A Pediatric Neurology Perspective on Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection and Pediatric Acute-Onset Neuropsychiatric Syndrome

Donald L. Gilbert, MD, MS, FAAP, FAAN[1], Jonathan W. Mink, MD, PhD, FAAN, FANA, FAAP[2], and Harvey S. Singer, MD[3]

The sudden onset of new neuropsychiatric symptoms in children is often a challenge for both parents and physicians. For the physician, there is a broad differential diagnosis to consider, and decisions must be made about the selection of diagnostic studies as well as the choice of therapy.[1] In addition, there is often a belief that, even without a documented etiology, an immediate pharmacologic treatment targeted toward an undiagnosed biological etiology will prevent worsening symptoms or permanent sequelae. Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS)[2] and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)[3] are 2 entities that have received much attention in recent years, with claims that 1% of children may be affected.[4] PANDAS was initially proposed 2 decades ago as a poststreptococcal autoimmune condition similar to Sydenham chorea, whereas PANS is a broader diagnosis without a single defined etiology or mechanism. In this commentary, we review updated information on PANDAS and PANS clinical symptoms, presumed etiologic associations, proposed autoimmune mechanisms, diagnostic testing, and recommended treatments. Our goal is to provide current information that will permit a clear and balanced approach when dealing with these controversial diagnoses.

Definitions

PANDAS

The concept of PANDAS was derived from observations that some individuals with Sydenham chorea (SC, acute rheumatic fever) have associated anxiety, emotional lability obsessive-compulsive symptoms, tics, or a combination.[5,6] In 1998, investigators at the National Institute of Mental Health reported a series of 50 patients with similar features and proposed a distinct, clinical entity, PANDAS, with 5 specific diagnostic criteria: (1) presence of obsessive-compulsive disorder (OCD) and/or a tic disorder; (2) prepubertal symptom onset (age 3 years to the beginning of puberty); (3) episodic course characterized by acute, severe onset and dramatic symptom exacerbations; (4) temporal relationship between group A beta-hemolytic streptococcal (GABHS) infections and symptom onset and exacerbations; (5) association with neurologic abnormalities (eg, choreiform movements, motoric hyperactivity, tics).[2]

Other investigators subsequently raised concerns about problematic aspects of the PANDAS criteria, including (1) the strength of GABHS association with the onset and recurrence of tics, OCD, or both; (2) the lack of data supporting the suppression of symptoms or prevention of recurrences with antibiotic therapy; (3) whether there is a meaningful distinction between PANDAS and tic disorders; and (4) the absence of neurologic/behavioral abnormalities during exacerbations.[1,7] Despite these and other concerns discussed below, physicians continue to diagnose PANDAS[8] and also create additional ambiguity by introducing terms such as "PANDAS variant" or "atypical PANDAS" based on the presence of other neuropsychiatric symptoms[9,10] or types of infections.[11] Motivated in part by a desire to clarify psychiatric diagnostic criteria and expand potential etiologies, a workshop was convened in 2010 and proposed a new diagnostic entity: PANS.[3]

PANS

The criteria for PANS include abrupt, dramatic overnight onset of OCD or severely restricted food intake; concurrent abrupt onset of additional severe neuropsychiatric symptoms from at

ADHD	Attention-deficit hyperactivity disorder
CNS	Central nervous system
CSF	Cerebrospinal fluid
GABHS	Group A beta-hemolytic streptococcal
IVIG	Intravenous immunoglobulin
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection
PANS	Pediatric Acute-onset Neuropsychiatric Syndrome
SC	Sydenham chorea

From the [1]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Department of Neurology, University of Rochester Medical Center, Rochester, NY; and [3]Johns Hopkins Hospital, Baltimore, MD

D.G. received honoraria and/or travel support from the Tourette Association of America/ Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Child Neurology Society, compensation for expert testimony for the US National Vaccine Injury Compensation Program, through the Department of Health and Human Services, research support from the National Institutes of Health (NIH) (National Institute of Mental Health, National Institute of Neurological Disorders and Stroke), funding for work as a clinical trial site investigator from Psyadon Pharmaceuticals (clinical trial, Tourette Syndrome) and EryDel (clinical trial, Ataxia Telangiectasia), book royalties from Elsevier and Wolters Kluwer. J.M. received honoraria from the American Academy of Neurology as Associate Editor of *Neurology*, grant support from NIH, Centers for Disease Control and Prevention, Beyond Batten Disease Foundation, Batten Research Alliance, Noah's Hope, Batten Disease Support and Research Association, and Abeona Inc, compensation for expert testimony for the US National Vaccine Injury Compensation Program, through the Department of Health and Human Services, served as a consultant to Abide Inc, Censa Inc, and Teva Inc, and has received book royalties from Elsevier and from John Wiley & Sons. H.S. received research support from the NIH and the Tourette Association of America, funding for work as a clinical trial site investigator from Ecopipam Pharmaceuticals, served as a consultant for Teva Brand Pharmaceutical Products Research and Development, and received book royalties from Elsevier. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.04.035

least 2 of the following 7 categories: (1) anxiety; (2) emotional lability and/or depression; (3) irritability, aggression, and/or severe oppositional behaviors; (4) behavioral (developmental) regression; (5) deterioration in school performance; (6) sensory or motor abnormalities, including heightened sensitivity to sensory stimuli, hallucinations, dysgraphia, complex motor, and/or vocal tics; (7) somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency; and (8) symptoms are not better explained by a known neurologic or medical disorder.[3] Three key differences within this new diagnosis worth emphasizing include (1) the PANDAS diagnostic criteria requires neurologic abnormalities (tics, motor hyperactivity, choreiform movements), whereas PANS can be diagnosed with only psychiatric symptoms; (2) PANDAS requires both an acute symptom onset and episodic (relapsing remitting) course whereas PANS can be diagnosed based solely on the initial presentation; (3) PANDAS has a proposed specific etiologic bacterial trigger (GABHS), whereas PANS has no specified precipitant. Nevertheless, similar to PANDAS, PANS presumes an infectious and autoimmune mechanism in most cases.[12]

Epidemiologic Studies—PANDAS

In the 20 years following publication of the seminal PANDAS case series,[2] a large number of observational epidemiologic studies have sought to confirm PANDAS as a clinical entity distinct from idiopathic or familial tic disorders or OCD. These studies can be grouped based on study design and evaluated using standard recommended guidelines for establishing (1) strength of associations; (2) consistency of results under different circumstances; (3) biological gradient or "dose" (amount of exposure) and "effect" (symptom severity); and (4) timing of the temporal association.[13] Using these guidelines, in the following sections we will review relative strengths and weaknesses of representative publications.

Studies of Consistency and Diagnostic Accuracy in Clinical Practice

In a study reported from an OCD/Tourette specialty clinic, 31 of 176 children referred for tics or OCD were previously diagnosed with PANDAS.[8] Of these, however, only 12 (39%) met established PANDAS diagnostic criteria. Antibiotic treatments were common, even in the absence of any laboratory evidence of infection.[8] This study illustrates the frequent diagnostic misclassification in PANDAS; this finding carries significant implications for confirming validity in the areas of consistency and timing, particularly for retrospective studies.

Systematic, Longitudinal Prospective Studies of Cohorts Designed to Identify Co-Occurrence of Streptococcal Infections and PANDAS Behavioral Symptoms

Two studies sought evidence for PANDAS in patients evaluated directly in the community. In the first, researchers enrolled 814 children ages 4-11 years from pediatric clinics. Streptococcal infections were present in 411 children, viral (presumed) pharyngitis in 207, and no infections (well care) in 196 children. At enrollment, 2 and 12 weeks after the visit, parents completed a 20-question survey about symptoms consistent with PANDAS. At 12 weeks, there were no differences across the 3 groups for obsessive-compulsive behaviors, tics, or other neuropsychiatric symptoms.[14] In the second study, researchers' enrolled 693 healthy children, aged 3-12 years, and collected streptococcal infection data (via throat cultures), observational motor examinations, and behavioral ratings for an 8-month period during the school year. Using a timing criterion of 3 months from the streptococcal infection to symptoms, the authors reported no increased risk of tics or chorea. They did identify increased "swaying" and "non-tic grimacing" in 37 (19%) children with vs 28 (6%) without infections, and nonspecific problem behaviors in 68 (35%) children with infections, vs 91 (18%) without. Further, they reported a dose-effect linking more streptococcal infections with more problem behaviors.[15] Nevertheless, this study's causality criteria, which included a strength, timing, and dose-effect, failed to confirm an association between a preceding streptococcal infection and a PANDAS diagnosis.

Retrospective Studies Using Claims Data

Several studies[16-19] have used claims data to probe relationships between coded events as well as to assist in determining whether the diagnosis of a streptococcal infection precedes the new diagnosis of OCD or tic disorders at a rate greater than expected by chance. Unfortunately, threats to validity are abundant in these approaches—the clinical practice for diagnosing streptococcal infections and behavioral conditions varying widely. For example, with respect to timing, the onset of a behavioral diagnostic code does not necessarily indicate the onset of the symptoms. In a recent cohort study from Denmark, which included all 1 067 743 individuals born over an 18-year period, investigators identified individuals who had streptococcal testing ordered. From this cohort, they ascertained those provided with antibiotic prescriptions within 1 week (15 408) and considered this a proxy for a "streptococcal infection" positive group. In contrast, the lack of an antibiotic prescription (11 315) in the streptococcal test cohort was used as a proxy for "other infection." No testing (13 712) was used to create matched controls, as a proxy for "no infection." Compared with controls, odds of OCD were 51% higher in the treated-infection and 28% higher in the untreated-infection groups. Odds of tics were 35% and 25% higher in those groups.[16] This study is broadly supportive in terms of strength. However, with respect to PANDAS, the certainty around the specific cause of infection is low, and the details about whether the effect is PANDAS (ie, dramatic onset and exacerbations), are nonexistent. Other unmeasured factors, such as possibly higher rates of healthcare utilization for individuals with OCD, might also confound these findings. Perhaps not surprisingly, results from these types of studies have been inconsistent.[17-19]

DIS 5.5.0 DTD ■ YMPD9956_proof ■ May 21, 2018