdiagnoses.7,10

Management techniques

None of the patients referred to the University of Michigan Pediatric Infectious Disease Clinic had an objective method for evaluating their referral symptomatology prior to referral (e.g., documenting and quantifying frequency and severity of symptoms), including the patients who had received plasmapheresis, IVIG, and ECT. Our approach to PANDAS is to coordinate care across all appropriate disciplines, consisting of a combination of Infectious Disease, Neurology, Behavioral Pediatrics, and/or Psychiatry. This combination depends on each patient’s presenting symptoms and is designed to objectively explore the relationship between the referring symptoms and the documentation/prevention of GAS. Three of the five PANDAS patients have had documented improvement in responses to anti-microbial treatment targeting GAS, one patient is on prophylactic antibiotics against GAS with documented improvement, and the final patient has had no known recurrences of GAS or symptoms. We currently have not treated any PANDAS patients with...
IVIG, although there is a pending NIH study examining the efficacy of IVIG for PANDAS patients. 11,12 There is no documented evidence in the literature that plasmapheresis or ECT are effective treatment options in the management of PANDAS. 8

PANDAS still remains a complex medical condition that, because of its potential impact on the patient and their family, provokes significant anxiety on both health care providers and patients. This anxiety results in over-diagnosis and inconsistent referral patterns and inappropriate management strategies. One of the major goals of our department was to decrease patient and family anxiety so that they do not pursue inappropriate management strategies.

**Follow-up**

Of the 16 patients in which we ruled out a PANDAS diagnosis, nine received follow-up from Psychiatry and/or Neurology and did not receive any treatment targeting PANDAS; three received follow-up from Infectious Disease for treatment unrelated to PANDAS and did not receive any treatment targeting PANDAS; two patients received

| Patient | PANDAS | Gender | Onset (Age) | OCD | Tics | Elevated Titers | Onset >3 and <12 | Documented GASI | Temporal GASI | Wax/Wane GASI |
|---------|--------|--------|-------------|-----|------|----------------|-----------------|----------------|---------------|---------------|
| 1 | Yes | M | 7 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | Yes | M | 3 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| 3 | Yes | M | 7 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | Yes | F | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| 5 | Yes | F | 6 | 0 | 1 | 0 | 1 | 1 | 1 | 1 |
| 6 | No | F | 13 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| 7 | No | M | 15 | 1 | 0 | 1 | 0 | 1 | 1 | 0 |
| 8 | No | F | 6 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 9 | No | M | 6 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 10 | No | M | 2 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| 11 | No | M | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| 12 | No | F | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| 13 | No | M | 14 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 14 | No | M | 7 | 0 | 1 | 0 | 1 | 1 | 0 | 0 |
| 15 | No | M | 10 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 16 | No | F | 7 | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| 17 | No | M | 9 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| 18 | No | F | 8 | 0 | 1 | 1 | 1 | 1 | 0 | 0 |
| 19 | No | F | 5 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 20 | No | M | 12 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 21 | No | M | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |

Yes: 23.8% M: 62.5% 7.2 43.8% 56.3% 56.3% 62.5% 56.3% 43.8% 0% *

Abbreviations: GASI, Group A Beta-hemolytic Streptococcal Infection; OCD, Obsessive Compulsive Disorder; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections.
of the five patients ultimately diagnosed with PANDAS: one patient followed-up with Psychiatry and received a tonsillectomy due to recommendation from otolaryngology with no further symptoms; one patient followed up with Infectious Diseases mainly via email with no known PANDAS-related treatment; one patient followed up with Infectious Diseases but elected to receive IVIG at an outside institution; one patient did not receive follow-up with Infectious Disease, Neurology, or Psychiatry at the University of Michigan, but per note from Orthopedic Surgery for unrelated treatment, the patient did not receive any PANDAS treatment from an outside location; one patient received follow-up outside the University of Michigan system and was lost to follow-up.

| Patient No. | PANDAS | Autism Spectrum | Additional Psychiatric Disorders | Hallucinations | AD(H)D |
|-------------|--------|----------------|---------------------------------|----------------|-------|
| 1           | Yes    | 0              | 0                               | 1              | 1     |
| 2           | Yes    | 0              | 0                               | 0              | 0     |
| 3           | Yes    | 0              | 0                               | 0              | 1     |
| 4           | Yes    | 0              | 0                               | 0              | 0     |
| 5           | Yes    | 0              | 0                               | 0              | 0     |
| 6           | No     | 0              | 0                               | 0              | 0     |
| 7           | No     | 1              | Depression, catatonia           | 1              | 0     |
| 8           | No     | 1              | 0                               | 0              | 0     |
| 9           | No     | 1              | 0                               | 0              | 1     |
| 10          | No     | 0              | 0                               | 0              | 0     |
| 11          | No     | 1              | 0                               | 0              | 1     |
| 12          | No     | 1              | 0                               | 0              | 1     |
| 13          | No     | 0              | Depression, catatonia           | 0              | 1     |
| 14          | No     | 0              | 0                               | 0              | 0     |
| 15          | No     | 1              | 0                               | 0              | 0     |
| 16          | No     | 0              | 0                               | 1              | 0     |
| 17          | No     | 0              | 0                               | 0              | 0     |
| 18          | No     | 0              | 0                               | 0              | 0     |
| 19          | No     | 0              | 0                               | 0              | 0     |
| 20          | No     | 0              | Depression                      | 1              | 0     |
| 21          | No     | 0              | 0                               | 0              | 0     |

0%* 0%* 20% 40%

Abbreviations: AD(H)D, Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections.
While Infectious Disease/Immunology may be most adept at managing the GASI, they are not trained for managing the primary symptoms associated with PANDAS. Thus, when necessary, the primary role for Pediatric Infectious Diseases should be the provision of a GASI-free period during which time the other specialties can evaluate the impact this has on the PANDAS symptoms. The initial referring team (i.e., the child’s primary care physician) carries out symptomatic management of GASI with infectious diseases providing the GAS medications and course of treatment; this is a similar approach to treatment of rheumatic fever with GAS prophylaxis. This approach has been most effective with the patients when PANDAS is being ruled out (approximately 80% of the time). The other appropriate specialty, based on primary symptoms, must first develop a quantitative objective scale in order to evaluate the effect if any of the GASI on symptom severity. They also have primary responsibility to manage the neurologic symptoms and provide alternative diagnoses once PANDAS has been ruled out.

**Limitations and strengths**

The limitations of this study include that it is a retrospective study and there are a limited number of patients involved in the study. Had this been a prospective study, patient satisfaction scores could have been generated to objectively assess the team approach. Additionally, the sample size of patients with major psychiatric disorders was small (n=8). The strengths of our study include finding the current deficit in physician knowledge about PANDAS, which we will attempt to remedy via teaching modules for pediatric residents at the University of Michigan Hospital and Health Systems. The use of objective symptom monitoring and a collaborative team approach of these patients will lead to more focused and increased quality care; ultimately preventing unnecessary, and potentially harmful, treatment of patients.

**References**

1. Bottas A, Richter MA. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *Pediatr Infect Dis J* 2002;21:67–71. doi: http://dx.doi.org/10.1097/00006454-200201000-00017.

2. Garvey MA, Giedd J, Swedo SE. PANDAS: The search for environmental triggers of Pediatric neuropsychiatric disorders. Lessons from rheumatic fever. *J Child Neurol* 1998;13:413–423. doi: http://dx.doi.org/10.1177/08830 7389801300901.

3. Pavone P, Parano E, Rizzo R, Trifiletti RR. Autoimmune neuropsychiatric disorders associated with streptococcal infection: Sydenham chorea, PANDAS, and PANDAS variants. *J Child Neurol* 2006;21:727–736. doi: http://dx.doi.org/10.1177/08830738060210091401.

4. Snider LA, Swedo SE. PANDAS: Current status and directions for research. *Mid Psychiatry* 2004;9:900–907. doi: http://dx.doi.org/10.1038/sj.mp.4001542.

5. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264–271.

6. Gabbay V, Coffey BJ, Babb JS, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcus: Comparison of diagnosis and treatment in the community and at a specialty clinic. *Pediatrics* 2007;122:273–278. doi: http://dx.doi.org/10.1542/peds.2007-1307.

7. Macerollo A, Martino D. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS): An evolving concept. *Tremor Other Hyperkinet Mov* 2013;3. doi: http://dx.doi.org/10.7916/D8ZC31M1.

8. Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: Hypothesis or entity? Practical considerations for the clinician. *Pediatrics* 2004;113:883–886. doi: http://dx.doi.org/10.1542/peds.113.4.883.

9. Martino D, Delazio G, Giovannoni G. The PANDAS subgroup of tic disorders and childhood-onset obsessive-compulsive disorder. *J Psychosom Res* 2009;67:547–557. doi: http://dx.doi.org/10.1016/j.jpsychores.2009.07.004.

10. Singer HS, Gilbert DL, Wolf DS. Moving from PANDAS to CANS. *J Pediatr* 2012;160:725–731. doi: http://dx.doi.org/10.1016/j.jpeds.2011.11.040.

11. NIH. PANDAS: Frequently asked questions about pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Washington, DC: National Institutes of Health, National Institute of Mental Health.

12. Singer HS, Loiselle C. PANDAS: A commentary. *J Psychosom Res* 2005;55:31–39. doi: http://dx.doi.org/10.1016/S0022-3999(02)00382-2.