Introduction

We are thrilled to introduce this special issue of JCAP on pediatric acute-onset neuropsychiatric syndrome (PANS) in youth. This is the first time a collection of articles concerning PANS and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) has been published, and hopefully represents the first group of many more data-driven studies to come regarding youth with these conditions. PANDAS was first described by Dr. Susan Swedo’s group at the National Institutes of Health in the late 1990s (Swedo et al., 1999). Since initial controversy regarding the appropriateness of this diagnosis versus “regular” obsessive compulsive disorder (OCD) or tic disorders, the field has undergone much change. Biological, phenomenological, and treatment studies in youth with PANDAS have provided evidence of biological models and unique medical treatments for these patients.

However, it became clear to PANDAS researchers that children without documented streptococcal infection were still subject to an array of acute-onset neuropsychiatric symptoms, including OCD, eating restriction, tics, depression, mania, cognitive impairment, urinary urgency, sleep disturbance, and hallucinations. Thus, the term PANS was coined in 2012 to address the wider group of children who may have underlying etiologies separate from documented streptococcal infection (Swedo et al., 2012). As this is a more recent expansion of the concept of PANDAS, there are few studies yet conducted in these youth. This special issue represents a major movement forward in this field, collecting reports detailing clinical presentations of youth with PANS, open and controlled treatment data, and the first consensus conference recommendations regarding clinical evaluation of these affected youth.

The clinical presentation of PANS has vexed clinicians, as it overlaps with many other disorders. There are several articles here that discuss this issue, including a case series highlighting various etiologies and rheumatologic symptoms (Frankovich et al. 2015b), detailed descriptions of findings from clinic patients (Frankovich et al. 2015a; Murphy et al. 2015b), presentations of food restriction (Toufexis et al. 2015), and presentations in the community (Swedo et al. 2015). These reports should aid the clinician in recognizing the various presentations of youth with PANS. A detailed consensus statement is provided from experts who actively treat PANS patients and conduct research, in order to aid clinicians in evaluating these youth and/or knowing when to refer to specialists. Biological findings regarding antineuronal antibodies and cytokine levels in these children are delineated in Cox et al. (2015) and Parker-Athill et al. (2015). Finally, as treatment trials in this population are few, included here are chart reviews of response to IVIG (Kovacevic, grant, and swedo, 2015) and plasmapheresis (Latimer et al. 2015), and a placebo controlled study of cefdinir in a related population (Murphy et al. 2015a).

Together, these articles represent the initial push in a coordinated effort to systematically study PANS and disseminate findings regarding recognition, evaluation, etiology, and treatment. When “new” disorders are recognized in the population, afflicted families often look to resources on the web or in the lay press, or word of mouth for assistance, as there is usually little established evidence-based guidance. It is hoped that these articles will help provide additional empirical data to what is already known about PANS to allay confusion in the community and spur larger, well-controlled—and thus well-funded—studies in youth with the syndrome.

The link between inflammation and psychiatric disorders is slowly becoming stronger, and understanding PANS may help us understand not just how to better diagnose and treat youth with this syndrome, but other youth with developmental neuropsychiatric syndromes and potentially the pathogenesis of psychiatric disorders as a whole.

References


Special Issue on Pediatric Acute-Onset Neuropsychiatric Syndrome

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Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference

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Abstract

On May 23 and 24, 2013, the First PANS Consensus Conference was convened at Stanford University, calling together a geographically diverse group of clinicians and researchers from complementary fields of pediatrics: General and developmental pediatrics, infectious diseases, immunology, rheumatology, neurology, and child psychiatry. Participants were academicians with clinical and research interests in pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) in youth, and the larger category of pediatric acute-onset neuropsychiatric syndrome (PANS). The goals were to clarify the diagnostic boundaries of PANS, to develop systematic strategies for evaluation of suspected PANS cases, and to set forth the most urgently needed studies in this field. Presented here is a consensus statement proposing recommendations for the diagnostic evaluation of youth presenting with PANS.

Background

IN THE 1980s, investigators at the National Institutes of Health (NIH) noted a subset of children with obsessive-compulsive disorder (OCD) who had a sudden onset of their psychiatric symptoms, typically following infection with a variety of agents, including Streptococcus pyogenes, varicella, and Mycoplasma pneumoniae. These were termed pediatric infection triggered autoimmune neuropsychiatric disorders (PITANDS) (Allen et al. 1995). The investigators chose to focus on the subset of cases triggered by infections with group A Streptococcus (GAS) because of parallels between acute-onset OCD and the prodromal period of Sydenham chorea (SC), suggesting that acute-onset OCD might be a forme fruste of SC (Swedo et al. 1989; Swedo 1994; Swedo et al. 1994). Systematic clinical investigations of SC and OCD led to discovery of a subgroup of OCD patients whose symptoms were triggered by GAS infections and labeled “pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections” (PANDAS) (Swedo et al. 1995). The PANDAS subgroup is defined by an acute prepubertal onset of tics or OCD symptoms, association with GAS infection, and specific neuropsychiatric symptoms (Swedo et al. 1998, 2004; Murphy et al. 2012). The requirement that GAS infections be associated with symptom onset/exacerbations proved difficult to operationalize, because of the prevalence of GAS infections in grade-school aged children, and the asymptomatic nature of rheumatogenic GAS organisms (Garvey et al. 1998); this resulted in both misdiagnoses and missed diagnoses of PANDAS (Gabbay et al. 2008). Additional problems were encountered in patients with tic disorders because the PANDAS subgroup is distinguished by an “abrupt onset and episodic course,” but tics are frequently described as having an acute (“off/on”) onset and a waxing/waning course (Leckman et al. 2011). As a...
result of the confusion surrounding the onset criteria, subsequent studies included youth likely to not meet criteria for PANDAS, and reported conflicting findings, making PANDAS an increasingly controversial diagnosis. Of greater concern, the criteria for PANDAS had been developed to define an etiologically homogeneous group of patients for research studies, and purposely excluded acute-onset cases not triggered by GAS infections, which inadvertently and unfortunately diverted attention from children with acute-onset OCD not related to GAS infections.

To address this, experts convened at the NIH in July 2010 and developed working criteria for pediatric acute-onset neuropsychiatric syndrome (PANS) (Swedo et al. 2012). Resulting PANS criteria describe a clinically distinct presentation, defined as follows.

I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake

II. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories:

1. Anxiety
2. Emotional lability and/or depression
3. Irritability, aggression, and/or severely oppositional behaviors
4. Behavioral (developmental) regression
5. Deterioration in school performance (related to attention-deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)
6. Sensory or motor abnormalities
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency

III. Symptoms are not better explained by a known neurologic or medical disorder, such as SC.

Many children with PANS are extremely ill, with extreme compulsions (licking shoes, barking), motor and phonic tics (whooping, wringing hands), behavioral regression, and terrifying episodes of extreme anxiety or aggression. The behavioral manifestations often prompt rapid referral to psychological or psychiatric services, but all patients should receive a full medical evaluation. It should be noted that PANS is a “diagnosis of exclusion” and that other known medical diseases must be ruled out before a diagnosis of PANS is assigned. By definition, the individual PANS symptoms overlap with a variety of psychiatric disorders, such as OCD, Tourette’s syndrome, ADHD, depression, and bipolar disorder. However, the acuity of onset and simultaneous presentation of these symptoms differentiate PANS from these psychiatric conditions. The PANS diagnosis is, therefore, limited to cases with acute-onset symptoms in multiple domains. In some instances, children with PANS experience visual or auditory hallucinations; these cases deserve special note, as symptoms can appear identical to the psychotic symptoms seen in conditions such as schizophrenia, bipolar disorder, and lupus cerebritis. Again, because PANS is a diagnosis of exclusion, a comprehensive evaluation is needed to eliminate disorders presenting with similar neuropsychiatric symptoms. Here we provide consensus recommendations for the clinical and laboratory evaluation of youth with potential PANS. Treatment recommendations will be addressed in a future report.

Diagnostic Evaluation

When PANS is suspected, it is important to obtain a comprehensive medical and psychiatric history and perform a thorough physical examination. Table 1 provides an overview of the evaluation that should be conducted by the treating physician(s). If findings warrant, then relevant specialists should be consulted. Table 2 provides an overview of the differential diagnosis for PANS, reflecting the need to assess multiple medical and psychiatric domains.

**Family history**

The family history should include review of neuropsychiatric, psychiatric disorders, autoimmune and autoimmune inflammatory diseases, immunodeficiency syndromes, and frequent infections, including recurrent streptococcal pharyngitis (Table 3).

In one report, first-degree relatives of children with PANDAS were noted to have increased rates of OCD, tic disorders, and acute rheumatic fever, suggesting that children may have inherited a specific vulnerability to nonpyogenic poststreptococcal sequelae (Lougee et al. 2000). Maternal autoimmune diseases are also reported to be common among patients who meet criteria for PANDAS (Murphy 2010). It should be noted that neuropsychiatric disorders among siblings are particularly common and important to assess for as well. Psychiatric family history may provide important clues to genetic susceptibilities to OCD, anxiety, or mood disorders, ADHD, pervasive developmental disorder (PDD), and others. It should be noted that a positive psychiatric family history does not preclude considering a diagnosis of PANS.

In fact, a National Institute for Mental Health (NIMH) study found a 10-fold increase in rates of OCD and tic disorders among first-degree relatives of PANDAS probands (Lougee et al. 2000).

**Medical history and physical examination**

The medical history and physical examination should address not only the signs and symptoms characteristic of PANS (such as

<table>
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<tr>
<th>Table 1. Overview of PANS Evaluation</th>
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<tr>
<td>• Family history</td>
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<td>• Medical history and physical examination</td>
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<td>• Psychiatric evaluation</td>
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<tr>
<td>• Infectious disease evaluation</td>
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<tr>
<td>• Assessment of symptoms and history that points to need for further evaluation of immune dysregulation (autoimmune disease, inflammatory disease, immunodeficiency)</td>
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<td>• Neurological assessment</td>
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<td>• Assessment of somatic symptoms, including possible sleep evaluation</td>
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<td>• Genetic evaluation</td>
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PANS, pediatric acute-onset neuropsychiatric syndrome.

<table>
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<th>Table 2. Differential Diagnosis for Youth with PANS</th>
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<tr>
<td>• Obsessive compulsive disorder</td>
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<tr>
<td>• Anorexia nervosa</td>
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<td>• Avoidant/restrictive food intake disorder (ARFID)</td>
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<td>• Tourette syndrome</td>
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<td>• Transient tic disorder</td>
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<td>• Bipolar disorder</td>
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<tr>
<td>• Sydenham chorea</td>
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<tr>
<td>• Autoimmune encephalitis</td>
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<tr>
<td>• Systemic autoimmune disease*</td>
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<td>• Wilson’s disease*</td>
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*Relatively rare conditions.

PANS, pediatric acute-onset neuropsychiatric syndrome.
Neuro/Psychiatric findings is of particular interest, regarding both susceptibility to, and records can help construct a timeline of early behavioral problems presentation and past medical history. Review of the child's medical Wilson’s disease, among others). Therefore, the comprehensive features of disorders that must be excluded (SC, lupus, and Autism/pervasive developmental disorder Attention-deficit/hyperactivity disorder (ADHD), learning disorders, intellectual disability Personality disorders Autoimmune or autoinflammatory diseases Rheumatologic Idiopathic thrombocytopenia purpura (ITP), hemolytic anemia Antiphospholipid (APL) antibody syndrome Neurologic Guillain–Barré syndrome, transverse myelitis Multiple sclerosis or neuromyelitis optica (Devic’s disease) Acute disseminate encephalomyelitis (ADEM) Autoimmune encephalitis, brain vasculitis Gastroenterologic Celiac disease Inflammatory bowel disease (Crohn’s disease, ulcerative colitis) Irritable bowel syndrome, food intolerances (i.e. gluten, dairy) Dermatologic Alopecia, vitiligo, psoriasis Recurrent infections and immunodeficiency syndromes Recurrent infections: sinusitis, tonsilitis (especially strep), pneumonia, skin infections (i.e. staph), other infections. Chronic granulomatous diseases (CGD), common variable immunodeficiency (CVID), other immunodeficiency syndromes Idiopathic diseases Chronic fatigue syndrome, fibromyalgia, and other pain disorders PANS, pediatric acute-onset neuropsychiatric syndrome.

sensory abnormalities or choreiform movements), but also clinical features of disorders that must be excluded (SC, lupus, and Wilson’s disease, among others). Therefore, the comprehensive evaluation must be individualized according to the patient’s presentation and past medical history. Review of the child’s medical records can help construct a timeline of early behavioral problems and childhood illnesses. The infection history of parents and siblings is of particular interest, regarding both susceptibility to, and potential sources of, PANS/PANDAS related infections (especially GAS infections). PANS-related abnormalities that might be present on physical examination include: Dehydration or emaciation secondary to restricted intake of fluids or food; sequelae of compulsive behaviors (e.g., red ring around the mouth from excessive lip-licking, chapped hands from excessive washing or irritation of the external genitalia from excessive wiping); motor and/or phonic tics; evidence of sinusitis, chronic otitis, tonsillitis, or pharyngitis; and/or signs of GAS infection (i.e., pharyngitis, anal or vulvar redness, skin lesions).

Most youth with PANDAS have fairly normal neurological findings, but the frequency of neurological findings in youth with PANS is not well established. Choreiform movements, defined as fine piano-playing movements of the fingers when the child has arms and hands extended and eyes closed (Swedo et al. 1998, Touwen 1979) can be seen in children with PANS, but if full chorea is noted, workup for SC, antiphospholipid syndrome (APLS), lupus, and basal ganglia encephalitis should be pursued.

In addition to documenting physical evidence of PANS symptoms, a comprehensive review of systems and physical examination can help to exclude other medical conditions. The following is a list of the most pertinent PANS findings, signs of relevant rheumatogenic strep infection (known to trigger PANDAS and SC), and findings that are suggestive of other related conditions.

I. Constitutional symptoms (fevers, hair loss, weight loss, night sweats) that may indicate systemic autoimmune/inflammatory disease, immunodeficiency, chronic infection, or thyroid disorder

II. Skin: Scarlatiniform rash (scarlet fever), erythema marginatum (acute rheumatic fever), malar rash (lupus), petechiae (APLS), chronic urticarial rash (vasculitis, other), livido reticularis (polyarteritis nodosa and other rheumatologic disorders), perianal redness (perianal strep).

III. Eyes: Dilated pupils or slow pupillary response to light examination (PANS and other neurological diseases), dark discoloration under eyes (allergies or chronic sinusitis), scleral injection (uveitis, episcleritis, or scleritis), or Kayser–Fleisher rings (Wilson’s disease)

IV. Ear, nose, and throat: Recurrent, recent, or current tonsillitis, rhinosinusitis (chronic nasal congestion, nasal or postnasal discharge, sinus pressure or tenderness), hoarseness, otitis media, swollen nasal turbinates or “allergic salute” sign, petechiae on palate (APLS or Group A beta-hemolytic streptococci [GABHS] infection), or ulcer on palate (lupus)

V. Neck: Tymphadenopathy, thyromegalgy, limited range of motion

VI. Chest: Chest pain, cough, dyspnea signs, rales (infection, rheumatologic disease), tachycardia, murmur or click, prolonged PR on electrocardiogram (ECG) (acute rheumatic fever, infection, other inflammatory disorder)

VII. Abdomen: Constipation, diarrhea, abdominal pain, abdominal tenderness, blood or mucous in stool, which may suggest underlying bowel disease

VIII. Musculoskeletal: Pain, warmth, tenderness, redness, pseudoparalysis (arthritis and acute rheumatic fever), myofascial tenderness or tender points (fibromyalgia)

IX. Neurological:

A. Cognition: PANS patients are frequently inattentive. If more severe impairment in cognition or memory is
present, one should consider evaluation for inflammatory brain disease/autoimmune encephalitis.

B. Cranial nerves: These are typically normal in PANS patients.

C. Strength: PANS patients typically have normal strength but may exhibit mildly reduced proximal muscle weakness and slouched posture.

D. Fine motor skills: These can be normal or abnormal depending upon presence or absence of adventitious movements and developmental regression. Abnormalities may be elicited by having the child write, draw, or copy simple figures.

E. Abnormal movements: Motor or phonic tics are common in patients with PANS. Choreaiform movements (piano playing fingers) may be present. These movements can be elicited with a Romberg test in which the child stands with the hands outstretched and eyes closed for 60 seconds. Hand movements are considered abnormal in children >8 years.

F. Reflexes: These can be normal or minimally depressed in the acute phase of PANS/PANDAS.

G. Cerebellar examination: This is normal in patients with PANS.

H. Gait: This is normal in patients with PANS unless compulsions or tics interrupt gait. Chorea may be elicited by stressed-gait evaluations and should prompt evaluation for SC.

Other positive neurological signs should be followed up with the appropriate tests or referral to a neurologist.

Psychiatric evaluation

A comprehensive psychiatric evaluation is important in order to understand the full range of psychiatric symptomatology, psychiatric history, developmental history, response to previous or current psychotropic medications, and response to past or current psychotherapy. Ideally, a child with PANS should be evaluated by an experienced child psychiatrist or psychologist. At minimum, however, primary care evaluation should include the full range of psychiatric and behavioral symptoms associated with PANS, including not only OCD and eating disorders, but also emotional lability, mood disorders, ADHD, anxiety disorders, tic disorders, psychosis, and neurodevelopmental disorders including autism spectrum disorder.

A structured diagnostic interview such as the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (KSADS-PL) (Kaufman et al. 1997) may be useful, although these instruments were designed for research purposes and may be too cumbersome for clinical practice. If a structured interview is not used, it is particularly important to explore areas of potential embarrassment or sensitivity, including sexual or violent images and impulses, as these are common among patients with PANS (Frankovich et al. 2015a, in press). Self-injurious thoughts and behaviors also occur frequently and can be particularly worrisome in children with developmental regression and increased impulsivity. For example, children with PANS have made attempts at jumping out of a moving car or a second story window (Murphy et al. 2014).

Mental status examination

During an acute PANS episode, the child may appear hyperalert, unsmiling, anxious, and in the “fight or flight” mode. Parents may report that their child has a “terror-stricken look,” although this is often present only in the first few days of illness. Memory impairments appear to be part of the PANS syndrome. Children often cannot recall details of their symptoms or their impact on functioning. Emotional lability (emotional incontinence) is a hallmark symptom of PANS and is characterized by involuntary and often uncontrollable episodes of crying or laughing that are often mood incongruent (i.e. a patient might laugh uncontrollably when angry or frustrated). Depression is also common, particularly during the later stages of the illness, so that the child may present with a flat or depressed affect. Agitation, irritability, aggression, and temper tantrums/rage episodes are also common. Speech is often affected, with a variety of notable observations, including “baby talk” secondary to developmental regression, a paucity of speech, selective mutism, or new onset of stuttering. Severe impulsivity and compulsive behavior may be present. Insight may be limited.

However, children with PANS will often willingly acknowledge the OCD thoughts once they are reassured that they will not have to reveal their content. Children may experience auditory or visual hallucinations, as well as violent imagery, and suicidal or homicidal ideation. These experiences should be assessed specifically. Children with PANS are often highly aware of their unwanted thoughts and actions, and may be embarrassed by them and apologetic afterward.

General laboratory studies

All patients meeting PANS criteria should have the following:

- Complete blood cell count with manual differential
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Comprehensive metabolic panel
- Urinalysis (to assess hydration) and to rule out inflammation for children with urinary complaints; clean-catch urine culture for those with pyuria
- Throat culture, anti-streptolysin O (ASO) and anti-DNAse B

The following laboratory tests should also be considered:

- If there are elevated inflammatory markers, fatigue, rashes, or joint pain, antinuclear antibody (ANA) or fluorescent antinuclear antibody (FANA) should be obtained; if ANA is elevated proceed with lupus workup.
- Antiphospholipid antibody work up should only be pursued if the patient has chorea, petechiae, migraines, stroke, thrombosis, thrombocytopenia, or levido rash. Workup includes: anticardiolipin antibody, dilute Russell’s viper venom time (dRVVT), β 2-glycoprotein I antibodies.
- If abnormal liver function tests or Kayser–Fleischer rings are present, there is a need to evaluate for Wilson’s disease with ceruloplasmin and 24 urine copper tests.

Infectious disease evaluation

PANDAS. The diagnosis of PANDAS is based on evidence of recent or current streptococcal infection with onset or acute exacerbations. Streptococcal pharyngitis is confirmed with a properly performed throat culture or rapid antigen test. Rapid antigen tests are insufficiently sensitive; therefore, follow-up culture is required if the test is negative. Culture-proven GAS infection may also be documented at other symptomatic (to distinguish from asymptomatic sites in General laboratory studies section) sites, including the nasal cavity, skin and skin structure, and perianal or vaginal
areas. Perianal streptococcal infection may accompany onset or exacerbation of neuropsychiatric symptoms (Toufexis et al. 2014). A history of scarlatiniform rash, impetigo, and perianal or vulvar dermatitis, or deep tissue GAS infection during the preceding 6 months should also be obtained. Culture of nasal secretions is advised, as a small fraction of sinusitis is caused by GAS (Cherry et al. 2014). Serologic diagnosis of recent GAS infection can be made by demonstrating a 0.2 log₁₀ rise (a 58% increase) in either ASO or ADB, ordinarily obtained 4–8 weeks apart, although only 62% of new GAS acquisitions were followed by such a rise (Johnson et al. 2010). A single high titer, rather than serial acute and convalescent titers, is not diagnostically reliable, but may be considered contributory if levels exceed twofold (0.3 log₁₀) above the laboratory's stated upper limit of normal, because these higher levels are uncommon in children without recent streptococcal infection.

Asymptomatic acquisition of GAS can initiate a rise in ASO or ADB (Johnson et al. 2010). It is not established whether such acquisition can initiate PANDAS in the absence of antimicrobial treatment, although analogous experience with rheumatic fever (Garvey et al. 1998), a prospective school-based study (Murphy et al. 2007) and our anecdotal experience support this potential.

Children with PANDAS, their family members, and other close contacts should be vigilantly observed for symptoms of pharyngitis and other streptococcal infections, with prompt clinical assessment and diagnostic testing when appropriate.

PANS. Most instances of PANS are suspected to be postinfectious in origin, although no single microbe other than GAS has yet been consistently associated with the onset of PANS. Therefore, a detailed review and documentation of associated febrile and nonfebrile illnesses, including signs and symptoms and diagnostic testing, is advised. The most commonly observed antecedent infection seems to be upper respiratory infection, including rhinosinusitis, pharyngitis, or bronchitis. It is not yet clear if any one of those three presentations is more likely than the others to be associated with the initiation of PANS.

*Mycoplasma pneumoniae* has been associated with a number of postinfectious neurologic disorders (Muller et al. 2004; Walter et al. 2008), including a serologically diagnosed case closely resembling PANS (Ercan et al. 2008). It has also been documented anecdotally in a few cases by our group, and is therefore strongly suspected of being a stimulus for PANS. Because this organism is both persistent and treatable, the diagnosis may be pursued when a child with PANS or a family member has a history of cough, particularly cough lasting 1 week or more, with up to ≥4 weeks between cases (American Academy of Pediatrics 2012). *M. pneumoniae* causes pharyngitis and tracheobronchitis more often than pneumonia, although it is unusual in rhinosinusitis. Both serologic testing and polymerase chain reaction (PCR) are commercially available. Like streptococcal serology, serologic diagnosis of *M. pneumoniae* is most accurate when rising titers are demonstrated in serial sera. Antibodies peak in 3–6 weeks. Single titer immunoglobulin (Ig)M serology, usually available as an enzyme immunoassay, is convenient, but subject to both false positives and false negatives. PCR is highly sensitive, and can be performed on sputum or a throat swab. It is most sensitive during the first 3 weeks of illness, but may also detect a carrier state for prolonged periods. A combination of both PCR for early diagnosis, and serology for later diagnosis, may, therefore, have the highest diagnostic yield (Waites et al. 2008). Both tests may be positive in children without apparent symptoms. It is not known whether asymptomatic colonization alone is sufficient to initiate PANS.

*Influenza* is associated with a number of PANS cases associated with well-documented acute influenza, including influenza H1N1. A characteristic syndrome in the patient or family member during a recognized epidemic period may be considered presumptive evidence of this disease; rapid testing during the acute illness is only ~ 75% sensitive, whereas PCR testing is > 90% sensitive for detection of this disease.

*Epstein Barr virus* infection has been reported to precede various neuropsychological disorders (Caruso et al. 2000). We have observed several children with an acute neuropsychiatric disorder associated with serologically diagnosed Epstein Barr virus infection. These examples seem to be somewhat more complex than typical cases of PANS.

*Borrelia burgdorferi* (Lyme disease) is under suspicion because it has been associated with a wide range of postinfectious neuropsychiatric disorders, including a small number of cases with obsessive-compulsive disorder (Fallon et al. 1998). However no known cases of post-Lyme disease PANS have been noted. Diagnostic testing for Lyme disease, according to guidelines of the Centers for Disease Control (Centers for Disease Control and Prevention 2011) may be considered for children with PANS who: 1) Have a history of an illness compatible with prior clinical Lyme disease, and 2) live in regions in which the presence of Lyme disease is established. In the United States, this is almost exclusively limited to the six New England states, New York, New Jersey, Pennsylvania, Maryland, Virginia, Minnesota, and Wisconsin. Focal regions are also found in North Dakota, Iowa, Indiana, West Virginia, Illinois, and California (Centers for Disease Control and Prevention 2013).

As for other infectious disorders, we have anecdotally documented a few instances of herpes simplex infection and varicella related to PANS onset or flares. We believe that numerous other infectious agents, particularly those with characteristically prolonged colonization, have the potential to activate PANS as well. Appropriate documentation of such infections is warranted whenever suggested clinically.

**Evaluation for autoimmune and autoinflammatory diseases**

Neuropsychiatric symptoms can be caused by autoimmune encephalitis, systemic autoimmune disease, and other inflammatory diseases. Therefore, it is important to consider these etiologies. However, workup for these conditions should be done in a thoughtful manner, and only pursued if relevant symptoms are present. False positive antibody tests are common, and are meaningless if criteria for a clinical syndrome are not met. The identification of antibodies in patients can be very distressing for families, because the concept of false positivity can be difficult for a layperson to understand, especially where there is a severely ill child.

The diagnostic guidelines and indications for workup of autoimmune encephalitis are broad, and not within the scope of this article to discuss, but these conditions should be considered in cases in which one of the following symptoms is prominent: 1) Delirium, psychosis, and/or diffuse encephalopathy; 2) pervasive cognitive decline; 3) persistent memory impairment; 4) pervasive behavior deterioration; 5) seizures; and 6) movement abnormality not consistent with tics. The evaluation for autoimmune encephalitis includes neuroimaging, electroencephalogram (EEG), neuronal antibody testing (e.g., N-Methyl-d-aspartate [NMDA] receptor antibodies, voltage gated potassium channel antibodies) in serum and cerebrospinal fluid (CSF), thyroid antibodies...
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<tr>
<th>Condition/disease</th>
<th>Description of pain</th>
<th>Important comorbid symptoms to consider</th>
<th>Physical examination</th>
<th>Objective data to help confirm diagnosis</th>
<th>What to do</th>
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<tr>
<td>Pain processing disorder (reflex sympathetic dystrophy, reflex neurovascular dystrophy, fibromyalgia)</td>
<td>Musculoskeletal pain often out of proportion to physical examination findings</td>
<td>Sleep dysfunction Waking unrefreshed Sensory amplification and sensory integration problems (hyperacusis, photophobia, disrupted taste/smell, vision changes) Abdominal pain Headaches/ temporomandibular joint (TMJ) pain</td>
<td>Fibromyalgia tender points and trigger points Diffuse tenderness/pain and hypersensitivities</td>
<td>None</td>
<td>Amitriptyline (5–10 mg before bed) Gabapentin Biofeedback Cognitive behavioral therapy Referral to pain medicine specialist</td>
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<td>Acute rheumatic fever</td>
<td>Migratory arthritis of large joints. If patient took nonsteroidal anti-inflammatory drugs (NSAIDS), then history of monoarthritis predominates. Joint pain is often out of proportion to physical examination findings</td>
<td>Carditis Erythema marginatum (evanescent faintly red, nonpuritic, annular rash with serpiginous borders, typically involving the trunk, which is more prominent after a hot bath) Sydenham's chorea (SC)</td>
<td>Tachycardia and/or heart murmur may indicate carditis. Pseudoparalysis of affected joint (as this is transient, it may not be seen on examination but may be elicited in history). Joint effusions are rare.</td>
<td>At time of carditis, rash, arthritis (but not SC) erythrocyte sedimentation rate (ESR), anti-streptolysin O (ASO), DNAseB are all highly elevated. Electrocardiogram (tachycardia, prolonged PR) Joint imaging typically normal or small effusion can be seen.</td>
<td>Refer back to PMD and/or pediatric rheumatologist for full work up and determination of antibiotic prophylaxis. Order echocardiogram if patient has pathologic heart murmur.</td>
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<td>Juvenile arthritis (including spondyloarthropathy, enthesitis-related arthritis, reactive arthritis, psoriatic arthritis, and idiopathic arthritis) Arthritis can also be seen in lupus, mixed connective tissue disease, and Sjögren's syndrome.</td>
<td>Pain and stiffness in one or more joints including the feet, heels, buttocks, neck, and/or back – worse in the morning and with prolonged stationary positions, may get better with movement and NSAIDS Finger pain and stiffness with writing TMJ pain with chewing</td>
<td>Red painful eye may indicate acute (symptomatic) uveitis/iritis. Asymptomatic uveitis/iritis will present with blurry vision only. TMJ pain may indicate pain processing disorder or destructive arthritis of TMJ joint. Quadriceps muscle weakness is common in patients with spondyloarthropathy. Psoriasis would indicate dry arthritis (swelling may not be apparent).</td>
<td>Warmth, swelling, and/or limited range of motion including neck and lower back (forward bending) Tenderness at insertion sites of tendons and ligaments (plantar fascia, Achilles tendon, patellar insertion sites, sacroiliac [SI] joints). Psoriasis (look behind ears, umbilicus, intergluteal cleft)</td>
<td>Ultrasound (if expertise available) or MRI to look for evidence of active inflammation. Radiographs show damage in cases of long-standing arthritis or destructive arthritis. Osteopenia and sclerosis can be present before erosive changes seen. ESR and C-reactive protein (CRP) are elevated in some patients.</td>
<td>Refer to pediatric rheumatologist for formal evaluation including interpretation of physical examination, and imaging, and to order blood work for categorization of arthritis. There are no laboratory tests that are diagnostic or are used to “screen” for arthritis. Diagnosis is based on physical examination and imaging.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Condition/disease</th>
<th>Description of pain</th>
<th>Important comorbid symptoms to consider</th>
<th>Physical examination</th>
<th>Objective data to help confirm diagnosis</th>
<th>What to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease or abdominal bowel disease</td>
<td>Recurrent abdominal pain, gaseousness (burping, flatulence), diarrhea, growth impairment</td>
<td>Sideropenic anemia, arthralgias, arthritis, enthesitis, fatigue and cognitive blunting, migraines, seizures, myelitis, stance and gait problems (afferent ataxia, vestibular dysfunction, cerebellar ataxia) Thyroiditis, type 1 diabetes, osteopenia, alopecia, hepatic steatosis, dental enamel hypoplasia</td>
<td>Abdominal tenderness and/or distension, Dermatitis herpetiformis</td>
<td>Elevated tissue transglutaminase antibodies Small bowel biopsy shows villous blunting.</td>
<td>Refer to gastroenterologist for formal evaluation.</td>
</tr>
<tr>
<td>Inflammatory bowel disease (IBD)</td>
<td>Abdominal pain or tenderness, diarrhea, constipation, mucus or blood in stool, growth impairment</td>
<td>Anemia Arthralgias or arthritis Enthesitis (knees, heels, feet) Back, neck, or buttock pain.</td>
<td>Abdominal tenderness Rectal tags</td>
<td>Barium studies, CT, MRI, and endoscopy (with pathology) can all show signs of IBD.</td>
<td>Refer to gastroenterologist for formal evaluation.</td>
</tr>
</tbody>
</table>

PANS, pediatric acute-onset neuropsychiatric syndrome.
(thyroglobulin antibodies, thyroperoxidase antibodies), and paraneoplastic evaluations.

All patients should have a screening complete blood count with differential (CBC-D) (with peripheral blood smear), ESR, and CRP to evaluate for systemic inflammatory process. If significant anemia is present, further medical workup should include iron studies and consideration of inflammatory bowel disease or systemic autoimmune disease. Persistent thrombocytopenia and/or leukopenia may be a sign of systemic autoimmune diseases including lupus and other connective tissue diseases. Systemic lupus erythematosus (SLE), Sjögren’s syndrome, and APLS can present with prominent neuropsychiatric symptoms including depression, headaches, seizures, psychosis, and movement disorders. OCD, eating restriction, and anxiety can be exacerbated by systemic illness (such as lupus) and severe anemia, and in patients experiencing a high level of stress from nonmedical causes.

If the patient presenting with PANS has elevated inflammatory markers (ESR or CRP) and/or cytopenias (low blood counts), and/or dry eyes or dry mouth (not caused by medications) then a screening ANA test should be obtained. If the ANA is positive, then ANA subtypes (i.e., the ANA panel) should be ordered so that lupus-specific antibodies (double stranded [ds]DNA, Smith, RNP) and Sjögren’s syndrome-related antibodies (SSA or anti-Ro and SSB or anti-La) may be detected. Additionally, if the ANA is positive, then obtaining complement levels (C3 and C4) can also guide evaluation. If the patient shows evidence of a positive result on the ANA panel and low complement levels or systemic features, the patient should be referred to a pediatric rheumatologist. It is important to keep in mind that a positive ANA is found in 12–13% of healthy children (Hilario et al. 2004; Satoh et al. 2012); therefore, a positive ANA alone does not warrant referral to rheumatology. The rate of positive ANAs in patients with PANDAS and PANS may be higher than the baseline in the pediatric population, an association that is currently undergoing additional examination.

Histone antibodies are associated with drug-induced lupus and lupus cerebritis, and have been reported to be positive in 17% of PANS patients (Frankovich et al. 2015b, in press). Although anti-histone antibodies are of research interest, at this time they do not inform clinical management of PANS patients except in cases in which patients also meet criteria for SLE.

APL antibodies should be ordered in for patients with PANS if the patient has any of the following: Persistent thrombocytopenia, persistent petechiae, chorea, clinical thrombosis, migraines, strokes, or livedo reticularis. The APL workup is costly and should only be ordered if indicated. The APL workup includes the following: β 2-glycoprotein antibodies, anticardiolipin antibodies (IgG, IgM, IgA), DRVVT, and lupus anticoagulant. Abnormal results should be interpreted by a rheumatologist.

Behcet’s disease can also present with neuropsychiatric symptoms, and should be considered in patients with recurrent oral and/or genital ulcers. It is necessary to examine the skin for signs of skin involvement (acneiform lesions, papulo-vesiculopustular eruptions, pseudofolliculitis, nodules, erythema nodosum, superficial thrombophlebitis, pyoderma gangrenosum-type lesions, erythema multiforme-like lesions, and palpable purpura), perform a pathergy test, consider HLA-B5 testing, and refer the patient to ophthalmology for evaluation of uveitis, as well as to rheumatology if criteria for Behcet’s disease is met.

Patients meeting criteria for PANS commonly report pain, including chest pain, abdominal pain, headaches, musculoskeletal pain, and fatigue. Many of these patients meet criteria for a pain processing disorder (e.g., fibromyalgia) (Frankovich et al. 2015a, in press), and a minority have comorbid autoimmune/inflammatory disease. The psychiatric symptoms that PANS patients report are often so severe that they overshadow pain complaints. Therefore, we recommend asking about pain in all patients with PANS. Depending upon the pattern of pain and the physical examination, one would consider the following causes of joint pain and/or abdominal pain: Acute rheumatic fever, juvenile arthritis, inflammatory bowel disease, and celiac disease. Table 4 provides details regarding the workup of pain in patients with PANS.

Immune complex panels and ferritin levels are of interest from the research standpoint, but at this juncture, these tests do not inform clinical management of patients with PANS unless disease-specific symptoms are also present.

Neural autoimmunity

Testing for the presence of cross-reactive antineuronal antibodies may help guide diagnosis toward or away from PANS. Serum samples from acutely ill children with SC or PANDAS show elevated titers of antibodies against lysosomanglioside (Kirvan et al. 2006a), tubulin (Kirvan et al. 2007), dopamine D2 receptor (Brimberg et al. 2012; Ben-Pazi et al. 2013; Cox et al. 2013), and dopamine D1 receptor (Ben-Pazi et al. 2013). More importantly, in both SC and PANDAS, the antibodies produced activation of calcium calmodulin protein kinase II (CaMK II) in the SK-N-SH human neuronal cell line (Kirvan et al. 2003, 2006b). Activation of CaMK II results in neuronal excitation and increased dopamine transmission (Kirvan et al. 2006b), which may be at least partially responsible for PANS symptoms. Recent studies have shown that IgG in youth with SC and PANDAS reacts with and signals the dopamine D2 receptor expressed in transfected cell lines (Cox et al. 2013). Similar results have also been shown for the D1 receptor expressed in transfected cell lines, but those data are not yet published (Cunningham, et al., unpublished data). Currently, Molecular Labs (www.moleculera.com) is the only Clinical Laboratory Improvement Amendments (CLIA)-certified/Commission on Office Laboratory Accreditation (COLA)-accredited laboratory that provides testing for antitubulin, antilysocephaglycoside and ant-idopamine receptor antineuronal antibody titers by enzyme-linked immunosorbent assay (ELISA), as well as assays to measure CaMKII signaling. Although the Moleculara panel can provide useful ancillary information for children with suspected PANDAS, it is not yet clear that the assays are helpful for the larger cohort of children meeting PANS criteria (without GAS etiology). More research is needed to delineate the sensitivity and specificity of these tests for youth with PANS.

Evaluation for immunodeficiency

Some reports indicate that certain patients with Tourette syndrome, OCD and PANDAS have an increased tendency to develop infections or to show other evidence of immune dysfunction (Hornig 2013). Preliminary studies highlight altered immunoglobulin profiles (IgM, IgG subclasses, IgA) and decreased regulatory T cell count among this population compared with healthy controls (Kawikova et al. 2007, 2010; Bos-Veneman et al. 2011).

PANS patients should undergo an immunodeficiency assessment if there is a history of repeated infections, infection with an atypical organism or an unusual clinical course, first-degree family member with a history of overwhelming and/or fatal infection, or if the clinician is considering intravenous immunoglobulin
(IVIG) treatment. Patients with solely autoimmune features should also have an immune evaluation, as autoimmunity may initially present as the sole feature of immune dysregulation.

Immunodeficiency screening should proceed in multiple steps, complemented with repeated clinical evaluation of the patient. Initial workup should include the following:

I. Lymphocyte subsets (T, B, natural killer [NK] cells) with CBC with manual differential.
II. Quantitative immunoglobulins (IgG, IgA, IgM, IgE) with IgG subclasses
III. Vaccine responses (Pneumococcus and tetanus antibody titers)

If the initial evaluation is reassuring, no further workup is needed. If the evaluation is abnormal and raises concerns about potential immune deficiency, the patient should be referred to an immunologist for further evaluation. Additional blood work may include: B and T cell maturation panel, postvaccination antibody titers at least 4 weeks following pneumococcal polysaccharide vaccine (Pneumovax 23), and T cell functional studies or any additional immune phenotyping relevant to the clinical history or prior laboratory findings.

Additional diagnostic evaluations

Brain MRIs are helpful when other conditions are suspected (e.g., central nervous system [CNS] small vessel vasculitis, limbic encephalitis) or when the patient has severe headaches, gait disturbances, cognitive deterioration, or psychosis. For particularly severe cases, an MRI with T-2 weighted images or contrast enhancement may be useful in demonstrating inflammatory changes in the basal ganglia, including volumetric changes (Giedd et al. 1996, 2000).

EEGs, particularly overnight evaluations, may be helpful in demonstrating focal or generalized slowing and/or epileptiform activity. These signs of abnormal brain activity or irritability were found in 7 of 42 (16%) patients with PANDAS (Zhou et al. 2014). Similarly, polysomnography (PSG) also called ‘sleep studies’ might reveal evidence of obstructive sleep apnea or abnormalities of sleep architecture, particularly in children with recent onset of insomnia or parasomnias (e.g., sleepwalking, night terrors). No data are yet available for results of PSG evaluations in PANS, but PSG studies in 11 children with PANDAS revealed parasomnias, periodic limb movements, and abnormalities of rapid eye movement (REM) sleep, including REM behavior disorder and non-specific REM motor disinhibition (Hommers et al. 2014). If the PSG reveals specific abnormalities of sleep architecture, they may be targets of specific pharmacologic interventions, such as use of benzodiazepines for REM behavior disorder.

Lumbar puncture (LP) should be considered if there are MRI or EEG abnormalities, or encephalopathic symptoms such as delirium, alteration of consciousness, seizures, or psychosis. If an LP is done, the CSF evaluation should include oligoclonal bands, as well as standard measures such as glucose and protein. In addition, assays for antineuronal antibodies, such as anti-NMDA receptor antibodies, should be performed by a reliable laboratory (e.g., the Neuroimmunology Laboratory at Mayo Clinic Laboratories, directed by Dr. Vanda Lennon.)

Swallowing studies might be indicated for children with restricted food intake, particularly when related to fears of choking or vomiting. In SC, swallowing studies revealed dysphagia related to motor abnormalities and dyscoordination of the voluntary/involuntary muscles of the esophagus (Swedo et al. 1994).

Discussion

The recommended diagnostic workup for youth with suspected PANS presented here represents a consensus of the expert panel assembled. It is not intended to be algorithmic; therefore, clinicians should use these guidelines along with their best judgment. Although we tried to be as comprehensive as possible, we are aware that individual cases may require evaluation that is not mentioned here. As with all new presentations of psychiatric disease and/or escalations of psychiatric symptoms, investigation into the history must include the medical history (with emphasis on recent illnesses, exposures, fevers, history of painful joints, abdominal pain), review of systems (including discussion about pain and relevant rashes, such as scarlatina rash, erythema marginatum), and physical examination (with focus on evaluating chorea and choreiform movements). Since this syndrome presents with prominent behavior regression and personality change, reactionary social disruptions (including issues with school functioning, friends, and parent accommodation) may give the appearance of there being a psychosocial cause to the illness. Acute-onset neuropsychiatric symptoms can be related to psychosocial traumas/stress, but trauma/stress response should be a diagnosis of exclusion. There is also clinical overlap between the symptoms of PANS and those of conversion disorder and psychosomatic illnesses. Therefore, a comprehensive history, psychiatric interview, and complete physical examination are critical in all cases of suspected PANS.

During the evaluation of children with PANS, it is particularly important to consider alternative medical explanations for the neuropsychiatric symptoms. Lupus cerebritis and the various autoimmune encephalitides may present with isolated cognitive and behavioral symptoms, personality change, and other symptoms (Dale and Brillot 2012). Referral to a neurologist or rheumatologist can be helpful in some cases, but should be focused on specific signs or symptoms of concern, as the subspecialists may not be experienced with the evaluation of psychiatric symptomatology. Therefore, the responsibility of evaluating PANS falls to primary care clinicians and child psychiatrists. In the future, empirically based algorithms for diagnosis and treatment will be developed.

Until then, we hope that this article serves as a starting template for the proper evaluation of youth with PANS.

Disclosures

Dr. Chang is an unpaid consultant for GlaxoSmithKline, Lilly, and Bristol-Myers Squibb. He is on the DSMB for Sunovion. In the past two years he has received research support from GlaxoSmithKline and Merck. Dr. Walter is on the Advisory Board of Baxter regarding IGHy, a new formulation of subcutaneous immunoglobulin.

Dr. Madeleine Cunningham is co-founder and chief scientific officer of Moleculera Labs, which provides specialized antineuronal antibody testing. Several members of the PANS Collaborative Consortium have scientific collaborations with Dr. Cunningham. The other authors have nothing to disclose.

References


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Characterization of the Pediatric Acute-Onset Neuropsychiatric Syndrome Phenotype

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Abstract

Objective: Pediatric acute-onset neuropsychiatric syndrome (PANS) is a subtype of obsessive compulsive disorder (OCD) marked by an abrupt onset or exacerbation of neuropsychiatric symptoms. We aim to characterize the phenotypic presentation of youth with PANS.

Methods: Forty-three youth (ages 4–14 years) meeting criteria for PANS were assessed using self-report and clinician-administered measures, medical record reviews, comprehensive clinical evaluation, and laboratory measures.

Results: Youth with PANS presented with an early age of OCD onset (mean = 7.84 years) and exhibited moderate to severe obsessive compulsive symptoms upon evaluation. All had comorbid anxiety and emotional lability, and scored well below normative means on all quality of life subscales. Youth with elevated streptococcal antibody titers trended toward having higher OCD severity, and presented more frequently with dilated pupils relative to youth without elevated titers. A cluster analysis of core PANS symptoms revealed three distinct symptom clusters that included core characteristic PANS symptoms, streptococcal-related symptoms, and cytokine-driven/physiological symptoms. Youth with PANS who had comorbid tics were more likely to exhibit a decline in school performance, visuomotor impairment, food restriction symptoms, and handwriting deterioration, and they reported lower quality of life relative to youth without tics.

Conclusions: The sudden, acute onset of neuropsychiatric symptoms, high frequency of comorbidities (i.e., anxiety, behavioral regression, depression, and suicidality), and poor quality of life capture the PANS subgroup as suddenly and severely impaired youth. Identifying clinical characteristics of youth with PANS will allow clinicians to diagnose and treat this subtype of OCD with a more strategized and effective approach.

Introduction

Swedo et al. (1998) first examined the clinical characteristics of youth with a sudden onset of obsessive compulsive disorder (OCD) and/or tic symptoms, using a systematic clinical evaluation of 50 youth who met diagnostic criteria for pediatric autoimmune neuropsychiatric disorder associated with Streptococcus (PANDAS). Although youth with PANDAS had symptoms similar to those with non-PANDAS OCD (e.g., obsessive thoughts, compulsive behaviors, avoidance), they differed notably in the onset of their obsessive compulsive symptoms. Youth with PANDAS experienced a sudden, severe onset of neuropsychiatric symptoms temporally associated with group A streptococcal (GAS) infection, relapsing-remitting symptom course, and early age of OCD onset (mean = 7.4 years), and frequently presented with psychiatric comorbidities, most notably attention-deficit/hyperactivity disorder (ADHD), mood disorders, and anxiety. Symptom severity of both OCD and tics was found to be in the moderate range. Although Swedo et al. (1998) found that episodic symptom exacerbations were associated with GAS exposure, documented GAS infection, pharyngitis and/or upper respiratory infection (e.g., no throat culture obtained), these infection-related indicators did not explain all episodic symptom exacerbations. Beyond this seminal study, few other studies have systematically explored associations between the PANDAS phenotype and clinical characteristics (Bernstein et al. 2010; Murphy et al. 2012).

Collectively, findings suggest associations between PANDAS and the presence of comorbid ADHD (Swedo et al. 1998; Murphy et al. 2007; Leslie et al. 2008; Murphy et al. 2012), separation anxiety (Swedo et al. 1998; Murphy and Pichichero 2002; Bernstein et al.

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Characterization of PANS Phenotype

2010), vocal and motor tics (Bernstein et al. 2010; Swedo et al. 2012), frequent urination (Murphy and Pichichero 2002; Bernstein et al. 2010; Murphy et al. 2012), handwriting deterioration (Bernstein et al. 2010; Murphy et al. 2012), and decline in school performance (Bernstein et al. 2010; Murphy et al. 2012). Additionally, Murphy et al. (2012) found that children with PANDAS were more likely to present with dramatic onset of symptoms, complete remissions, temporal association of symptoms with GAS infection, and clumsiness. For youth with PANDAS, the presence of elevated streptococcal titers has been linked with greater OCD symptom severity (Murphy et al. 2004; Lewin et al. 2011), visual-spatial memory deficits (Hirschlitt et al. 2009; Lewin et al. 2011), impaired executive functioning, lower speeded dexterity (Lewin et al. 2011), and an ADHD diagnosis (Peterson et al. 2000).

While these studies have documented and characterized the presence of PANDAS among youth with OCD and/or tics, there are several challenges confronting a comprehensive investigation of youth who experience a sudden onset of obsessive compulsive symptoms (e.g. small sample size, varied methodology, narrow diagnostic criteria). Most notably, clinicians are confronted with the difficulty of diagnosing youth who meet all but one criterion of the PANDAS subtype, namely evidence of GAS infection before symptom onset. For example, Swedo et al. (1998) and Murphy et al. (2012) excluded 27 and 15 youth, respectively, with acute-onset OCD because of lack of evidence of GAS infection. In response to these concerns, pediatric acute-onset neuropsychiatric syndrome (PANS) was proposed as a broader term that encompasses acute-onset neuropsychiatric symptoms without a specified environmental or immune-related trigger (Swedo et al. 2012). This newly minted PANS criteria encompass youth who experienced an abrupt onset of OCD and/or food restriction with at least two neuropsychiatric symptoms (e.g., sensory symptoms, handwriting deterioration, separation anxiety, and emotional lability) whose collective presentation cannot be better explained by another neurological or medical disorder.

Given that prior research to date has only focused on youth meeting full PANDAS criteria, this narrow perspective may have limited our understanding of acute-onset OCD by overlooking youth with neuropsychiatric symptoms brought on by other exposures, including viral illnesses (Hoekstra et al. 2005), mycoplasma (Müller et al. 2004), environmental triggers (Molina and Shoenfeld 2005), or no immune-related dysfunction at all. This study examined the phenotypic presentation of 43 youth who met the proposed PANS criteria, making it one of the largest cohorts to examine for factors influencing PANS presentation to date. Based on prior reports, we hypothesized that differences in presentation may exist secondary to the presence or absence of tics and/or evidence of infectious trigger. Additionally, given that acute-onset food restriction is a primary diagnostic criterion for PANS, we hypothesized that this presentation may have characteristics that distinguish it from non-food restriction OCD.

Methods

Participants

Participants were recruited at the University of South Florida’s pediatric neuropsychiatry clinic, into an ongoing study investigating azithromycin as a PANS treatment. Youth were briefly pre-screened (n=202) for approximate eligibility via a telephone interview that assessed onset characteristics, presence of OCD, and relevant medical history (e.g., rheumatic fever, autism diagnosis, chronic degenerative neurological disease). Among the youth that met screen criteria but did not participate in the study (n=97), most could not commit because of the long travel distance and a preference to pursue treatment locally.

Youth were eligible to participate in the study if they met the following criteria: Having an acute-onset or relapse of moderate to severe OCD symptoms (Children’s Yale-Brown Obsessive Compulsive Scale [CY-BOCS] Total Severity Score ≥ 16; Lewin et al. 2013) within 6 months of evaluation; having a sudden and severe co-occurrence of at least two neuropsychiatric symptoms (e.g., anxiety, emotional lability, tics, frequent urination, food restrictive symptoms; Swedo et al. 2012); being between the ages of 4 and 14 years; and being either medication free or on a stable dose of a neuropsychiatric medication (4 weeks for most medications and 8 weeks for selective serotonin reuptake inhibitors [SSRIs]).

Youth were excluded from participation if any of the following criteria were met: Gradual onset or duration of OCD symptoms >6 months; receiving extended course antibiotics and/or other immune therapy for PANS; a primary diagnosis of tics (rather than OCD); receiving exposure-based cognitive behavioral therapy (CBT); a history of nonresponse to a prior antibiotic trial; or a diagnosis of autism spectrum disorder, intellectual deficiency, and/or chronic neurological disease. Forty-three youth between 4 and 14 years of age (mean=8.06, SD=2.72) were enrolled, and 42 met inclusion criteria. One participant had a severe onset of OCD 6 weeks before baseline, and was placed on amoxicillin/clavulanic acid 8 days before assessment. He showed dramatic improvement within 3 days of starting the antibiotic course, and had mostly remitted by the time of consent. Therefore, his reported symptoms are included in the analysis. Approximately half of participating youth were male (n=24, 56%), with race and ethnicity being represented as follows: Caucasian (n=40, 93%), Hispanic (n=1, 2%), Asian American (n=1, 2%), and African American (n=1, 2%).

Measures

Clinician ratings. Raters were trained using the same training videos, and rater training was overseen by the first author (T.K.M.). The Infection-related OCD/Tic Evaluation (I-ROTE) (Murphy et al. 2012) was created and administered by first author (T.K.M.), to the parents of each participant. This measure provided information that was relevant to diagnosis, including the nature of symptom onset and temporal association with infectious trigger, symptom course from onset to baseline assessment, presence of comorbidities, and descriptive information about the participant’s presenting problems. The I-ROTE has demonstrated high interrater reliability (intraclass correlation coefficient = 0.86) when used to determine PANS/PANDAS caseness (Murphy et al. 2012).

The CY-BOCS (Scahill et al. 1997) is a clinician-rated measure to assess the severity of a child’s obsessions and compulsions. Children and parents were asked to indicate the presence of specific obsessions and compulsions and rate overall severity based on frequency, interference, distress, resistance, and control over symptoms. The CY-BOCS Total Score has demonstrated good reliability and validity (Scahill et al. 1997; Storch et al. 2004; Lewin et al. 2013).

The study physician used the Clinical Global Impressions-Severity (CGI-S) scale (Guy 1976) to assess the severity of OCD, tics, mood, and neurocognitive symptoms for each of the symptom domains. This is a seven item scale that ranges from no illness/remitted (0 points) to extremely severe/completely nonfunctional (6 points).
The CGI-PANS (CGI-P), an adapted version of the CGI-S created by the first author (T.K.M.), assessed the severity and presence of core PANS symptoms. Core PANS symptoms were chosen based on the criteria described by the PANS Consortium (Swedo et al. 2012). Validity support for the measure has come from positive associations with relevant PANS criteria.

The Child-Global Assessment Scale (C-GAS) (Shaffer et al. 1983) was used to assess a child’s overall level of psychological functioning based on clinical information obtained from the parent and child. Scores range from 0 to 100, with higher scores indicating better functioning at home and school, and with peers.

The Yale Global Tic Severity Scale (YGTSS) (Leckman et al. 1989) is a psychometrically sound clinician-rated measure designed to assess the presence and severity of a child’s tics. Children and parents were asked to indicate the presence of motor and/or vocal tics, and rate the overall severity based on number, frequency, intensity, complexity, and interference of symptoms. The YGTSS Total Tic score ranges from 0 to 50, with higher scores representing greater tic severity.

The Rey-Osterrieth Complex Figure Test (REY-O) (Meyers and Meyers 1995) is a test of visuospatial constructional ability, organizational skill, planning, and memory for complex information. The measure consists of four subtests: Copy, immediate recall, delayed recall, and recognition tasks. Strong psychometric properties have been observed for individuals between 6 and 89 years of age and it has been used extensively among youth with OCD (Lewin et al. 2014). Age-corrected t scores were provided, except in the case of the copy task, where an age-based percentile was utilized. Normative data for children ≥ 6 years of age are available (Meyers and Meyers 1995), with no normative data available for youth < 6 years of age. Youth scoring < 1% on the copy task were classified as having significant visuospatial/motor impairment.

The Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition (BEERY VMI) (Beery 1997) is a test of visual-motor abilities that consists of 24 geometric forms arranged in order of increasing difficulty, particularly targeted to preschool populations (Klein 1978). The scores are determined by the number of figures that are copied successfully prior to three consecutive failures. This assessment was conducted in youth ages 4–7 in lieu of the Rey-O. Youth were classified as having significant visuospatial/motor impairment when scoring in the 37th percentile or below (approximately one standard deviation or greater below the mean).

Parent/child ratings. The PANDAS/PANS Scale is a parent self-report form developed by the first author (T.K.M.) to assess common PANDAS/PANS symptoms (i.e., frequent urination, obsessions, compulsions, tics, and separation anxiety), based on the criteria proposed by the PANS Consortium (Swedo et al. 2012). This measure is also effective in capturing PANS exacerbation, as it asks the rater whether each current symptom had been possibly better/same (0 points) within the past week. The maximum score possible is 54.

The Swanson, Nolan, and Pelham-IV Scale (SNAP-IV) (Swanson 1995) is a parent-rated measure to assess the presence of ADHD-related symptoms, including inattention, impulsivity/hyperactivity, and oppositionality. Each item is scored for severity on a four point scale, ranging from not at all (0 points) to very much (3 points). Total scores were averaged to assess overall severity of the sample, and individual item scores were assessed to identify participants who met cutoffs for each ADHD-related symptom (see Table 1 for cutoff values).

### Table 1. Frequency of Clinical Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Panic/Somatic</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Generalized anxiety disorder (GAD)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Separation anxiety disorder (SAD)</td>
<td>33 (77)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>12 (28)</td>
</tr>
<tr>
<td>School avoidance</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Mood and behavioral symptoms</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Emotional liability and/or increased irritability</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Anxious/Depressed</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Withdrawal/Depression</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Social problems</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Thought problems</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Attention problems</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Rule-breaking behavior</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Suicidality (n = 33)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Behavioral regression</td>
<td>36 (84)</td>
</tr>
<tr>
<td>Deterioration in school performance</td>
<td>36 (88)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>36 (84)</td>
</tr>
<tr>
<td>Tics</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Simple</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Complex</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Sensory abnormalities</td>
<td>26 (61)</td>
</tr>
<tr>
<td>Urinary problems</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Frequent urination (pollakiuria)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Emuresis</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Handwriting deterioration in youth ages 7–14 years (n = 30)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Food restriction</td>
<td>20 (47)</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Inattention</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Impulsivity/hyperactivity</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Oppositionality</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Irrational thinking and/or psychotic symptoms</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Olfactory hallucinations</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Choreiform movements</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Anorexia (not caused by PANS-OCD)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Visuospatial/Motor impairment (n = 42)</td>
<td>28 (67)</td>
</tr>
<tr>
<td>Obsessive compulsive symptoms</td>
<td>39 (91)</td>
</tr>
<tr>
<td>Harm to self and/or others</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Ordering and/or arranging, symmetry</td>
<td>29 (67)</td>
</tr>
<tr>
<td>Contamination</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Sexual and/or religious</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Collecting and/or hoarding</td>
<td>14 (32)</td>
</tr>
</tbody>
</table>

Symptom headings are proposed core PANS diagnostic criteria symptoms.

*As measured by the Swanson, Nolan, and Pelham-IV Scale (SNAP-IV) copy subtest or < 37% on the Rey-Osterrieth Complex Figure Test (REY-O) copy subtest or < 3% on the Swanson, Nolan, and Pelham-IV Scale (SNAP-IV) inattention (cutoff = 1.78), impulsivity/hyperactivity (cutoff = 1.44), and oppositionality (cutoff = 1.88).

As measured by the Child Behavior Checklist (CBCL) subscales (n = 41). T scores > 70 were considered clinically significant.
The Screen for Child Anxiety Related Emotional Disorders-Child and Parent (SCARED) (Birmaher et al. 1997) is a child and parent self-report form to measure severity of child anxiety symptoms, including general anxiety, separation anxiety, panic disorder, social anxiety, and school anxiety. Each item is scored for severity on a three point scale, ranging from not true or hardly ever true (0 points) to very true or often true (2 points). The SCARED total scores were averaged to assess overall anxiety severity of the sample, and individual item scores were used to identify presence of anxiety subtypes.

The Tourette’s Disorder Scale (TODS) (Shytle et al. 2003) is a 15 item parent self-report form that assesses child behaviors (i.e., hobbies, responsibilities, friendships) and items that describe children’s tendencies. The CBCL provides a Total Behavior Problem Score and several subscales, including: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. For each subscale, participants were considered to have clinically significant symptoms if they had a T score > 70.

The Screen for Child Anxiety Related Emotional Disorders-Parent (SCARED-P) (Birmaher et al. 1997) is a 118 item parent self-report form that assesses child anxiety (i.e., worry, perfectionism, social anxiety, and panic attacks), depression (i.e., suicidal ideation, sadness, and irritability), and ADHD (i.e., hyperactivity, impulsivity, and inattention). Parent reports were considered to have clinically significant symptoms if they had a T score > 70.

The Child Health Questionnaire Parent Form 50 (CHQ-PF50) (Landgraf et al. 1996) is a parent-rated form to assess the child’s quality of life. Measured domains include physical and role functioning, general health, bodily pain, mental health, self-esteem, and behavior, with scores less than the national norms for each subscale indicating clinically significant impairment. Summary scales, including psychosocial and physical, are calculated based on weighted combinations of certain subscales.

Laboratory tests. Anti-deoxyribonuclease B (anti-DNAse B), anti-streptolysin O (ASO), Mycoplasma pneumoniae immunoglobulin (IgG/IgM, antinuclear antibody (ANA), Raji cell (C3d-bound circulating immune complexes), and quantitative immunoglobulins were performed at a clinical laboratory (LabCorp). A comprehensive metabolic panel (CMP), complete blood count (CBC), and urinalysis were also conducted.

ASO titer elevations begin 1 week after an infection and peak after 2–3 weeks. Comparatively, anti-DNase B titer elevations peak after 4–8 weeks. Titer elevations may persist for several months, decreasing the ability to determine if a result is related to GAS exposure regardless of the infection site. However, as titer elevations may persist for 2–3 weeks, after an infection, and typically persist for 2–3 months, but can remain elevated for several months. Positive mycoplasma IgM results ideally should be confirmed by polymerase chain reaction (PCR) analyses for a definitive diagnosis, as a positive IgM result does not equate to the presence of an acute infection (Nilsson et al. 2008). ANA testing was done by a multiplex immunoassay. Tiers > 1:80 indicated a positive result. C3d-bound circulating immune complexes were measured through enzyme immunoassay. Elevations in immune complexes may indicate presence of systemic diseases or infections that could potentially cause damage to organs and tissues. Quantitative IgGs, including IgG, IgA, IgM, and IgE were tested. Low values of IgG, IgA, and IgM may indicate a greater risk for acquiring an infection, and elevated levels of IgE may suggest presence of allergies. Furthermore, a screen for Lyme disease (IgM/IgG) was performed by enzyme immunoassay (EIA) to identify a possible exposure to Borrelia burgdorferi. All positive or equivocal EIA results were confirmed with Western blot testing, as advised by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 1995). Laboratory values were categorized as elevated and normal based on reference ranges determined by the clinical laboratory for each result.

Physical and neurological examination. A physical and neurological examination was conducted by the physician to assess for overall health and for any neurological abnormalities (i.e., in attention, activity, eye contact, language, and affect), reflexes and strength, cranial nerves, ambulation, cerebellar tasks, and movements (i.e., tremors, chorea, and tics). Height, weight, blood pressure, and heart rate were also measured. An electrocardiogram (ECG) was performed and subsequently read by a board-certified pediatric cardiologist (G.H.D) to determine presence of abnormalities that could suggest risk of rheumatic carditis or QT prolongation.

Procedures

All study procedures were approved by the All Children’s Hospital Institutional Review Board. Written informed consent and assent was obtained from parents and participants, respectively. Afterward, youth underwent a comprehensive evaluation including a review of family and medical history, and the measures described previously. Blood was drawn utilizing aseptic techniques to obtain clinical laboratory measures. PANS diagnoses were determined by an experienced child psychiatrist (T.K.M.) based on clinical evaluation of symptoms.

Data analysis

First, descriptive statistics were used to characterize the sample and symptom presentation of youth with PANS. Second, Ward’s hierarchical agglomerative cluster analysis was used to analyze the hypothesized symptoms and antibody titers associated with PANS based on expert consensus (Swedo et al. 2012). The absence/presence of these symptoms were determined using the I-ROTE
(documented GAS infection, handwriting deterioration, ADHD diagnosis, urinary symptoms, hallucination and/or psychotic symptoms), PANS CGI-S (emotional lability and/or irritability, deterioration in school performance, anxiety symptoms, sleep disturbances, behavioral regression, sensory abnormalities, food restriction), Withdrawn/Depressed scale of the CBCL (depressive symptoms), YGTSS (simple tics, complex tics), Rey-O and BEERY (visuospatial/motor impairment), laboratory values (elevated ASO, elevated anti-DNAse B, elevated Mycoplasma IgM antibody), and medical evaluation (mydriasis, fatigue, gastrointestinal symptoms). This method progressively forms clusters of dichotomous variables until all are subsumed into a single unifying cluster. The stages of agglomerations are displayed as a dendrogram with the formation of clusters plotted along a scaled, between-stage distance axis at each stage (Borgen and Barnett 1987). Consistent with previous research (McGuire et al. 2013), symptoms were classified into a cluster when: 1) Their dendrogram lines converged within a 10 unit window on the dendrogram cluster distance axis; and 2) convergence occurred before 50 (0 = individual symptoms, 100 = unitary cluster of all symptoms). Afterward, cluster models that met the above-mentioned criteria were evaluated using investigator experience and clinical interpretability. Third, $\chi^2$ and independent sample t tests were used to compare youth with and without tic symptoms, food restriction symptoms, and a streptococcal trigger. Finally, an independent sample t test compared OCD severity (CGI-S for OCD, CY-BOCS Total Score) between youth with and without elevated titers (e.g., anti-DNAse B and ASO). Given the exploratory nature of these comparisons, significance was set at $p = 0.05$.

### Results

#### Characteristics of youth with PANS

Participants experienced an onset of OCD at an early age (mean = 7.84, SD = 2.65), with an average duration of presenting OCD of ~10 weeks (mean = 10.14, SD = 6.67), and symptoms in the moderate to severe range (MCCUS = 3.98, SDCCUS = 0.83). Intrusive worries about “harm to self and/or others” and related compulsions were the most commonly reported OCD symptoms (see Table 1 for a list of endorsed PANS symptoms). Males more frequently reported having sexual and/or religious obsessions than females ($\chi^2 = 3.80, p = 0.05$), but no gender differences were found between other obsessions and compulsions indicated on the CY-BOCS checklist.

All participants presented with comorbid anxiety and emotional lability, satisfying the requirement for presence of two associated PANS symptoms. Most exhibited visuospatial impairment at evaluation (see Table 1). Separation anxiety (77%) was the most common type of anxiety seen in the sample, followed by generalized anxiety (47%) and school avoidance (47%). Clinically significant depressive symptoms were noted in nearly 25% of PANS youth.

#### Medical history

Concomitant medications at time of evaluation included anticonvulsants ($n = 2, 5\%$); SSRIs ($n = 6, 14\%$); and medications for sleep ($n = 12, 30\%$), allergy or asthma ($n = 8, 19\%$), and ADHD ($n = 2, 5\%$). All participants were stable for at least 4 weeks on psychotherapeutic medications (8 weeks for SSRIs) before evaluation. A history of frequent infections was commonly noted in PANS youth following review of medical records and parent report (see Table 2 for frequencies of prior illnesses and infection triggers). A majority of participants (72%) had a history of frequent streptococcal pharyngitis. Frequent upper respiratory infections (URIs) were also reported in a majority of the sample (58%), and 28% of children had had a tonsillectomy and/or adenoidectomy. Immune-based illnesses (i.e., Kawasaki’s disease, Hashimoto’s thyroiditis, psoriasis, Henoch–Scholein purpura, neutropenia, asthma, and allergies) were noted in several participants. ECGs were performed on 41 children and were read as normal for age by a cardiologist. In our sample, two children had mild neutropenia and two had low white blood cell counts. Immunoglobulin A deficiency trended toward more significant presentation in youth with tics ($\chi^2 = 3.35; p = 0.08$). Four children had mild liver enzyme elevations. Based on medical history and clinical evaluation, GAS was identified as the most common infectious trigger, followed by URI, and suspected M. pneumoniae (see Table 2). Several participants presented with more than one infectious trigger, and a few had unclear triggers including gastrointestinal illness, rash, and unknown exposures (i.e., undiagnosed illness in siblings). Furthermore, a few participants presented with no apparent infectious trigger. A majority of participants (91%) presented with elevated antibody titers, including M. pneumoniae IgM, anti-DNAse B, ASO, and/or Lyme IgG/IgM antibodies. Anti-DNAse B antibody was the most frequently elevated titer, with significantly more frequent elevation in males ($n = 20, 47\%$) than females ($n = 10, 23\%$) ($\chi^2 = 6.00, p = 0.01$). All positive Lyme screens were found to be negative when confirmed with a Western blot test. See Table 3 for titer elevation frequencies.

#### Impairment and quality of life in PANS youth

More than half of all participants (51%) scored in the clinically significant range for thought problems on the CBCL, which assesses symptoms such as seeing or hearing things, strange ideas and
behaviors, repeating compulsions, and thoughts or actions directed toward self-harm. For participants between the ages of 6 and 18, nearly one third (30%) checked suicidal items on the CBCL, including “talks about killing self” and/or “deliberately harms self or attempts suicide.” Average overall functioning, as measured by the C-GAS (mean = 48.0), was found to be in the 41–50 range, indicating moderate social impairment in most areas or severe impairment in one area. Although C-GAS scores ranged from 30 (unable to function in almost all areas) to 65 (some difficulty in one area), most participants (n = 30, 75%) scored between 41 and 60, and 20% (n = 8) of participants scored ≤ 40, indicating major impairment or inability to function. Only 5% (n = 2) of participants scored ≥ 61. Additionally, one third of children (33%) were put on a hospital/homebound program because of the severity of their symptoms. In regards to quality of life as measured by the CHQ-PF50, the average score for Mental Health (Well-Being) was well indicating a higher frequency of anxiety and depressive symptoms in this sample. Parental Impact-Emotional average score was the lowest of all the subscales (Msample = 27.78, MNational = 80.30), indicating the severity of parents’ worries and concerns as a result of the child’s physical and psychosocial impairment. The average score for Self-Esteem (Msample = 51.00, MNational = 79.80) revealed significant dissatisfaction in PANS youth regarding their abilities, appearance, family and peer relationships, and life overall. Three participants did not complete the CHQ-PF50 measure at baseline. Average scores for all quality of life subscales are shown in Table 4.

**Tic and non-tic PANS OCD**

The majority of participants had co-occurring simple tics at time of onset or shortly after, and presented with mild tic severity (MYSYD = 15.50, SDYSYD = 7.81). A smaller portion of the sample had complex tics (28%) compared with simple tics (70%). Youth with tics were more likely to experience a decline in school performance (χ² = 4.38, p = 0.03), food restriction symptoms (χ² = 4.11, p = 0.04), and handwriting deterioration (χ² = 6.92, p = 0.01), and were more likely to be placed on a hospital/homebound program because of overall symptom severity (χ² = 5.23, p = 0.02). Table 5 compares the symptom severity of tic and non-tic PANS OCD youth. Participants with tics exhibited significantly higher PANS symptom severity and visual-spatial memory impairment than those without tics (see Table 5). Additionally, participants with tics scored lower on all quality of life (CHQ-PF50) subscales except Family Cohesion, with significant group differences observed on the Self-Esteem, Role (Emotional/Behavioral), and Family Activities subscales (see Table 4).

**Food restriction in PANS youth**

Nearly half (47%) of all participants had food restriction symptoms at the time of evaluation. Ten participants experienced significant impairment related to food restriction (i.e., weight loss, dehydration, and/or hospitalizations), and also met diagnostic criteria for avoidant restrictive food intake disorder (ARFID). Of this subset, one participant presented with food-related OCD symptoms only, whereas the remaining nine participants met OCD criteria for food and non-food-related symptoms. Contamination from germs and/or toxins, poison, fear of vomiting, choking, and fear of weight gain were the most common causes of restrictive eating behavior in PANS youth. Youth with food restriction behavior had significantly higher averages on the SCARED and lower averages on the following CHQ-PF50 subscales: Bodily Pain, Global Behavior Item, and Parental Impact-Emotional than youth without food restriction (see Tables 4 and 5). Youth with food restriction were also more likely to have mydriasis (χ² = 9.91, p = 0.002), tics (χ² = 4.11, p = 0.04), and choreiform movements (χ² = 4.47, p = 0.03) than youth without food restriction. No other significant differences were found in PANS symptoms for youth with and without food restriction.

**Comparison of OCD symptoms and severity relative to GAS findings**

Participants with elevated ASO titer (mean = 4.25, SD = 0.77) trended toward exhibiting greater OCD severity on the CGI-S relative to youth without elevated ASO titer (mean = 3.80, SD = 0.83), t(40) = −1.71, p = 0.09. No significant difference was

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**Table 3. Characteristics of Youth with PANS and a Comparison by Tic Presence**

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n = 43)</th>
<th>Youth with tics (n = 30)</th>
<th>Youth without tics (n = 13)</th>
<th>χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24 (56)</td>
<td>19 (63)</td>
<td>5 (38)</td>
<td>2.28</td>
<td>0.13</td>
</tr>
<tr>
<td>Comorbid ADHD</td>
<td>20 (47)</td>
<td>16 (53)</td>
<td>4 (31)</td>
<td>1.86</td>
<td>0.17</td>
</tr>
<tr>
<td>Comorbid non-OCD anxiety disorder</td>
<td>43 (100)</td>
<td>30 (100)</td>
<td>13 (100)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Elevated laboratory results

<table>
<thead>
<tr>
<th>Test</th>
<th>Total sample (n = 43)</th>
<th>Youth with tics (n = 30)</th>
<th>Youth without tics (n = 13)</th>
<th>χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-DNAse B</td>
<td>30 (71)</td>
<td>21 (70)</td>
<td>9 (69)</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Anti-streptolysin O (ASO)</td>
<td>16 (37)</td>
<td>12 (40)</td>
<td>4 (31)</td>
<td>0.33</td>
<td>0.57</td>
</tr>
<tr>
<td>Anti-nuclear antibodies</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>0</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Mycoplasma immunoglobin M (IgM)</td>
<td>9 (21)</td>
<td>5 (17)</td>
<td>4 (31)</td>
<td>1.41</td>
<td>0.23</td>
</tr>
<tr>
<td>Mycoplasma immunoglobin G (IgG)</td>
<td>27 (64)</td>
<td>20 (67)</td>
<td>7 (54)</td>
<td>0.64</td>
<td>0.42</td>
</tr>
<tr>
<td>Lyme screen</td>
<td>5 (12)</td>
<td>5 (17)</td>
<td>0</td>
<td>2.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Western blot confirmation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Raji cell</td>
<td>14 (33)</td>
<td>11 (37)</td>
<td>3 (23)</td>
<td>0.53</td>
<td>0.47</td>
</tr>
<tr>
<td>Low IgG</td>
<td>2 (5)</td>
<td>2 (7)</td>
<td>0</td>
<td>0.94</td>
<td>0.33</td>
</tr>
<tr>
<td>Low IgA</td>
<td>6 (14)</td>
<td>6 (20)</td>
<td>0</td>
<td>3.15</td>
<td>0.08</td>
</tr>
<tr>
<td>Low IgM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated IgE</td>
<td>13 (31)</td>
<td>8 (27)</td>
<td>5 (38)</td>
<td>0.50</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; PANS, pediatric acute-onset neuropsychiatric syndrome.
Table 4. Quality of Life in Youth with PANS as Assessed by the CHQ-PF50 Subscales

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Youths without food restriction (n=19)</th>
<th>Youth with food restriction (n=39)</th>
<th>Youth without GAS (n=19)</th>
<th>Youth with GAS (n=20)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>t [40]</th>
<th>p</th>
<th>Cohen’s d</th>
<th>t [40]</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>96.1 (25)</td>
<td>81.5 (27.3)</td>
<td>79.7 (25.9)</td>
<td>86.7 (80)</td>
<td>0.76</td>
<td>0.45</td>
<td>0.15</td>
<td>0.90</td>
<td>0.01</td>
<td>0.96</td>
<td>0.01</td>
<td>0.96</td>
<td>0.01</td>
<td>0.96</td>
</tr>
<tr>
<td>Role/social limitations-emotional/behavioral</td>
<td>75.6 (18.8)</td>
<td>87.7 (18.8)</td>
<td>50.0 (20.9)</td>
<td>79.1 (40.5)</td>
<td>1.55</td>
<td>0.13</td>
<td>0.47</td>
<td>42.7</td>
<td>0.34</td>
<td>0.74</td>
<td>0.47</td>
<td>0.75</td>
<td>0.34</td>
<td>0.74</td>
</tr>
<tr>
<td>Bodily pain/discomfort</td>
<td>81.7 (31.2)</td>
<td>62.1 (31.2)</td>
<td>58.3 (33)</td>
<td>73.0 (23.6)</td>
<td>1.30</td>
<td>0.20</td>
<td>0.34</td>
<td>47.0</td>
<td>0.24</td>
<td>0.81</td>
<td>0.14</td>
<td>0.75</td>
<td>0.34</td>
<td>0.75</td>
</tr>
<tr>
<td>Global health perceptions</td>
<td>48.2 (32.6)</td>
<td>44.3 (33.6)</td>
<td>59.5 (28)</td>
<td>42.7 (26.6)</td>
<td>1.28</td>
<td>0.21</td>
<td>0.47</td>
<td>38.2</td>
<td>0.24</td>
<td>0.81</td>
<td>0.11</td>
<td>0.75</td>
<td>0.34</td>
<td>0.75</td>
</tr>
<tr>
<td>Parental impact-item</td>
<td>62.3 (26.1)</td>
<td>62.2 (23.3)</td>
<td>62.4 (28.5)</td>
<td>62.4 (29.5)</td>
<td>0.02</td>
<td>0.98</td>
<td>0.47</td>
<td>21.3</td>
<td>0.01</td>
<td>0.99</td>
<td>0.01</td>
<td>0.99</td>
<td>0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Parental impact-emotional</td>
<td>80.3 (19.3)</td>
<td>82.5 (19.7)</td>
<td>62.4 (28.5)</td>
<td>62.4 (29.5)</td>
<td>0.02</td>
<td>0.98</td>
<td>0.47</td>
<td>28.9</td>
<td>0.01</td>
<td>0.99</td>
<td>0.01</td>
<td>0.99</td>
<td>0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Family cohesion</td>
<td>72.3 (15.6)</td>
<td>68.4 (24.3)</td>
<td>69.6 (30.4)</td>
<td>69.6 (30.4)</td>
<td>0.43</td>
<td>0.67</td>
<td>0.07</td>
<td>72.8</td>
<td>0.16</td>
<td>0.86</td>
<td>0.07</td>
<td>0.86</td>
<td>0.07</td>
<td>0.86</td>
</tr>
</tbody>
</table>

PANS symptom clusters

A hierarchical cluster analysis using hypothesized PANS symptoms and antibody titers was conducted to identify symptom groupings. The dendrogram displays the results from the agglomerative hierarchical cluster analysis (Fig. 2). These results suggest the presence of three distinct symptom clusters. Cluster 1 included five symptoms that were predominantly consistent with the hallmark symptoms of PANS (e.g., emotional lability, anxiety symptoms, sleep disturbances, deterioration in school, and behavioral regression), and was operationally defined as “core characteristic PANS symptoms.” Most participants had between four and five symptoms in this cluster (93%), with all participants having at least two symptoms in this cluster. Cluster 2 included eight symptoms that predominantly consisted of streptococcal tics, symptoms previously described as being associated with GAS infection (e.g., urinary symptoms, ADHD, handwriting deterioration) (Murphy and Pichichero 2002), sensory problems, and simple tics. This cluster was operationally defined as “streptococcal-related symptoms.” Most participants had three or more symptoms on this cluster (92%), with all participants having at least one symptom in this cluster. Cluster 3 predominantly included symptoms that are often described as part of cytokine sickness behavior (e.g., food restriction, mydriasis, fatigue, gastrointestinal problems, and depressive symptoms) (Dantzer and Kelley 2007), elevated mycoplasma, hallucinations and/or psychotic symptoms, and complex tics. Cluster 3 was operationally defined as “cytokine-driven/physiological symptoms.” Approximately half of the participants had two or more symptoms in this cluster (51%), with 76% of all participants having at least one symptom in this cluster.

Discussion

This study aimed to characterize PANS through phenotypical analysis of 43 youth meeting the proposed diagnostic criteria for PANS (Swedo et al. 2012). All participants presented with several comorbid symptoms, most frequently anxiety and emotional lability. Although children with traditional OCD also commonly present with comorbidities such as anxiety, ADHD, and tics (Geller et al. 2003; Storch et al. 2008; Lewin et al. 2010), they do not typically exhibit these acutely and concurrently with OCD onset, nor do they exhibit the additional neuropsychiatric symptoms observed in our sample (i.e., behavioral regression, frequent urination, deterioration in handwriting). Furthermore, the mean age of OCD onset of our sample (M = 7.84, SD = 2.65) is ~2 years younger than the mean age of onset for non-PANS presentations of OCD (Geller et al. 2012) and slightly younger than the mean age of

observed on the CY-BOCS Total Score between ASO titer groups, r(40) = −0.11, p = 0.91. No significant differences were found between participants with elevated anti-DNAse relative to normal values on either the CGI-S (t[40] = −1.55, p = 0.13) or CY-BOCS Total Score (t[40] = −0.48, p = 0.63). No significant differences were found for OCD severity on the CGI-S (t[40] = 0.53, p = 0.60) and CY-BOCS (t[40] = 0.69, p = 0.50) between youth with and without a GAS trigger. However, participants with a GAS trigger (58%) were more likely to present with ordering, arranging, and/or symmetry-related compulsions (n = 22, 88%) than were participants without a GAS trigger (n = 8, 44%) (χ² = 9.41, p = 0.002). No other differences in symptom presentation were observed between youth with and those without a GAS trigger. Figure 1 displays the proportion of youth with elevated ASO, elevated anti-DNAse B, and/or temporal GAS association or recorded exposure.

PANS symptom clusters

A hierarchical cluster analysis using hypothesized PANS symptoms and antibody titers was conducted to identify symptom groupings. The dendrogram displays the results from the agglomerative hierarchical cluster analysis (Fig. 2). These results suggest the presence of three distinct symptom clusters. Cluster 1 included five symptoms that were predominantly consistent with the hallmark symptoms of PANS (e.g., emotional lability, anxiety symptoms, sleep disturbances, deterioration in school, and behavioral regression), and was operationally defined as “core characteristic PANS symptoms.” Most participants had between four and five symptoms in this cluster (93%), with all participants having at least two symptoms in this cluster. Cluster 2 included eight symptoms that predominantly consisted of streptococcal tics, symptoms previously described as being associated with GAS infection (e.g., urinary symptoms, ADHD, handwriting deterioration) (Murphy and Pichichero 2002), sensory problems, and simple tics. This cluster was operationally defined as “streptococcal-related symptoms.” Most participants had three or more symptoms on this cluster (92%), with all participants having at least one symptom in this cluster. Cluster 3 predominantly included symptoms that are often described as part of cytokine sickness behavior (e.g., food restriction, mydriasis, fatigue, gastrointestinal problems, and depressive symptoms) (Dantzer and Kelley 2007), elevated mycoplasma, hallucinations and/or psychotic symptoms, and complex tics. Cluster 3 was operationally defined as “cytokine-driven/physiological symptoms.” Approximately half of the participants had two or more symptoms in this cluster (51%), with 76% of all participants having at least one symptom in this cluster.

Discussion

This study aimed to characterize PANS through phenotypical analysis of 43 youth meeting the proposed diagnostic criteria for PANS (Swedo et al. 2012). All participants presented with several comorbid symptoms, most frequently anxiety and emotional lability. Although children with traditional OCD also commonly present with comorbidities such as anxiety, ADHD, and tics (Geller et al. 2003; Storch et al. 2008; Lewin et al. 2010), they do not typically exhibit these acutely and concurrently with OCD onset, nor do they exhibit the additional neuropsychiatric symptoms observed in our sample (i.e., behavioral regression, frequent urination, deterioration in handwriting). Furthermore, the mean age of OCD onset of our sample (M = 7.84, SD = 2.65) is ~2 years younger than the mean age of onset for non-PANS presentations of OCD (Geller et al. 2012) and slightly younger than the mean age of
### Table 5. Demographics and Symptom Severity of Youth with PANS

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n = 42)</th>
<th>Youth with tics (n = 30)</th>
<th>Youth without tics (n = 12)</th>
<th>Youth with food restriction (n = 20)</th>
<th>Youth without food restriction (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t p value</td>
<td>Cohen's d</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>8.1 (2.7)</td>
<td>7.6 (2.4)</td>
<td>9.4 (3.0)</td>
<td>1.98 0.06</td>
<td>8.2 (2.4)</td>
</tr>
<tr>
<td><strong>Age of OCD onset</strong></td>
<td>7.8 (2.7)</td>
<td>7.5 (2.4)</td>
<td>9 (3)</td>
<td>2.14 0.09</td>
<td>8.1 (2.3)</td>
</tr>
<tr>
<td><strong>Duration of OC symptoms</strong></td>
<td>10.1 (6.7)</td>
<td>9.5 (6.8)</td>
<td>12.2 (6.5)</td>
<td>0.24 -0.40</td>
<td>10.0 (7.1)</td>
</tr>
<tr>
<td><strong>Symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CY-BOCS Total Score</td>
<td>28.3 (5.0)</td>
<td>28.6 (5.3)</td>
<td>27.7 (4.2)</td>
<td>0.54 0.59</td>
<td>28.5 (5.3)</td>
</tr>
<tr>
<td>PANDAS Total Score</td>
<td>27 (11.5)</td>
<td>29.3 (11.4)</td>
<td>21.3 (10.2)</td>
<td>2.14 0.04*</td>
<td>29.6 (11.9)</td>
</tr>
<tr>
<td>SCARED Total Score</td>
<td>28.9 (17.6)</td>
<td>31.9 (18.7)</td>
<td>21.7 (12.6)</td>
<td>0.09 0.59</td>
<td>35.9 (19)</td>
</tr>
<tr>
<td>YGTSS Total Score</td>
<td>11.1 (9.7)</td>
<td>15.5 (7.8)</td>
<td>0</td>
<td>2.29 13.5 (8.5)</td>
<td>8.9 (10.3)</td>
</tr>
<tr>
<td>TODS Total Score</td>
<td>71.4 (35)</td>
<td>76.5 (35.8)</td>
<td>59.3 (30.6)</td>
<td>1.46 0.15</td>
<td>79.1 (39.8)</td>
</tr>
<tr>
<td><strong>Neuropsychological functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REY-O Copy raw scorea</td>
<td>14 (9)</td>
<td>10.7 (6.6)</td>
<td>23 (8.8)</td>
<td>4.10 &lt;0.001 -1.69</td>
<td>12.5 (7.8)</td>
</tr>
<tr>
<td>REY-O Immediate Recall t scorea</td>
<td>28.5 (8.2)</td>
<td>28 (6.1)</td>
<td>29.9 (12.2)</td>
<td>0.55 0.59</td>
<td>29.5 (6.3)</td>
</tr>
<tr>
<td>REY-O Delayed Recall t scorea</td>
<td>26.9 (8)</td>
<td>25.8 (5.3)</td>
<td>29.4 (12.5)</td>
<td>1.06 0.30</td>
<td>27.2 (6.3)</td>
</tr>
<tr>
<td>REY-O Recognition t scorea</td>
<td>45.8 (12.9)</td>
<td>45.7 (13.5)</td>
<td>46 (12)</td>
<td>0.06 0.96</td>
<td>46.8 (13.5)</td>
</tr>
<tr>
<td>BEERY VMI t scoreb</td>
<td>47 (9.6)</td>
<td>47.6 (7.5)</td>
<td>45 (17)</td>
<td>0.40 0.70</td>
<td>50 (3.6)</td>
</tr>
</tbody>
</table>

*p* values are reported for significance level of 0.05.

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**Legend:**
- *REY-O* was only completed by 29 of the 43 participants, with *t* scores being available for 27 participants.
- *BEERY* was only completed by 13 participants.

**Notes:**
- BEERY VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; CY-BOCS, Children’s Yale-Brown Obsessive Compulsive Scale; OCD, Obsessive Compulsive Disorder; PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcus; PANS, PANS, pediatric acute-onset neuropsychiatric syndrome; REY-O, Rey-Osterrieth Complex Figure Test; SCARED-P, Screen for Child Anxiety Related Emotional Disorders - Parent; TODS, Tourette’s Disorder Scale; YGTSS, Yale Global Tic Severity Scale.

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onset identified in pediatric OCD at the University of South Florida’s pediatric neuropsychiatry clinic ($M_{\text{age}} = 8.2$, $SD_{\text{age}} = 3.0$) (Lewin et al. 2014). All participants exhibited an abrupt onset of OCD and associated neuropsychiatric symptoms, in contrast to the gradual onset experienced by children with non-PANS OCD (Geller et al. 2012). Consistent with findings evaluating children with PANDAS (Lewin et al. 2011) and pediatric OCD (Abramovitch et al. 2012; Lewin et al. 2014), visuospatial and recall deficits were evident in our sample.

Although certain PANS symptoms (GAS-related and cytokine-related physiological symptoms) clustered together with elevated titers, $\chi^2$ analysis did not reveal any significant associations between immune findings and PANS symptoms, suggesting a more nuanced relationship between PANS symptoms and trigger type. However, we found a trend toward higher OCD symptom severity in youth with an elevated anti-DNAsE antibody titer. The average OCD global severity of those who had this streptococcal titer elevated was closer to 5, indicating severe impairment and functioning mainly with assistance, whereas those who had normal levels of this antibody were closer to 3, indicating moderate impairment and functioning with effort. These findings suggest a direct relationship between titer elevations and OCD symptom severity that warrants further exploration.

In regard to demographic findings, gender and age of onset have not been known to predict obsessive/compulsive symptom type or severity in youth with traditional pediatric OCD (Geller et al. 2012). However, associations between gender and sexual or religious obsessions have been observed in samples of adults with OCD (Bogetto et al. 1999; Labad et al. 2008). Similarly, we found a strong association between gender and type of compulsion, particularly the elevated presence of sexual and/or religious obsessions.

FIG. 2. Hierarchical agglomerative cluster analysis of Pediatric acute-onset neuropsychiatric syndrome (PANS) symptoms and infectious triggers. Cluster 1, core characteristic PANS symptoms; cluster 2, strep-related symptoms; cluster 3, cytokine-driven physiological symptoms.
in males. Elevated anti-DNase antibodies were also significantly more prevalent in males.

In regard to quality of life, our findings demonstrate significant impairment in youth with PANS, which were consistent with previous studies that found strong associations between poor quality of life and pediatric psychopathology (Bastiaansen et al. 2005; Lack et al. 2009). We also found that youth with comorbid tics had lower self-esteem and poorer family functioning, and were more limited in their daily activities because of emotional and behavioral problems than youth without comorbid tics. Although previous studies in child psychopathology found girls to have overall worse quality of life than boys (Bastiaansen et al. 2005; Lack et al. 2009), we did not observe a significant gender association for most concepts. However, average physical functioning in girls (CHQ-PF mean = 71.5) was significantly lower than in boys (mean = 88.4), suggesting that girls felt more impaired in performance of physical activities (including self-care) because of their poor health. Additionally, we found that PANS youth with food restriction symptoms had lower quality of life than PANS youth without food restriction. Specifically, youth with food restriction experienced more severe, frequent, and limiting bodily pain, and their parents experienced a greater amount of emotional concern about their children’s physical and psychosocial health. These findings suggest that the presence of food restriction in PANS is a major source of impairment in both child and family functioning.

Limitations

There are several limitations that are worthy of note. First, positive mycoplasma IgM antibody results were not confirmed with PCR analysis; therefore, a definite relationship of OCD onset caused by M. pneumoniae cannot be confirmed (Nilsson et al. 2008). Second, our sample of treatment-seeking youth and parents may not be representative of all children with PANS. Third, the retrospective nature of parent report of initial symptom onset as well as presence and type of infectious trigger needs to be considered. However, most histories were supported by medical record documentation. Fourth, the design of this study did not utilize a non-PANS OCD group or a healthy control group for comparative analyses, although the majority of measures used in this study are well standardized and provide age-corrected scores used for comparison. Fifth, because of the novel nature of the PANDAS/PANS scale, psychometric properties have not yet been determined. However, the PANS Consortium (Swedo et al. 2012) is currently assessing interrater reliability, validity, and treatment sensitivity for this measure.

Conclusion

Despite these limitations, this study presents the phenotypic presentation of 43 youth who met the proposed criteria for PANS diagnosis, making it one of the largest cohorts to examine factors influencing PANS presentation to date. Our findings indicated that youth with PANS presented with an early age of OCD onset (mean = 7.84 years) and exhibited moderate to severe obsessive-compulsive symptoms. Most had evidence of a GAS trigger. All participants had comorbid anxiety and emotional lability, and reported low quality of life compared to normative samples. PANS youth with elevated streptococcal antibody titers were more likely to have more severe OCD and dilated pupils compared to youth without elevated titers. A cluster analysis of core PANS symptoms revealed three distinct symptom clusters that included core characteristic PANS symptoms, streptococcal-related symptoms, and cytokine-driven/physiological symptoms. Youth with PANS who had comorbid tics were more likely to exhibit a decline in school performance, visuomotor impairment, food restriction symptoms, handwriting deterioration, IgA deficiency, and reported lower quality of life relative to PANS youth without tics.

Clinical Significance

By identifying baseline characteristics of children with PANS, this study has important clinical implications in the diagnosis, treatment, and identification of positive treatment response predictors. Identifying clear differences in symptom presentation between PANS and non-PANS OCD will allow clinicians to correctly identify PANS and adapt treatment accordingly. This distinction is of particular importance as youth with PANS phenotype often have acute and severely impairing symptoms, and may respond to psychiatric medications and/or therapy differently than youth with classic presentations of OCD. As part of a larger randomized controlled trial evaluating the safety and efficacy of azithromycin in PANDAS/PANS youth, the present data will inform the predictors of antibiotic treatment response in future analyses.

Acknowledgments

The authors acknowledge the contributions of Laura Ramirez, Caroline DeOleo, Henry Storch, and all of the participating families.

Disclosures

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References


Murphy TK, Snider LA, Mutch PJ, Harden E, Zaytoun A, Edge PJ, Storch EA, Yang MC, Mann G, Goodman WK: Relationship of...

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Clinical Presentation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections in Research and Community Settings

Susan E. Swedo, MD,1 Jakob Seidlitz, BS,1 Miro Kovacevic, MD,2,4 M. Elizabeth Latimer, MD,3,4 Rebecca Hommer, MD,1 Lorraine Lougee, LCSW-C,1 and Paul Grant, MD1

Abstract

Background: The first cases of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were described > 15 years ago. Since that time, the literature has been divided between studies that successfully demonstrate an etiologic relationship between Group A streptococcal (GAS) infections and childhood-onset obsessive-compulsive disorder (OCD), and those that fail to find an association. One possible explanation for the conflicting reports is that the diagnostic criteria proposed for PANDAS are not specific enough to describe a unique and homogeneous cohort of patients. To evaluate the validity of the PANDAS criteria, we compared clinical characteristics of PANDAS patients identified in two community practices with a sample of children meeting full research criteria for PANDAS.

Methods: A systematic review of clinical records was used to identify the presence or absence of selected symptoms in children evaluated for PANDAS by physicians in Hinsdale, Illinois (n = 52) and Bethesda, Maryland (n = 40). Results were compared against data from participants in National Institute of Mental Health (NIMH) research investigations of PANDAS (n = 48).

Results: As described in the original PANDAS cohort, males outnumbered females (95:45) by ~ 2:1, and symptoms began in early childhood (7.3 ± 2.7 years). Clinical presentations were remarkably similar across sites, with all children reporting acute onset of OCD symptoms and multiple comorbidities, including separation anxiety (86–92%), school issues (75–81%), sleep disruptions (71%), tics (60–65%), urinary symptoms (42–81%), and others. Twenty of the community cases (22%) failed to meet PANDAS criteria because of an absence of documentation of GAS infections.

Conclusions: The diagnostic criteria for PANDAS can be used by clinicians to accurately identify patients with common clinical features and shared etiology of symptoms. Although difficulties in documenting an association between GAS infection and symptom onset/exacerbations may preclude a diagnosis of PANDAS in some children with acute-onset OCD, they do appear to meet criteria for pediatric acute-onset neuropsychiatric syndrome (PANS).

Introduction

The first 50 cases of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were described in 1998. (Swedo et al. 1998). The PANDAS subgroup was distinguished from other cases of childhood-onset obsessive-compulsive disorder (OCD) by five clinical criteria: Presence of OCD or tic disorder, prepubertal onset, acute symptom onset and episodic (relapsing-remitting) course, presence of associated neurological abnormalities (particularly choreiform movements), and temporal association with Group A streptococcal (GAS) infection (Swedo et al. 1998, 2004). Early reports demonstrated that the unique clinical presentation of the PANDAS subgroup was useful in determining which children would benefit from treatment with antibiotics (Murphy and Pichichero 2002) or immunomodulatory therapies (Garvey et al. 1999; Perlmutter et al. 1999; Snider et al 2005), such as intravenous immunoglobulin (IVIG) and plasmapheresis (interventions that are not helpful for non-PANDAS tic disorders and OCD, respectively) (Hoeckstra 2004; Nicolson et al. 2000). In addition, cross-reactive autoantibodies were
found in sera of acutely ill PANDAS patients (Kirvan et al. 2006, 2007; Swedo 1994); these autoantibodies were not present in convalescent samples or in samples obtained from patients with non-PANDAS OCD or tic disorders (Singer et al. 2008).

Although the early literature provided strong support for the distinctive clinical and laboratory presentation of the PANDAS subgroup, a series of editorials labeled the diagnosis “controversial” and questioned the nature, postulated etiology, and even the existence of PANDAS (Kurlan 1991; Kurlan and Kaplan 2004; Gilbert and Kurlan 2009; Singer et al. 2012). Particular criticism was leveled against the requirement that symptoms have an acute onset/episodic course and be temporally related to GAS infections, as these were reported to be difficult to operationalize in community settings (Gabbay et al. 2008). However, investigators who systematically applied the PANDAS criteria have reported samples of patients with remarkable similarity to the initial cohort (e.g., Murphy et al. 2012). To determine if the criteria could be successfully applied in clinical settings, we compared characteristics of patients evaluated by two pediatric practitioners (M.E.L., M.K.) with those of children meeting full research criteria for PANDAS (National Institute of Mental Health [NIMH]). We hypothesized that the clinical characteristics of the three patient samples would be comparable, and, therefore, that the PANDAS diagnostic criteria defined a clinically distinct patient group.

Methods

A systematic records review was conducted at each of the sites (NIMH, Hinsdale, and Bethesda). Data were culled from all available sources, including documentation of phone conversations, emails, and physician notes, as well as clinical and research records. In addition to evaluating clinical presentations and documenting evidence that cases met criteria for PANDAS, we also examined whether cases met criteria for pediatric acute-onset neuropsychiatric syndrome (PANS) (Swedo et al. 2012). NIMH records were reviewed by a child psychiatrist (R.H., P.G.), who also accessed the research databases for archived information. Hinsdale and Bethesda records were reviewed by a bachelor’s level research assistant with oversight from the attending clinicians (M.E.L., M.K.). All of the outside information was de-identified prior to analysis at NIMH.

The cases presented here include 48 participants in clinical investigations at NIMH, and 92 children receiving clinical evaluations and treatment in the community. The community cases were evaluated by a pediatric neurologist (M.E.L.) in Bethesda (n=40), or a pediatrician (M.K.) in Hinsdale (n=52). Both community physicians have extensive experience in the diagnosis and treatment of PANDAS, and children were referred to these clinics specifically for evaluation of symptoms consistent with a PANDAS diagnosis.

The NIMH sample included children evaluated for participation in a study (n=42) of IVIG for the treatment of PANDAS (Protocol 11-M-0058; NCT 01281969) or a natural history investigation (n=6) of childhood neuropsychiatric disorders (Protocol 13-M-0028; NCT 01778504). Both studies were approved by the Central Nervous System Institutional Review Board (CNS IRB) at the National Institutes of Health. Parents provided informed consent and children assented for participation. More than 200 potential subjects were screened for participation through telephone interviews with parents and referring clinicians and review of comprehensive medical records, and 58 were evaluated in person. Of these, two children refused study participation (prohibiting collection of necessary clinical information) and eight did not meet criteria for inclusion in the PANDAS research cohort: Three did not have acute symptom onset, two did not have a primary diagnosis of OCD/tics (one had generalized anxiety disorder, one had PANDAS OCD or tic disorders (Singer et al. 2008).

### Table 1. PANDAS Criteria by Site

<table>
<thead>
<tr>
<th></th>
<th>NIMH (n=48)</th>
<th>Hinsdale (n=52)</th>
<th>Bethesda (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>1. Prepubertal symptom onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at PANDAS first episode</td>
<td>8.22</td>
<td>2.39</td>
<td>6.66</td>
</tr>
<tr>
<td>Age at site evaluation</td>
<td>8.58</td>
<td>2.38</td>
<td>9.19</td>
</tr>
<tr>
<td>Males</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Females</td>
<td>40%</td>
<td>37%</td>
<td>29%</td>
</tr>
<tr>
<td>2. Presence of OCD and/or a tic disorder</td>
<td>48%</td>
<td>52 100%</td>
<td>40 100%</td>
</tr>
<tr>
<td>3. Acute symptom onset and episodic (relapsing-remitting) course</td>
<td>48%</td>
<td>52 100%</td>
<td>40 100%</td>
</tr>
<tr>
<td>4. Association with neurological abnormalities</td>
<td>48%</td>
<td>52 100%</td>
<td>40 100%</td>
</tr>
<tr>
<td>5. Temporal association between GABHS infection and symptom onset/exacerbations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented evidence of exposure</td>
<td>48%</td>
<td>42</td>
<td>30 100%</td>
</tr>
<tr>
<td>a. Positive GAS culture</td>
<td>20%</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>b. High ASO and/or DNAse-B titer</td>
<td>22%</td>
<td>28</td>
<td>16 54%</td>
</tr>
<tr>
<td>c. Other evidence of exposure</td>
<td>6 12%</td>
<td>8</td>
<td>7 15%</td>
</tr>
<tr>
<td>No evidence of GABHS</td>
<td>-</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Data not found in chart</td>
<td>-</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; NIMH, National Institute of Mental Health; OCD, obsessive-compulsive disorder; GABHS, Group A beta-hemolytic streptococcus; GAS, Group A streptococcus; ASO, antistreptolysin O; DNAse-B, deoxyribonuclease-B.
psychosis), and three had no evidence of streptococcus infection or exposure prior to symptom onset (but would have met criteria for PANS). Therefore, 48 children were included in the NIMH PANDAS sample.

Chi square analyses (Yates) were conducted to assess for significant differences between the community and research samples.

Results

Table 1 shows the PANDAS criteria by site. All subjects in Bethesda, Hinsdale, and at NIMH met at least four of the five PANDAS criteria: Presence of OCD and/or tics, pre-pubertal onset, acute onset and episodic course, and presence of motor abnormalities (Swedo et al. 1998). All 48 patients in the NIMH research group showed evidence of a GAS infection or exposure within 3 months prior to the onset of symptoms. In Bethesda, 5 of the 40 records showed no evidence of preceding GAS infection, and the information was incomplete in another 5, leaving 30 patients (75%) who met all five PANDAS criteria in Bethesda. Ten potential subjects similarly were excluded in the Hinsdale practice (4 had no documented GAS infections, and 6 were missing key clinical data); therefore, 42 patients (82%) fully met PANDAS criteria in Hinsdale.

Although the medical records did not contain sufficient information to determine if the PANDAS diagnosis was based on a primary tic disorder or primary OCD, it was clear that all of the children had a history of abrupt onset of obsessions and/or compulsions accompanied by a variety of comorbid neuropsychiatric symptoms. As shown in Table 2, on average, children had comorbid symptoms in five different domains, indicating that they would easily meet the PANS requirement for co-occurring symptoms in at least 2 of 7 domains (Swedo et al. 2012).

Table 2. Comorbid Symptomatology

<table>
<thead>
<tr>
<th></th>
<th>NIMH (n=48)</th>
<th>Hinsdale (n=42)</th>
<th>Bethesda (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>1. Anxiety</td>
<td>44</td>
<td>92%</td>
<td>40</td>
</tr>
<tr>
<td>2. Emotional lability and/or depression</td>
<td>45</td>
<td>94%</td>
<td>28</td>
</tr>
<tr>
<td>3. Irritability, aggression, and/or severely oppositional behaviors</td>
<td>18</td>
<td>38%</td>
<td>11</td>
</tr>
<tr>
<td>4. Behavioral (developmental) regression</td>
<td>30</td>
<td>63%</td>
<td>29</td>
</tr>
<tr>
<td>5. Deterioration in school performance</td>
<td>36</td>
<td>75%</td>
<td>37</td>
</tr>
<tr>
<td>6. Sensory or motor abnormalities</td>
<td>37</td>
<td>77%</td>
<td>40</td>
</tr>
<tr>
<td>7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency</td>
<td>43</td>
<td>90%</td>
<td>41</td>
</tr>
</tbody>
</table>

Average number of categories present per patient: 5.65, 4.86, 4.97

NIMH, National Institute of Mental Health.

Table 3. Comparison of Clinical Characteristics of PANDAS Patients in Community and Research Settings

<table>
<thead>
<tr>
<th></th>
<th>NIMH (n=48)</th>
<th>Community (n=72)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>44</td>
<td>92%</td>
<td>62</td>
</tr>
<tr>
<td>Behavioral regression (tantrum, baby talk)</td>
<td>30</td>
<td>63%</td>
<td>47</td>
</tr>
<tr>
<td>OCD symptoms</td>
<td>48</td>
<td>100%</td>
<td>72</td>
</tr>
<tr>
<td>Intrusive thoughts</td>
<td>19</td>
<td>40%</td>
<td>53</td>
</tr>
<tr>
<td>Phobias/contamination fears</td>
<td>40</td>
<td>83%</td>
<td>40</td>
</tr>
<tr>
<td>Unfounded fears</td>
<td>24</td>
<td>50%</td>
<td>48</td>
</tr>
<tr>
<td>Repetitive behaviors</td>
<td>36</td>
<td>75%</td>
<td>39</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>20</td>
<td>42%</td>
<td>26</td>
</tr>
<tr>
<td>Hyperactivity or inattentiveness</td>
<td>44</td>
<td>92%</td>
<td>34</td>
</tr>
<tr>
<td>Violent images or hallucinations</td>
<td>13</td>
<td>27%</td>
<td>10</td>
</tr>
<tr>
<td>Dysgraphia</td>
<td>21</td>
<td>44%</td>
<td>46</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>16</td>
<td>33%</td>
<td>45</td>
</tr>
<tr>
<td>Tics</td>
<td>32</td>
<td>67%</td>
<td>43</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>25</td>
<td>52%</td>
<td>58</td>
</tr>
<tr>
<td>Frequency and/or urgency</td>
<td>14</td>
<td>29%</td>
<td>40</td>
</tr>
<tr>
<td>Daytime or night-time enuresis</td>
<td>9</td>
<td>19%</td>
<td>33</td>
</tr>
<tr>
<td>Increased sensory sensitivity</td>
<td>21</td>
<td>44%</td>
<td>31</td>
</tr>
<tr>
<td>School issues</td>
<td>39</td>
<td>81%</td>
<td>54</td>
</tr>
<tr>
<td>Inability to concentrate</td>
<td>38</td>
<td>79%</td>
<td>47</td>
</tr>
<tr>
<td>Trouble in math</td>
<td>16</td>
<td>33%</td>
<td>30</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>34</td>
<td>71%</td>
<td>51</td>
</tr>
<tr>
<td>Restricted food intake</td>
<td>23</td>
<td>48%</td>
<td>17</td>
</tr>
</tbody>
</table>

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; NIMH, National Institute of Mental Health; OCD, obsessive-compulsive disorder.
Comparisons of the community cases meeting PANDAS criteria (n=72) with the NIMH PANDAS research subjects (n=48) revealed similarities in demographics including: Sex distribution (approximately two boys: one girl), age of first PANDAS episode (7.6 ± 2.7; range, 1–14), and age at first evaluation (8.9 ± 2.6; range, 3–17). These results were also comparable to those reported in the first cohort of PANDAS patients (Swedo et al. 1998). Further, the frequency of co-occurring symptoms was strikingly similar across samples, as is shown in Table 3. Differences were noted for only 1 of the 14 symptom categories, hyperactivity/inattentiveness. Separation anxiety was the most common comorbid symptom in both the NIMH and community samples (92% and 86%, respectively), followed closely by school issues (81% and 75%), and sleep problems (71% for both). It is also noteworthy that restricted food intake was observed in nearly one half of the NIMH sample and one quarter of the patients evaluated by the community clinicians. Further, as noted, all patients had sufficient comorbidity to fulfill the PANS diagnostic criteria.

Discussion

This report summarizes the clinical characteristics of three groups of children evaluated and treated for PANDAS. The samples included 92 patients in two community practices (a pediatrician’s and a pediatric neurologist’s) and 48 children participating in research studies at the NIMH. The mean duration of illness at NIMH was only 6 months, whereas that of the community samples was >2 years. Further, and not unexpectedly, diagnostic and data collection procedures at NIMH were quite different from those employed in Bethesda or Hinsdale. Despite these differences, the community and research samples had remarkably similar clinical presentations, with differences noted only in the frequency of co-occurring hyperactivity/inattentiveness. The lower rate recorded for the community sample may reflect the methodologic limitations of this retrospective chart review, as motor hyperactivity appeared to have been included in the “associated neurologic symptoms” required for the PANDAS diagnosis. Similarly, it was not possible to separate cases with primary OCD from those with a primary tic disorder because the PANDAS criteria require only one of the disorders. Our study was further limited by lack of documentation of GAS infections in 22% of the community cohort. Often, this was because a history of exposure and/or throat culture had not been obtained by the child’s primary healthcare provider. These omissions are particularly concerning in light of a report from Murphy and Pichichero (2002) documenting that OCD symptoms completely abated in 8 of 12 PANDAS children who received antibiotics within a few days of symptom onset.

The results of this study confirm the utility of the PANDAS diagnostic criteria in identifying a unique, clinically homogeneous group of patients (Swedo et al. 1998). The distinctive clinical presentations described in this report are not only similar to those described in the initial PANDAS cohort (Swedo et al. 1998), but also are comparable to more recent samples acquired in research settings (e.g., Murphy et al. 2012). Acuity of onset appears to be particularly important in the diagnosis of PANDAS, as demonstrated by a comparison of cases diagnosed in community and research settings (Gabbay et al. 2008) and by investigations that fail to find clinical and laboratory differences between PANDAS and non-PANDAS cases when PANDAS is defined by an “episodic course,” rather than “an acute onset and relapsing-remitting symptom course” (e.g., Singer et al 2008; Leckman et al. 2011). The importance of acute symptom onset is further highlighted by its prominence in the nomenclature and diagnostic criteria of PANS, which requires that OCD (or eating restrictions) and comorbid symptoms reach peak severity within 24–48 hours of onset. PANS is conceptualized as an “umbrella” diagnosis that includes not only PANDAS and other infection-triggered cases (Allen et al. 1995), but also those without infectious precipitants (Swedo et al. 2012). The relative distribution of these various subgroups is presently unknown, and can be determined only with prospectively collected information about premorbid infections and exposures. It is interesting that >80% of our cases who met PANS criteria also had evidence of a “temporal association between GAS infection and symptom onset/exacerbation.” Therefore, in this case series, four of five children with PANS also met diagnostic criteria for PANDAS.

The comparability of clinical presentations across community and research settings confirms the utility of the PANDAS criteria in defining a unique, clinically distinctive patient group. The results also highlight the importance of assessing acuity of symptom onset in both PANDAS and PANS. Establishing a more clearly delineated and universally available framework for evaluating children with acute-onset neuropsychiatric symptoms is an important next step in confirming these findings and informing future research.

Disclosures

No competing financial interests exist. Drs. Swedo, Hommer, and Grant and Mr. Seiditz and Ms. Lougee are employees of the Intramural Research Program of the National Institute of Mental Health (NIMH).

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Five Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome of Differing Etiologies

Jennifer Frankovich, MD, Margo Thienemann, MD, Sonal Rana, MD, and Kiki Chang, MD

Abstract

Background: Pediatric acute-onset neuropsychiatric syndrome (PANS) is diagnosed by the abrupt onset of new obsessive compulsive disorder (OCD) or food-restricting symptoms, and at least two of a variety of other neuropsychiatric symptoms. Detailed clinical presentation of youth with this condition has not yet been provided in the literature.

Methods: We review the clinical charts of five youth meeting criteria for PANS in our PANS Clinic. These five patients were selected for differing underlying causes thought to be driving an inflammatory response that appeared to impact psychiatric symptoms.

Results: Five youth with varying potential etiologies impacting neuropsychiatric symptoms were identified. These youth were from 8 to 18 years old at the onset of their PANS illness, and had bacterial, autoimmune, and unknown etiologies. Treatment directed at presumed etiologies ranged from antibiotics to intravenous gamma globulin (IVIG) to other immuno-modulatory regimens, and appeared to improve the psychiatric illness.

Conclusions: Youth with PANS may present in differing ways, with psychiatric and physical symptoms overlapping with inflammatory or infectious diseases, pain syndromes, and other psychiatric diagnoses. Patients’ psychiatric symptoms may respond to treatments targeting the underlying cause of physical illness. Faced with a pediatric patient demonstrating the abrupt onset or exacerbation of psychiatric and physical symptoms, clinicians should consider PANS in their differential diagnosis.

Introduction

As its name implies, the diagnosis of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection syndrome (PANDAS) requires documentation of a temporal association between the sudden onset or exacerbation of neuropsychiatric symptoms and a preceding infection with group A streptococci (GAS). This requirement for association with GAS created diagnostic difficulties for clinicians (Gabbay et al. 2008). It has been recognized that other pathogens may also contribute to acute neuropsychiatric disorders in youth, including herpes simplex virus, influenza A virus, varicella zoster virus, human immunodeficiency virus, Mycoplasma pneumoniae, Borrelia burgdorferi, and the common cold (Ercan et al. 2008; Morer et al. 2008; Chambert-Loir et al. 2009; Rhee and Cameron, 2012). Although originally described as “pediatric infection-triggered neuropsychiatric disorders” (PITANDs) (Allen et al. 1995), etiologic agents could not always be identified. Therefore, the diagnostic category was broadened to include all acute-onset neuropsychiatric cases and was named “pediatric acute-onset neuropsychiatric syndrome” (PANS) (Swedo et al. 2012).

Diagnosing PANS requires documentation of an abrupt onset of obsessive compulsive disorder (OCD) or food restriction, and at least two of the following associated symptoms: 1) Anxiety; 2) emotional lability and/or depression; 3) irritability, aggression and/or severely oppositional behaviors; 4) behavioral (developmental) regression; 5) deterioration in school performance; 6) sensory or motor abnormalities; and 7) somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

In the fall of 2012, we started the first interdisciplinary clinic at Stanford Children’s Health, designed to evaluate and treat youth who meet criteria for PANS. Many of these youth have been extremely ill, with destructive rage outbursts, extreme compulsions (licking shoes, barking), motor and vocal tics (whooping, wringing hands), school dysfunction (caused by attention-deficit/hyperactivity disorder [ADHD] symptoms, memory impairment, and cognitive regression) and serial psychiatric hospitalizations.

In an effort to begin to describe the spectrum of presentations and clinical courses of these patients, and to describe some etiologies that have not been reported, we present five cases of youth who met criteria for PANS, who have been seen in our clinic.

Cases

Case 1 (PANS and probable inflammatory brain disease/autoimmune encephalitis)

A 13-year-old female with mild cognitive and learning disabilities (but good school performance, as she achieved As and Bs in a private/academically challenging school), no premorbid
psychiatric history, and good social functioning, was prescribed minocycline by her pediatrician for facial acne. Within 1 week of starting the antibiotic, she developed extreme anxiety. Minocycline was, therefore, discontinued, and the anxiety symptoms fully resolved within 3 days. One month later she developed abrupt (overnight) onset of severe obsessions regarding her braces, and eating restrictions. She could not feed herself, swallow, or chew, and food would fall out of her mouth if her mother fed her. For example, it took 1.5 hours for her mother to coax her into drinking one can of Ensure (237 mL), and she subsequently had an 11 pound weight loss over the 1st week of illness. She also had severe insomnia (not sleeping for 4 consecutive days), nearly absent communication (both talking and writing) except to discuss her braces, constant wiping of her face with her right hand, and inconsolable crying and screaming, and she was unable to engage in daily life activities including bathing and other personal hygiene activities. All of these symptoms developed overnight, and were at their maximum intensity within 24 hours of illness onset. Her illness stayed at this intensity with continued behavioral regression, cognitive deterioration, anxiety, perseverations, repetitive self-soothing, delayed or absent verbal responses, persistent insomnia, poor hygiene, poor oral intake with ongoing weight loss, and jaw tremor. Her behavioral issues became unmanageable because of her constant and obsessive hitting of her parents, crying and screaming, running into the streets, hiding, and trying to jump out of moving cars. Three weeks into the course of this illness she developed urinary incontinence, and extreme persistent urinary frequency of unknown cause, ultimately requiring her to wear diapers.

The patient was seen by a psychiatrist and diagnosed with bipolar disorder. The family psychiatric history was significant for bipolar disorder (maternal aunt) and an unknown mood disorder (maternal grandmother). Over the ensuing 6 months, the patient was admitted to inpatient psychiatric hospitals on six occasions and was treated with medications from nearly every psychotropic medication class, with little beneficial effect, and significant adverse effects, including sedation, drooling, and Parkinsonian movements. Benzodiazepines caused severely disinhibited behavior (sexualized gestures, cognitive impairment, and developmental regression). Divalproex, quetiapine, and aripiprazole were titrated to full dosages but were not helpful. Benzotropine at 1 mg twice daily caused sedation, but did not improve extrapyramidal symptoms. Lithium was initiated, and propranolol was given for a presumed lithium-induced tremor. This regimen had some benefit in stabilizing the patient’s mood, but other psychiatric symptoms continued. Other psychotropic trials included antidepressants (trazodone, escitalopram, venlafaxine, bupropion) and benzodiazepines (lorazepam, clonazepam). Multiple medications were used to help with sleep, with poor efficacy.

Because her condition was refractory to these psychiatric medications, she was referred for electroconvulsive therapy. At this point (1 year after her initial presentation) the patient was evaluated for a second opinion by a psychiatrist in the Stanford Pediatric Bipolar Disorders Program, who immediately suspected an inflammatory etiology based on the sudden-onset nature of her illness, unusual course of the mania, significant OCD symptoms, poor response to psychotropics, encephalopathic features, persistent tremor, and choreiform movements of her fingers (piano playing finger movements). She was, therefore, referred to the pediatric neurology and rheumatology departments and was evaluated for inflammatory encephalitis and systemic autoimmune diseases.

Based on brain imaging and serological and cerebrospinal fluid analysis, the following diagnoses were excluded: Limbic encephalitis (negative voltage gated ion channel antibodies, negative N-methyl-d-aspartate [NMDA]-receptor antibodies, negative paraneoplastic panel per Mayo Clinic), Hashimoto’s encephalitis (negative thyroid antibodies), lupus cerebritis (negative lupus specific antibodies), and Sjögren’s disease (negative anti-Ro and anti-La antibodies). Given her chorea, she was worked up for antiphospholipid antibodies and found to have normal values for lupus anticoagulant, dilute Russell’s viper venom time, anticoagulins and β-2-glycoprotein I.

Primary and secondary central nervous system small vessel vasculitis was ruled out with a normal brain MRI, including perfusion studies, negative antibodies previously mentioned, and negative antineutrophil antibodies. Ongoing infectious encephalitis was thought to be unlikely given the patient’s course. She also had negative infection screens (negative evaluations for Bartonella species, Erhlichia chaffeensis, Babesia microti, Leishmania, Lyme disease, West Nile virus, herpes simplex virus 1 and 2, Epstein–Barr virus [EBV], syphilis, and enterovirus). Metabolic/genetic evaluation was also negative for detectable abnormalities, and included normal results for lactate, pyruvate, ammonia, fatty acid profile, acylcarnitine profiles, serum/urine/cerebral spinal fluid (CSF) amino acid profiles, mucopolysaccharide and oligopoly saccharide profiles, cytogenetic fluorescence in situ hybridization (FISH), Fragile X, array comparative genomic hybridization, and mercury. The CSF study analysis was normal, including cell counts, glucose, protein, and immunoglobulin (Ig)G index. CSF studies also indicated negative IgG bands and the negative infectious and metabolic workup mentioned previously.

However, the patient was found to have an elevated antinuclear antibody (ANA) titer (1:320), positive antihistone antibodies, and low complement (C4) findings, which are nonspecific, but are known to be associated with lupus. Minocycline-induced lupus cerebritis was considered, but the short interval between minocycline and symptom development is atypical for this condition. The patient was later found to have antineuronal antibodies targeting dopamine 1 receptors, dopamine 2 receptors, lysoganglioside, and tubulin, which were detected under a research protocol by Dr. Madeleine Cunningham. Preliminary research on these antibodies suggests a link to the clinical syndromes of Sydenham’s chorea and PANDAS (Kirvan et al. 2003, 2006, 2007). Both these disorders are thought to be caused by inflammation involving the striatum (i.e., basal ganglia) (Dale and Brilot 2012; Kumar et al. 2014).

The working diagnosis of inflammatory brain disease, most likely striatal encephalitis (based on the acute and severe psychiatric presentation and choreiform movements of the patient’s fingers) served as the basis for her treatment regimen. She received 3 days of high dose methylprednisolone (1000 mg daily for 3 days) followed by a slow prednisone taper (60 mg p.o. twice daily for 4 weeks followed by 10% reduction every 3 days). The high dose steroid trial resulted in remarkable and sustained improvement, thus meeting criteria for “steroid responsive encephalitis” (Vernino et al. 2007). The patient returned to 90% of her baseline functioning, and psychotropic medications were streamlined. However, when attempts were made to wean the prednisone below 60 mg daily, the patient started to develop a recurrence of symptoms, most notably the return of insomnia and OCD symptoms such as washing, cleaning, and measuring herself repeatedly. She was re-hospitalized for a second steroid induction with methylprednisolone (1000 mg daily for 3 days), again with good results, and mycophenylate mofetil was added to her regimen in hopes that this would allow further tapering of prednisone.
During our second attempt to taper prednisone, now with mycophenylate added, there was a re-escalation of the patient’s psychiatric symptoms at 15 mg/day, resulting in a second medical hospitalization that lasted 3 months. The re-escalation of symptoms was severe, and associated with a GAS exposure (from her sister), but the patient did not test positive for streptococcus herself. Monthly intravenous gamma globulin (IVIG) (2 g/kg) was added to her regimen for 3 consecutive months. When the pre-IVIG anti-neuronal antibody testing returned positive (i.e., Cunningham Research Panel), and given the connection of these particular antibodies to Sydenham’s chorea/PANDAS, antibiotics to treat and prevent GAS were added to the patient’s regimen.

Although she improved on her new regimen of IVIG and mycophenylate, she again failed our third attempt to taper the prednisone, which then resulted in a third prolonged hospitalization. During all three prolonged hospitalizations the patient required a 1:1 sitter for 24 hour supervision because of severe behavior deterioration and OCD symptoms with regard to drinking fluids (e.g., water intoxication caused by obsessive water drinking; the patient also drank nail polish remover and her own urine). Interestingly, with each flare up of her disease, the nature of her OCD symptoms changed.

During the third hospitalization, steroid escalation failed. Given the patient’s critical state, she was treated with plasma exchange (PEX) (1.5 volume exchange for 3 consecutive days) followed by two infusions of rituximab (750 mg per infusion separated by 2 weeks). This regimen resulted in daily steady improvement and allowed for successful weaning of prednisone. The patient achieved 80% of her baseline functioning at month 3, and 100% of baseline at month 6 post-PEX/rituximab with no residual OCD, food restriction, anxiety, sleep issues, or other psychiatric symptoms. At this point we considered her as having “quiescent disease on aggressive immunosuppressive therapy.”

The patient has had three disease flares after achieving “quiescence.” Each of these disease flares corresponded to our attempts to wean her off of immunosuppressive therapy. She had a minor disease flare up at month 6 following the initial rituximab/PEX, and coincident with waning effects of the rituximab and prednisone taper to low dose (7.5 mg/day), despite ongoing mycophenylate therapy. This flare up consisted of behavior regression, return of OCD, and polyuria, but her symptoms remitted 1 month after re-dosing with rituximab. She had a more severe flare (same symptoms as mentioned, but also including life-threatening impulsivity) at month 12 following initial rituximab/PEX, which also corresponded to waning rituximab (second round) effect and another attempt at decreasing her prednisone to low dose (7.5 mg/day). Her third disease flare up occurred after stopping mycophenylate mo- fetil, despite being adequately treated with rituximab. At this point, she appears to require combined rituximab/mycophenylate therapy, which is not unusual in inflammatory brain disease/autoimmune encephalitis.

The patient has now had 22 months of relative quiescent disease (90% of baseline), with only three disease flares, as mentioned, which corresponded to reduction in immunosuppression and re- sponded to re-escalation of steroids, rituximab, and mycophenylate mo- fetil. Her new baseline is absent of OCD symptoms, impulsive behavior, anxiety, sleep dysfunction, tremors, and other movement abnormalities. Recent school testing indicates that her cognitive function is currently above her premorbid baseline. After 2 years of living in psychiatric institutions, our medical hospital, and a group home, all of which provided 1:1 care; she is now living a normal teenage life at home and has been successfully integrated back into public school. She remains on mycophenylate mo- fetil, rituximab, hydroxychloroquine, low dose prednisone, and GAS prophylaxis with cefadroxil. Lithium and all other psychotropic medications were tapered and discontinued early in the course of her immu- notherapy, except for quetiapine used as needed during her three flare ups for sleep and mood control. She now functions well at school and home without any the use of psychotropics.

While writing up this case, and having more understanding that the patient’s antibody profile and symptom presentation were similar to reports of Sydenham’s chorea and PANS, we went back and questioned the family about prior episodes of chorea and OCD. The family reported that in the fourth grade, the patient had had abrupt-onset OCD (regarding frequent need to urinate) which self-resolved after 4 days. Simultaneously, her best friend, who was also in her school class, went through a similar illness of abrupt onset OCD that lasted 3 months. We cannot definitively say that GAS was the trigger for our patient’s earlier episode or her more fulminant presentation described here. Also, we do not know why the first episode of OCD was mild and self-limited whereas the second episode was severe and requires ongoing immunosuppres- sion to control symptoms. Given her response to and dependence on immunotherapy, her case more closely matches striatal/basal ganglia encephalitis.

**Case 2 (PANDAS)**

An 11-year-old boy, with a history of dyslexia and learning disability, presented to our clinic with sudden-onset separation anxiety and rage 2 weeks after a febrile illness with pharyngitis (no throat culture was obtained). Four weeks after the onset of the separation anxiety, he suddenly developed OCD symptoms, motor tics, and vocal tics. OCD symptoms included tapping hallway walls, checking rituals, counting rituals, contamination fears, repeating words, asking the same question repeatedly, and a need for symmetry and exactness. His tics included blinking, shoulder and neck movements, and complex vocal tics in which he would repeat “Ga ga ga.” The following month he developed a mood disorder characterized by depressed mood, anhedonia, insomnia, and irri- tability that was punctuated by violent anger explosions. Ad- ditionally, this illness was accompanied by new-onset physical symptoms, including nocturia and severe joint pain requiring crutches. His joint pain primarily involved his feet, knees, and elbows, lasted 3–7 days at a time, and coincided with escalations in anxiety and rage.

Six weeks after the presentation of psychiatric symptoms, the patient’s pediatrician ordered antistreptolysin O (ASO) and antideoxyribonuclease B titers (anti-DNase B) which were 368 and 666 Todd units/mL, respectively. As both of these were elevated (Kaplan et al. 1998), suggesting recent GAS infection, his pedi- atrician suspected PANS, and put him on azithromycin for 5 days, which resulted in temporary improvement in his OCD; for example, his checking routine prior to bed that had previously lasted 2 hours took only 2 minutes. His anxiety, motor tics, and vocal tics completely resolved. However, impulsivity and im- paired concentration continued, causing difficulties in school and academic functioning.

Approximately 5 days following discontinuation of the antibi- otics, the patient’s OCD, anxiety, tics, and irritability recurred. Administration of azithromycin (250 mg daily) for 4 weeks resulted in rapid and sustained improvement of the patient’s anxiety, tics, OCD, and irritability. The psychiatric and physical symptoms recurred when azithromycin was discontinued after 10 days;
therefore, the pediatrician restarted the azithromycin and added amoxicillin/clavulanate 500 mg twice daily.

Over the next year, the patient had falling ASO and anti-DNase B titers, but had ongoing flare ups in psychiatric symptoms, tics, nocturia, and joint pains that seemed to correlate with viral illnesses. He was referred to a pediatric immunologist at our institution who prescribed IVIG, 2 g/kg. This infusion occurred 14 months after the patient’s initial presentation, and was associated with subjective improvement. However, 2 weeks after his IVIG infusion, he developed an upper respiratory infection and had an acute worsening of his neuropsychiatric symptoms that eventually self-resolved.

The patient was first evaluated in our PANS clinic 22 months after the onset of his initial psychiatric/medical illness. At that time, he had a pattern of waxing and waning neuropsychiatric symptoms (oppositional behavior, irritability, depressed mood, checking behaviors, motor tics) and physical symptoms (joint pains, heel pain, neck pain, and nocturia). His symptoms seemed to worsen after viral illnesses, but he would improve 2–3 weeks later. He had a more severe exacerbation that corresponded to an increase in his ASO and anti-DNase B titers. Multiple attempts were made to discontinue the antibiotics, but his symptoms would recur 1–2 weeks after the antibiotic was discontinued, according to the family. Approximately 2.5 years after onset, his antibiotics were discontinued, and he remained largely symptom free, with good functioning. He also benefited from weekly cognitive behavior therapy (CBT) aimed at addressing his anxiety and mood disorders.

The family refused prophylactic antibiotics.

Case 3 (PANS and mycoplasma)

A 10-year-old girl presented to our clinic for evaluation of sudden-onset behavioral changes, compulsions, and involuntary movements. Three months prior to these behavior changes, her parents reported that she had had an illness consisting of episodic low-grade fever, unproductive cough, and sore throat, causing her to miss school. After the third episode, she had an episode of prolonged sleep (from 2:30 p.m. to 4:30 a.m.), after which she awoke disoriented to time. Over the next few hours, she was extremely irritable and had tantrums, throwing furniture off the balcony and racing around the house punching and kicking. She stated that she could not control her legs. She huddled in her bed, thinking her medication regimen, again with moderate improvement in symptoms. Concomitantly, she had a 9 d decrease in symptoms, and the patient remained asymptomatic on the antibiotic for the ensuing 12 weeks. She has remained asymptomatic without antibiotics.

Case 4 (PANS and chronic sinusitis)

This female patient presented at 13 years of age with a chief complaint of OCD and rage episodes that had been ongoing for 2 years. OCD symptoms were only partially responsive to cognitive behavioral therapy, sertraline, and risperidone. OCD symptoms suddenly began at 11 years of age. 2 months after her aunt died of breast cancer. The patient felt that many things, including her family, were contaminated by grease, so she avoided contact with greasy food, her family, and their belongings. She saved wrappers and paper towels. She became physically aggressive, hitting and kicking if her (OCD) demands were not met. During these episodes, she would flip from being aggressive and angry to feeling remorseful and sad.

A community psychiatrist diagnosed OCD, the onset of which was attributed to stress caused by the loss of her aunt. Treatment with CBT began when she was 11 years of age, which was slightly helpful. Seven months after exposure therapy began, her teachers reported that she appeared distracted in class and met criteria for ADHD, except for age of onset. She was highly sensitive to sound, which was a new symptom for her. Her mood became labile, shifting within the week from manic euphoria, with rapid speech, increased activity and increased irritability, to depression, with crying spells and decreased appetite, sleep, and motivation. The addition of risperidone improved mood symptoms. Concomitantly, she had a 9 day upper respiratory illness that coincided with the descent of a “black cloud of depressed mood” and further escalation of rage. Divalproex was added to her medication regimen, again with moderate improvement in her mood symptoms.

Over the following months, her OCD and rage worsened, and when she was 13 years of age, a new psychiatrist suspected PANS. Her evaluation elicited a history of worsening of penmanship with escalations in OCD, which is consistent with the PANDAS phenotype (Snider and Swedo 2004). Workup (ASO, anti-DNase B, and throat culture) was negative. However, the window of opportunity to detect GAS most likely had passed.

Medical history was significant for parental report of ongoing chronic sinus infections and a deviated septum. In addition to her psychiatric medication, the patient had routinely taken loratadine (to treat nasal allergies) and had many courses of antibiotics. Because of concern for ongoing sinusitis as an infectious source for PANS, the psychiatrist gave her amoxicillin, which coincided with a marked improvement in her symptoms.

Following a 3 week course of amoxicillin, the patient’s sinus and psychiatric symptoms remained remarkably improved. Three months later, she experienced another acute sinus infection that was associated with worsening of her mood, and she was treated with cefdinir for 2 weeks. Sinus and emotional symptoms improved and the patient remained stable for 6 months.
She had an acute exacerbation of psychiatric symptoms in the winter of that year, with an abrupt return of mood lability, agitation, OCD, and hypersensitivity to sounds and smells, but without changes in urinary frequency, handwriting, or tics. She developed severe irritability and aggression, leading her to kick and dent the dishwasher, cut off pieces of her skin, cut on her wrists, and threaten to jump from a moving car. Later, she did not remember these violent outbursts. Over that winter and spring, her OCD, mood issues, and aggression were so severe she was admitted to a specialized residential OCD unit for adolescents, and received cognitive behavior therapy for 2 months. She achieved remission of OCD and mood symptoms.

Over the following 2 years, when she was 14–16 years of age, she experienced many exacerbations of psychiatric symptoms coincident with acute sinusitis symptoms and responsive to antibiotic treatment. She was seen by her otolaryngologist, who observed the severely deviated septum, hypertrophied turbinates, and enlarged maxillary sinus cyst seen on CT scan (obtained 4 years earlier) and on recent MRI. He recommended sinus surgery, but the family declined. Eleven months later, at age 17, the patient developed another sinus infection associated with irritability, mood lability, poor concentration, worsening OCD, and frequent urination. Treatment with azithromycin and ibuprofen was initiated. Laboratory results, including ANA, ASO, Anti-DNase B titers, erythrocyte sedimentation rate (ESR), complete blood count (CBC), EBV, Coxsackie A, and M. pneumoniae IgM titers were all negative.

Because of the persistence of debilitating psychiatric symptoms for 2 months, the patient opted to go through with sinus cyst removal and turbinate resection and reduction. Immediately following the surgery, she experienced an almost complete remission of her psychiatric symptoms, including her OCD and mood symptoms. She reported that, “They pulled the OCD right out of me when they pulled out the cyst!” She was maintained on cefdinir postoperatively. Overall, she improved in her school and family function. She continues on sertraline and risperidone. In the 12 months since the sinus surgery, she has had several exacerbations, each of which was associated with GAS pharyngitis, and which resolved with antibiotic treatment. Interestingly, on these occasions, the family contacted the psychiatrist with concerns about worsening OCD, without searching for preceding or concomitant infection. We are in the process of conducting streptococcus screening for family members and other close contacts with the goal of identifying and eradicating close contacts who may be reinfecting her. If this approach does not improve the issue with recurrent streptococcus, then we will recommend prophylactic antibiotics.

**Case 5 (PANS following PANDAS, immunodeficiency, spondyloarthopathy, and gluten sensitivity)**

A 25-year-old man with a 7 year history of OCD, anxiety, musculoskeletal pain, and abdominal complaints was evaluated for continuing symptoms. His past medical history was notable for two early episodes of PANDAS. At age 5 years, a few days after a febrile illness, he had a sudden onset of irrational fears, separation anxiety, OCD symptoms and polyuria. The symptoms self-resolved in ~2 months. At age 8, he had another febrile illness followed by a sudden onset of OCD, intense fears of the night, highly ritualized bedtime routine, anger episodes, and depressed mood. The symptoms slowly remitted with the exception of mild anxiety. At age 18, while taking citalopram, he had another symptom exacerbation characterized by return of OCD and escalation in anxiety. Anti-DNase B titers were elevated, but ASO titer was normal. Testing for Lyme and mycoplasma were negative.

He was placed on azithromycin for 10 days, with a working diagnosis of PANDAS. His OCD and anxiety symptoms improved initially, then re-escalated after the antibiotic was stopped. Therefore, he was restarted on azithromycin and his escitalopram dose was increased. Although this helped initially, his symptoms eventually re-escalated to the point that he could not attend school.

At 18 years of age, he also developed chronic back pain, knee pain, heel pain, pain on the bottoms of his feet, and vague abdominal symptoms that included tenderness, discomfort, and bloating. In addition, his past medical history was significant for motor tics, migraines, frequent ear infections, and frequent GAS pharyngitis. His family history was notable for acute rheumatic fever (maternal grandmother) and celiac disease (paternal grandfather).

An immunology evaluation found him to have high IgE and low IgG levels, and poor response to pneumococcal vaccine, suggesting mild immunodeficiency. Therefore, he underwent a trial of IVIG (2 g/kg), which was complicated by a hemolytic reaction, but resulted in marked improvement in his OCD and anxiety symptoms. Unfortunately, he contracted GAS pharyngitis 6 weeks later and had re-escalation of his psychiatric symptoms. He requested repeat IVIG treatment, which was denied because of the risk of another hemolytic reaction and the lack of sustained improvement with the initial IVIG treatment.

He was referred for rheumatologic examination at age 25. He ranked his back pain as 4–6/10 on most days, with pain and stiffness worse in the morning and with prolonged sitting or standing. Movement made his pain better. Physical examination revealed tenderness over his temporomandibular joints, sternocostal joints, Achilles tendon insertion points, and sacroiliac joints. He had pain with internal rotation of hips and a limited Schober’s test (limited forward bending flexibility). Laboratory testing revealed negative human leukocyte antigen (HLA) B27 but positive HLA B51. Because his presentation was consistent with inflammatory back pain, he was started on naproxen (500 mg twice daily) and given a referral to physical therapy for core strengthening.

At rheumatology follow-up, the patient reported overall improvement of axial skeletal pain and stiffness, but he had ongoing discomfort in his back requiring him to move every 60 seconds in order to keep his back comfortable. Additionally, he described ongoing distress from his neuropsychiatric symptoms including OCD, anxiety, insomnia, difficulties with concentration, racing thoughts, and mood instability. He again requested IVIG, which was again denied, because the benefit of IVIG did not outweigh the risk of a potentially life-threatening hemolytic reaction. Given his continued back pain, and concern for spondyloarthropathy, the rheumatologist initiated a trial of sulfasalazine and requested an MRI of the patient’s back and sacroiliac joints.

When the patient was seen 4 months after starting sulfasalazine, his back pain and stiffness had mostly resolved and, therefore, the MRI was not pursued. He reported that his pain was 0–1/10 on most days, and it was the first time that he recalled that he did not have to be in constant movement to prevent back pain. He also had resolution of knee, hip, heel, and foot pain. Interestingly, his OCD and anxiety symptoms were also much improved and he stated that his psychiatric symptoms were now “managable.” However, he had occasional “flares” of pain and stiffness associated with abdominal symptoms. In the interim, he had been treated by his primary care physician with clarithromycin for presumed sinusitis. It is not clear
which medication (sulfasalazine or clarithromycin) helped his
neuropsychiatric symptoms, because both were given during the
same time period.

Given the patient’s abdominal symptoms, associated back pain,
and OCD flares, his holistic medicine physician and rheumatologist
suggested a limited trial of removing wheat/gluten, dairy, and soy
from his diet. Four months later he reported that his back pain and
neuropsychiatric symptoms had completely resolved, and that he
had “never felt so good in his life.” He adhered to his gluten/dairy/
soy-free diet with occasional slips. Interestingly, he reported that
when he initially went on a gluten-free diet, he developed head-
aches, dizziness, sleep difficulties (severe nightmares and night
sweats), mood instability, and agitation, but that these symptoms
self-resolved over a 10 day period. After achieving his new baseline
of no neuropsychiatric or musculoskeletal symptoms, accidental
exposures to gluten or soy triggered deterioration in the following
manner: 4–12 hours after the food exposure (especially gluten) he
would develop abdominal pain and distention; 12–24 hours after
exposure, back pain would ensue; 24–48 hours later headaches,
worsening mood symptoms, OCD, and anxiety would ensue. This
pattern was repeated at least eight times over the next 12 months.
He self-discontinued the sulfasalazine and did well overall, but he
noticed that while not taking the sulfasalazine, gluten and soy ex-
posures resulted in more intense abdominal symptoms, back pain,
and psychiatric symptoms as compared with when he was taking
sulfasalazine.

Overall, his new baseline was improved, as he was pain free and
had minimal psychiatric symptoms. Because multiple therapies
were introduced (limited course of antibiotics for sinusitis, anti-
rheumatic medication, dietary changes, and previous escalation of
selective serotonin reuptake inhibitor [SSRI]) it is not clear which
therapies were responsible for his recovery.

Discussion

The overlap of PANS and inflammatory disease processes (in-
fec tion, autoimmune disease, and rheumatological disorders) in
youth has not been previously described, and begs further investi-
gation into the role of inflammation in the etiology of PANS. All of
the youth described here meet the proposed criteria for PANS:
acute onset within 24–48 hours of OCD symptoms, with at least two
associated symptoms. Most youth had significant mood symptoms,
in some cases meeting criteria for major depression or manic epi-
isodes. Motor tics, vocal tics, and cognitive impairment were also
common. Physical symptoms and medical illnesses were observed
(abdominal pain, musculoskeletal pain, and sinus pain) and in some
cases led to medical interventions that appeared to improve both the
physical and psychiatric symptoms. Despite the consistency of their
psychiatric presentations, the youth had a variety of underlying
inflammatory illnesses/triggers including autoimmune encephalitis
(case 1), immunodeficiency (case 5), inflammatory back pain and
food intolerance (case 5), GAS (cases 2 and 5 and possibly 1),
mycoplasma (case 3), and sinusitis caused by an unknown pathogen
(case 4).

We have had little precedent to guide treatment in our PANS
clinic; therefore, we base our interventions on those useful for
PANDAS, for which youth receive antibiotics (Snider et al.
2005) and failing a satisfactory response, IVIG, or plasma ex-
change (Perlmutter et al. 1999). In the cases presented, treatments
were aimed at controlling underlying infectious/inflammatory
disease: Immunosuppression for autoimmune process (case 1);
anti-inflammatory medication for rheumatic disease (case 5); IVIG
for PANDAS (cases 2, 4, and 5), autoimmune encephalitis (case 1)
and immunodeficiency (case 5); antibiotics to treat mycoplasma,
sinusitis, and GAS (all cases); sinus surgery for recurrent sinusitis
(case 4); and removal of offending foods in a case of spondylo-
thropathy/irritable bowel (case 5). These treatments resulted in
moderate to complete improvement, even in cases in which mul-
tiple psychotherapies had failed. Although relapses were common
in the cases presented, the relapses appeared to correspond to
withdrawal (weaning) of medical treatments (immunosuppres-
sion and/or antibiotics) or return/flare up of a medical illness (re-
exposure to streptococcus, recurrence of sinusitis, re-exposure to
a poorly tolerated food). Beneficial response to medical therapi-
suggests that the underlying etiology of these PANS cases is
different from “typical” OCD, tic disorder, bipolar disorder,
and depression. Currently, it is unknown if any “typical” child-
hood psychiatric illness would also respond to antibiotic, anti-
inflammatory or immunomodulatory treatments. It is known that
OCD that is not PANDAS-related does not improve with PEX
(Nicolson et al. 2000).

The common underlying thread appears to be inflammation. For
PANDAS and post-streptococcal striatal encephalitis (basal gan-
glia encephalitis) this may be caused by antineuronal antibodies
(Kirvan et al. 2003, 2006 2007; Dale and Brilot, 2012; Dale et al.,
2012; Cox et al. 2013), a mechanism that is supported by studies in
rats exposed to GAS or IgG from GAS-exposed rats (Yaddanapudi
et al. 2010; Lotan et al., 2014). But for non-GAS causes, the in-
flammation might or might not be caused by similar mechanisms.
Exposure to other infectious agents, such as mycoplasma pneu-
miae, might also lead to similar cross-reactive antibodies (Dale
and Brilot 2012). Underlying causes could also include other au-
toinflammatory and autoimmune processes as is the case in lupus
(Slattery et al. 2004) and other systemic autoimmune diseases,
in which an infection or medication can trigger dysregulation of the
adaptive and/or innate immune systems. Inflammation has in-
creasingly been investigated and implicated in psychiatric illness,
particularly depression and bipolar disorder (Goldstein et al., 2009;
Berk et al., 2013), although it is not clear if it is etiologic or if it
occurs as a result of mood episodes. Therefore, whereas inflam-
mation could be occurring in all these patients, the mechanisms
of inflammation, and the reasons for neuropsychiatric symptoms,
could be subtly to grossly different.

PANS is diagnosed using clinical course and symptoms that may
stem from a variety of etiologies, acting through different disease
mechanisms. Even within the presumed neuroinflammatory cases
of PANS, it is likely that there are different immune dysregula-
tions that affect subgroups of PANS patients. Such is the case with
juvenile idiopathic arthritis (JIA), in which a broad clinical cate-
gory involves many distinct clinical subtypes with heterogeneous
mechanisms of dysfunction. The PANS phenomenon deserves
further empirical study in order to determine etiologies and proper
treatment algorithms.

Conclusion

Acute-onset neuropsychiatric symptoms in youth signal a seri-
ous risk for cognitive and psychosocial impairment. The hetero-
geneity of presentation and potentially serious sequelae of PANS
require clinicians to be alert to the possibility of PANS when faced
with youth who abruptly develop psychiatric and physical symp-
toms. When suspicious, psychiatrists need to work with pediatri-
cians and physicians with expertise in other disciplines to diagnose
and treat the underlying infectious and/or inflammatory diseases.

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our cases, psychiatrists, pediatricians, immunologists, rheumatologists, neurologists, otolaryngologists, and infectious disease specialists collaborated. Alertness to the possibility of PANS and cross-discipline coordination can lead to a positive treatment response in youth with the illnesses described as PANS.

Clinical Significance

This case series highlights the varied presentation of youth with PANS and how severe these cases can be. With proper diagnosis, medical workup, and management, youth with PANS can have significant improvement in their psychiatric symptoms and function. Long-term follow-up of these and other children with PANS needs to be conducted to understand their course and outcome. Even though we do not yet understand the mechanisms of how inflammation affects the brain in PANS, it is our experience, as illustrated here, that addressing the source of inflammation in patients with PANS (e.g., treating infections and rheumatologic conditions) is associated with improvement in neuropsychiatric symptoms overall.

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Multidisciplinary Clinic Dedicated to Treating Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome: Presenting Characteristics of the First 47 Consecutive Patients

Jennifer Frankovich, MD, MS, Margo Thienemann, MD, Jennifer Pearlstein, BS, Amber Crable, MA, BA, Kayla Brown, BA, and Kiki Chang, MD

Abstract

**Background:** Abrupt, dramatic onset obsessive-compulsive disorder (OCD) and/or eating restriction with at least two coinciding symptoms (anxiety, mood dysregulation, irritability/aggression/oppositionality, behavioral regression, cognitive deterioration, sensory or motor abnormalities, or somatic symptoms) defines pediatric acute-onset neuropsychiatric syndrome (PANS). Descriptions of clinical data in such youth are limited.

**Methods:** We reviewed charts of 53 consecutive patients evaluated in our PANS Clinic; 47 met PANS symptom criteria but not all met the requirement for “acute onset.” Patients meeting full criteria for PANS were compared with patients who had a subacute/insidious onset of symptoms.

**Results:** Nineteen of 47 (40%) patients in the study had acute onset of symptoms. In these patients, autoimmune/inflammatory diseases and psychiatric disorders were common in first-degree family members (71% and 78%, respectively). Most acute-onset patients had a relapsing/remitting course (84%), prominent sleep disturbances (84%), urinary issues (58%), sensory amplification (66%), gastrointestinal symptoms (42%), and generalized pain (68%). Inflammatory back pain (21%) and other arthritis conditions (28%) were also common. Suicidal and homicidal thoughts and gestures were common (44% and 17%, respectively) as were violent outbursts (61%). Group A streptococcus (GAS) was the most commonly identified infection at onset (21%) and during flares (74%). Rates of the abovementioned characteristics did not differ between the acute-onset group and the subacute/insidious-onset group. Low levels of immunoglobulins were more common in the subacute/insidious-onset group (75%) compared with the acute-onset group (22%), but this was not statistically significant ($p = 0.06$).

**Conclusions:** In our PANS clinic, 40% of patients had acute onset of symptoms. However, those with and without acute onset of symptoms had similar symptom presentation, rates of inflammatory conditions, somatic symptoms, and violent thoughts and behaviors. GAS infections were the most commonly identified infection at onset and at symptom flares. Because of the wide variety of medical and psychiatric symptoms, youth with PANS may require a multidisciplinary team for adequate care management.

Introduction

Pediatric acute-onset neuropsychiatric syndrome (PANS) is a condition characterized by the abrupt, dramatic onset of obsessive-compulsive disorder (OCD) or eating restriction accompanied by equally abrupt and severe comorbid neuropsychiatric symptoms, which include anxiety, emotional lability, depression, irritability, aggression, oppositionality, deterioration in school performance, behavioral (developmental) regression, sensory amplification, movement abnormalities, sleep disturbance, and urinary frequency (Brimberg et al. 2012). PANS is felt to be caused by infection, inflammation, or some other trigger that is associated with a brain response that leads to these symptoms (Swedo et al. 2012; Chang et al. 2015; Murphy et al. 2014). In an effort to organize etiologic research and treatment trials for this disorder, we started the Stanford PANS Clinic, an interdisciplinary clinic designed to evaluate and treat youth with suspected PANS. Many of these children have been extremely ill with destructive rage outbursts, debilitating compulsions, motor and vocal tics, school dysfunction, and multiple psychiatric hospitalizations. As little precedence exists to guide treatment, our interventions are based on those thought to be useful in pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) (Garvey et al. 1999; Perlmuter et al. 1999; Snider et al. 2005; Murphy et al.
2014) and related conditions such as acute rheumatic fever, postinfectious/reactive arthritis, and Sydenham chorea. In an effort to increase knowledge about this condition, we report here on the first 53 patients evaluated in the Stanford Children’s PANS Clinic.

Methods

Pediatric referrals and parents desiring evaluation for a child were referred to our intake coordinator who did the initial screening of patients. Forty-seven of 53 patients who were ultimately evaluated in PANS clinic met research criteria for diagnosing PANS, except for the criteria for acuity of onset. Patients who had an abrupt onset of symptoms were compared with patients who did not have an abrupt onset of symptoms. We reviewed the results from clinical evaluations, patient questionnaires, PANS Impairment Scale (Table S1), and Caregiver Burden Inventory (Fig. S1) (see online supplementary material at http://www.liebertonline.com/jcap).

Clinical evaluations

Patients underwent standard psychiatric (with K.C., M.T.) and medical evaluation (with J.F.), results of which were recorded in the electronic medical record (EMR).

Laboratory workup

All patients underwent evaluation for Group A streptococcus (GAS) (throat culture, perianal culture [if there were symptoms of redness, pain, or itching], antistreptolysin O [ASO], and antideoxyribonuclease B [DNase B]) at presentation to PANS clinic or flare after being established in PANS clinic. GAS infection was indicated if culture was positive and antistreptococcus antibodies were outside the expected range for age (Kaplan et al. 1998). Mycoplasma titers were ordered by the primary medical doctor (PMD) or Stanford PANS Clinic staff if the patient had a chronic cough, tonsillitis, or sinusitis and/or had had close contact with someone who had these symptoms. We attempted to order an antinuclear antibodies (ANA) test and a histone antibody test on every patient for workup of primary lupus and drug-induced lupus, given the high prevalence of OCD in patients with lupus (Slattery et al. 2004) and concern for lupus cerebritis. We attempted to evaluate thyroid antibodies in all patients with behavior regression and/or hallucinations, given the association of these symptoms with steroid responsive encephalitis associated with thyroiditis (SREAT) (Mahmud et al. 2003). We obtained tissue-transglutaminase (TTG) antibodies in all patients with abdominal complaints (pain, bloating, flatulence, diarrhea), arthritis, and/or unexplained weight loss or failure to gain weight. Autoimmune encephalitis and paraneoplastic antibody panels were sent on all patients with psychosis, memory impairment, cognitive impairment, and a deteriorating course. Summary of physical and occupational therapy reports, neurological consults, and phone calls to school teachers/nurses were recorded in the medical record as per routine.

Record review

Treating clinicians (J.F., M.T., K.C.) reviewed medical records including those from primary care physicians and urgent care visits.

Patient questionnaire

Caregivers completed an extensive intake questionnaire, which required severity scoring of psychiatric and somatic symptoms (including a pain questionnaire). Detailed medical history, including infections and infectious exposures, past medical history, and family history was also elicited by this questionnaire.

PANS Impairment Scale

The PANS Impairment Scale is a parent-rated scale of impairment from PANS symptoms that generates scores ranging from 0 to 50 (see Supplementary Table 1). The PANS Impairment Scale was developed by Dr. James Leckman and his colleagues at Yale and the National Institute of Mental Health (personal communication).

Caregiver Burden Inventory

All parents completed the Caregiver Burden Inventory (see Supplementary Fig. 1) to assess the level of family stress and burden of the illness (Novak and Guest 1989). Retrospective review of patient medical records was approved by the Stanford Panel on Human Subjects Institutional Review Board. Difference in means was evaluated with the Student t test. Difference in proportions was evaluated with the \( \chi^2 \) test. This was an exploratory study, and no corrections for multiple comparisons were performed.

Results

Psychiatric symptoms started acutely (≤3 days) in 40%, subacutely (3 days–8 weeks) in 31%, and insidiously (>8 weeks) in 29%. In patients with subacute onset, the mean time for all the PANS symptom criteria to be met was 3.9 weeks. When the timing of onset was unclear and/or each symptom onset spanned >8 weeks, patients were classified as having had an insidious symptom onset. Patients meeting full research criteria for PANS (i.e., meeting the required symptoms and “abrupt” onset) were compared with the non-PANS cohort (i.e., those who satisfied the symptom criteria but did not have “abrupt” onset).

The mean age at onset for the acute-onset group (PANS group) was 9.6 years (SD 3.5) and for the subacute/insidious-onset group (non-PANS group) it was 7.7 years (SD 2.9). The age at presentation to our clinic for the PANS group was 11.8 years (range 3–17) and for the non-PANS group it was 10.3 years (range 3–17) (Table 1). Most patients in our cohort were male (77%). Preexisting but low-level neuropsychiatric symptoms were common in both the acute-onset and subacute/insidious-onset groups (71% and 63%, respectively) and included sensory disturbance (11% and 14%), attention disorder (0% and 14%), hyperactivity (0% and 14%), anxiety (16% and 14%), behavior problems (0% and 21%), learning disorder (16% and 7%), irritability/anger (5% and 7%), mood disorder (5% and 18%), OCD (11% and 7%), movement disorder (5% and 4%), fine motor difficulties (16% and 18%), gross motor difficulties (5% and 11%), and autism spectrum (21% and 4%). Psychiatric disorders and autoimmune diseases in first-degree family members were commonly reported by parents in both groups (Table 1).

Course of illness is reported in Table 2. Most PANS and non-PANS patients (89%) had a relapsing/remitting course and 74% generally returned to baseline after flares, as determined by parents and psychiatrists (M.T. and K.C.). Three patients had a chronic static course: One patient was admitted to a psychiatric facility shortly after presentation because of extreme violence, and the other two eventually developed choreic movements. Of these two patients with chronic static course and choreic movements, one had a definitive GAS infection and the other did not have evidence of GAS and had undetectable ASO and anti-DNase B antibodies.
Patients had a high rate of somatic symptoms (sleep disturbances, urinary frequency and enuresis, gastrointestinal symptoms) and sensory amplification (hyperacusis, photophobia, generalized pain), the details of which are reported in Table 4. Patients also had high rates of suicidality, aggressive ideation, violent behavior, and psychosis (see Table 4).

All patients underwent a medical evaluation including a full history and physical examination at intake and at each follow up evaluation. The most common immunological and rheumatological examination findings (reported in Table 5) indicated a high rate of axial skeletal pain and conditions relating to inflammatory arthritis. Six patients were thought to have arthritis triggered by an infection (reactive arthritis) based on the pattern and timing of symptoms and the limited course of arthritis. The remainder had a clinical picture of mild but persistent arthritis, and met clinical criteria for enthesitis-related arthritis, spondyloarthritis, or psoriatic arthritis; in these cases, it was unclear as to whether or not the arthritis was infection triggered. Hematological and immunological abnormalities are also reported in Table 5, but should be interpreted with caution, because blood samples were retrospectively reviewed and it is possible that infections may have skewed the results, as laboratory blood draws were typically obtained at the time of a deterioration in clinical status. The most common motor findings in the PANS and non-PANS groups included simple tics (21% and 32% respectively), complex tics (5% and 4% respectively), chorea (5% and 7% respectively), and choreiform movements (11% and 0% respectively).

Despite having known household contacts with GAS. These two latter patients were included in the overall analysis because OCD symptoms predominated in the clinical picture and the choreic movements were not interfering with the patient’s activities of daily living. Two patients were classified as having a progressive course: One patient was thought to have an illness resembling, but not definitively, lupus cerebritis (positive ANA, positive antiphospholipid antibodies [β 2-glycoprotein antibodies], thrombocytopenia [platelets less than 100,000/mm3, in the absence of offending drugs]). The other patient was eventually diagnosed with autoimmune encephalitis caused by chronic, deteriorating speech and cognition (in addition to the OCD and other psychiatric symptoms), nonspecific autoimmune markers, and dramatic responsiveness to high dose intravenous corticosteroids. Both of these latter patients demonstrated complete response (returned to baseline) with aggressive immunosuppression and relapse when weaned from immunosuppression.

The prevalence of psychiatric symptoms is reported in Table 3. Anxiety was the most prevalent symptom and anorexia was the least common. All patients met the required secondary symptom criteria, but only 40% had an abrupt onset qualifying them for the diagnosis of PANS. Only 17% had documented evidence of GAS infections (within 12 weeks prior to or during presentation) and/or elevated streptococcal titers at presentation as well as having acute-onset of symptoms. Most patients had not been evaluated for streptococcus infection prior to or at presentation and, therefore, GAS status was unknown. Symptom severity scores and caregiver burden scores were highly elevated.

### Table 1. Demographics of 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, but Only the Acute-Onset Group Met Full Criteria for PANS

<table>
<thead>
<tr>
<th>Patient demographics and medical history</th>
<th>Total cohort (n = 47)</th>
<th>Acute-onset (PANS group) (n = 19)</th>
<th>Subacute/insidious-onset (not PANS group) (n = 28)</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at full symptom onset</td>
<td>10.9 (SD = 3.3)</td>
<td>9.6 (SD = 3.5)</td>
<td>7.7 (SD = 2.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean age at presentation to PANS clinic</td>
<td>10.9 (SD = 3.7)</td>
<td>11.8 (SD = 4.0)</td>
<td>10.3 (n = 27, SD = 3.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Male</td>
<td>36/47 (77%)</td>
<td>14/19 (74%)</td>
<td>22/28 (78%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Preexisting neuropsychiatric disorder in patient (n = 44)</td>
<td>29/44 (66%)</td>
<td>12/17 (71%)</td>
<td>17/27 (63%)</td>
<td>0.83</td>
</tr>
<tr>
<td>First degree family member with history of psychiatric illness (n = 27)</td>
<td>21/27 (78%)</td>
<td>7/9 (78%)</td>
<td>14/18 (78%)</td>
<td>0.53</td>
</tr>
<tr>
<td>First degree family member with history of autoimmune disease or inflammatory disorder (n = 45)</td>
<td>30/45 (67%)</td>
<td>12/17 (71%)</td>
<td>18/28 (64%)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Difference in means was evaluated with the student t test. Difference in proportions was evaluated with the χ² test.

### Table 2. Course of Psychiatric Illness in 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, but Only the Acute-Onset Group Met Full Criteria for PANS

<table>
<thead>
<tr>
<th>Course of disease</th>
<th>Total cohort (n = 47)</th>
<th>Acute-onset (PANS group) (n = 19)</th>
<th>Sub-acute/insidious-onset (not PANS group) (n = 28)</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing/remitting course of those relapsing/remitting (n = 42)</td>
<td>42 (89%)</td>
<td>16 (84%)</td>
<td>26 (93%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Generally returned to baseline after flares</td>
<td>31 (74%)</td>
<td>12 (75%)</td>
<td>19 (73%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Generally worsened to baseline after flares</td>
<td>8 (19%)</td>
<td>3 (19%)</td>
<td>5 (19%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Unclear or variable return to baseline</td>
<td>3 (6%)</td>
<td>1 (6%)</td>
<td>2 (8%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Chronic course (symptoms persist at same level)</td>
<td>2 (5%)</td>
<td>1 (7%)</td>
<td>1 (4%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Progressive course (symptoms worsen over time)</td>
<td>3 (8%)</td>
<td>2 (13%)</td>
<td>1 (4%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*Difference in proportions was evaluated with the χ² test.
In patients with psychosis (n = 11) and/or chronic, static, or progressive courses (n = 5), we obtained paraneoplastic and autoimmune encephalitis antibody panels (Mayo Medical Laboratory), and all but one was negative. The one positive paraneoplastic antibody found was low titer and did not match the patient’s clinical phenotype; therefore, it was considered a nonspecific finding and not relevant to the patient’s illness.

We attempted to collect data on reported infections and illnesses thought to be associated with the psychiatric illness; however, this type of data collection has significant limitations (outlined in the Discussion); therefore, the following data should be interpreted with caution and should only be used to plan future prospective studies. An illness within 3 weeks prior to or during the development of the first PANS symptom was commonly reported in patients with PANS and non-PANS OCD (84% and 93% respectively). The primary symptoms of the illness included fever (47% and 25% respectively), sore throat (42% and 14% respectively), upper respiratory infection (URI) symptoms (5% and 18% respectively), myalgias and/or arthralgias (11% for both cohorts), sinusitis (11% and 0% respectively), otitis media (5% and 4% respectively), rash (5% and 4% respectively), gastroenteritis symptoms (11% and 4% respectively), headache (0% and 4% respectively), and fatigue (0% and 4% respectively). Documented GAS infection within 12 weeks of development of psychiatric symptoms, was found in PANS and non-PANS groups at presentation (21% vs. 61%) and with at least one major flare (74% vs. 39%). Positive mycoplasma immunoglobulin (Ig)M (not confirmed with polymerase chain reaction (PCR)) was found at the time of presentation (5% vs. 7%) or with at least one flare (26% vs. 18%); however, this test was only ordered on patients with suspected clinical symptoms of mycoplasma infection. Other illnesses reported within 3 weeks prior to or during presentation included: Sinusitis and/or otitis media (5), impetigo (1), dental infection (1), vaccine (1), anaphylactic reaction (1), and acute-onset hip pain requiring hospitalization (2). Other illnesses reported within 3 weeks prior to or during major flares included: Otitis media and/or sinusitis (19), urinary tract infection (1), anaphylactic reaction (1), mononucleosis (1), pneumonia (1), impetigo (1), and arthritis/inflammatory disease flare (1). In 16% of the PANS group and 21% of the non-PANS group, parents did not feel that illnesses preceded neuropsychiatric deteriorations. However, in 63% of PANS patients and 61% of non-PANS patients, parents reported that all or most deteriorations were preceded by an infection. This was subjective data collected from our parent questionnaire; there were no clear dates or timeline information of infection and subsequent flares. Parents also reported a high rate of sinopulmonary infections and/or recurrent tonsillitis on the medical history form in both the PANS and non-PANS groups (47% and 44% respectively).

Discussion

Forty-seven patients evaluated in the Stanford Children’s PANS Clinic had prominent OCD and/or eating restriction and significant comorbid psychiatric symptoms including anxiety, mood disorders, behavior regression, academic deteriorations, sensory, and somatic symptoms. All these patients met secondary symptom criteria for PANS (Table 3), whereas a smaller but clinically important fraction (40%) met full criteria for PANS by having symptoms starting abruptly. The minority of patients (17%) met criteria for PANDAS. However, many patients without a history of preceding GAS had been evaluated fully for streptococcal disease (i.e., throat culture, perianal cultures, ASO, and anti-DNase B antibodies) prior to or during their initial presentation, and we suspect that PANDAS was underdiagnosed in our cohort.

The age of onset in our cohort was older compared with the mean age reported in prior reports of youth with PANS and PANDAS.
### Table 4: Somatic Symptoms, Violence, and Psychosis Reported in the Clinical Charts of 47 Consecutive Patients Presenting to the Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Clinic

<table>
<thead>
<tr>
<th>Ancillary symptoms – new or highly escalated at time of psychiatric symptom presentation or major flare*</th>
<th>Total cohort ( (n=47) )</th>
<th>Acute-onset ( (n=19) )</th>
<th>Subacute/insidious-onset ( (n=28) )</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>39 (83%)</td>
<td>16 (84%)</td>
<td>23 (82%)</td>
<td>0.85</td>
</tr>
<tr>
<td>General fatigue</td>
<td>34 (72%)</td>
<td>11 (58%)</td>
<td>23 (82%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Not feeling rested in morning</td>
<td>27 (57%)</td>
<td>9 (47%)</td>
<td>18 (64%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Urinary complaints (polyuria, enuresis, other)</td>
<td>21 (45%)</td>
<td>11 (58%)</td>
<td>10 (36%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Weight loss</td>
<td>26 (55%)</td>
<td>12 (63%)</td>
<td>14 (50%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>18 (38%)</td>
<td>8 (42%)</td>
<td>10 (36%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Weakness with or without exercise intolerance</td>
<td>41 (87%)</td>
<td>16 (84%)</td>
<td>25 (89%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Headaches</td>
<td>5 (11%)</td>
<td>2 (11%)</td>
<td>3 (11%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sensory amplification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity to touch</td>
<td>30 (64%)</td>
<td>13 (68%)</td>
<td>17 (61%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hyperacusis</td>
<td>21 (45%)</td>
<td>10 (53%)</td>
<td>11 (39%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Photophobia</td>
<td>28 (60%)</td>
<td>13 (68%)</td>
<td>15 (54%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypersensitivity to smell or taste</td>
<td>35 (74%)</td>
<td>14 (74%)</td>
<td>21 (75%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Generalized pain</td>
<td>31 (66%)</td>
<td>13 (68%)</td>
<td>18 (64%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Violence questionnaire and/or structured interview.</td>
<td>( (n=42) )</td>
<td>( (n=18) )</td>
<td>( (n=24) )</td>
<td></td>
</tr>
<tr>
<td>Any suicidality</td>
<td>17 (40%)</td>
<td>8 (44%)</td>
<td>9 (38%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>17 (40%)</td>
<td>8 (44%)</td>
<td>9 (38%)</td>
<td></td>
</tr>
<tr>
<td>Gestures</td>
<td>6 (14%)</td>
<td>2 (11%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>Intent</td>
<td>1 (2%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Any homicidality</td>
<td>8 (19%)</td>
<td>3 (17%)</td>
<td>5 (21%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Homicidal Ideation</td>
<td>8 (19%)</td>
<td>3 (17%)</td>
<td>5 (21%)</td>
<td></td>
</tr>
<tr>
<td>Gestures</td>
<td>4 (10%)</td>
<td>1 (6%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>Intent</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Injury/damage from violence</td>
<td>25 (50%)</td>
<td>11 (61%)</td>
<td>14 (58%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Self</td>
<td>15 (36%)</td>
<td>6 (33%)</td>
<td>9 (38%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>18 (43%)</td>
<td>7 (39%)</td>
<td>11 (46%)</td>
<td></td>
</tr>
<tr>
<td>Objects</td>
<td>21 (50%)</td>
<td>8 (44%)</td>
<td>13 (54%)</td>
<td></td>
</tr>
<tr>
<td>Life-threatening violence</td>
<td>6 (14%)</td>
<td>2 (11%)</td>
<td>4 (17%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Psychosis (hallucinations)</td>
<td>11 (26%)</td>
<td>4 (22%)</td>
<td>7 (29%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*These ancillary symptoms were either new or highly escalated at or following presentation or major flare of the psychiatric illness. Data were obtained through patient questionnaires and patient interviews. We assessed suicidality, homicidality, violence, injury, and psychosis through patient questionnaires and structured interviews.

(Swedo et al. 1998; Bernstein et al. 2010; Murphy et al. 2012, 2015), we believe that our result reflects an inaccurate estimate because of the small patient population studied. Additionally, many patients reported earlier and milder PANS-like episodes, but we did not adjust the age of onset for undocumented psychiatric deteriorations, even though we believe that these earlier episodes may have been the first presentation of the PANS illness.

The co-occurrence of psychiatric symptoms from a number of diagnostic categories is not unique to PANS (Table 3). For example, non-PANS pediatric OCD is often associated with tics, mood disorders, anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD) (Peterson et al. 2001; O’Rourke et al. 2011; Gomes de Alvarenga et al. 2012; Selles et al. 2014). Taken out of the PANS context, many of our patients could otherwise be diagnosed with multiple psychiatric disorders. OCD symptoms in our PANS group were severe, and similar to those in children with non-PANS OCD. Many spent multiple hours each day performing compulsive activities, and many of our patients reported violent imagery that was severe and persistent. In most cases, the violent imagery was a source of anxiety (especially separation anxiety). Depressed mood (including full depressive episodes) and mood lability were common. Patients and families frequently reported patient suicidal and homicidal ideation, gestures, and intent (Table 4). Impulsive dangerous behavior, such as attempting to jump out of moving cars and out of windows, was common. Patients were also reported to exhibit violence toward themselves, family members, and/or objects. No person died or was hospitalized as a result of injury. Psychotic symptoms were also reported in some patients including auditory and visual hallucinations.

Preexisting neuropsychiatric symptoms – such as anxiety, ADHD symptoms, and mood difficulties – were common in both the acute- and subacute-onset groups of patients in our cohort, but these symptoms were usually subclinical, and did not cause significant impairment. It is possible that this premorbid pathology was the sequela of previous, undetected infections and/or inflammatory reactions. Therefore, the finding of preexisting neuropsychiatric symptoms should not dissuade clinicians and researchers from considering the possibility of PANS and looking into infectious and inflammatory triggers.

Most patients had a relapsing/remitting course (89%) and the minority (11%) had a chronic static or progressive course, which may be suggestive of a different illness. In general, the course of most autoinflammatory diseases – which are driven by abnormalities of the innate immune system – tend to be relapsing and remitting, whereas autoimmune diseases (driven by the adaptive immune system; i.e., T cells and B cells) are typically chronic or progressive (Masters et al. 2009). In addition to autoinflammatory diseases, postinfectious inflammatory diseases (i.e., acute rheumatic
CLINICAL FEATURES OF FIRST 47 CONSECUTIVE PATIENTS WITH PANS

Table 5. Rheumatological and Immunological Evaluation in 47 Consecutive Patients Evaluated in Our Stanford Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) Clinic Who Met Symptom Criteria for PANS, But Only the Acute-Onset Group Met Full Criteria for PANS

<table>
<thead>
<tr>
<th>Medical evaluations</th>
<th>Fraction (%) of patients with medical finding (n=47)</th>
<th>Acute-onset (PANS group) (n=19)</th>
<th>Subacute/insidious-onset (not PANS group) (n=28)</th>
<th>Significance between PANS and not PANS groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported neck and/or, back and/or sacroiliac joint pain.</td>
<td>19/47 (40%)</td>
<td>5/19 (26%)</td>
<td>14/28 (50%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Patients meeting criteria for inflammatory back pain</td>
<td>10/47 (21%)</td>
<td>4/19 (21%)</td>
<td>6/28 (21%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Patients having at least one episode consistent</td>
<td>13/47 (28%)</td>
<td>6/19 (32%)</td>
<td>7/28 (25%)</td>
<td>0.61</td>
</tr>
<tr>
<td>with reactive arthritis or persistent arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(enthesitis-related arthritis, spondyloarthropathy-related arthritis, or psoriatic arthritis).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient erythematous flat rashes</td>
<td>6/47 (13%)</td>
<td>0/19 (0%)</td>
<td>6/28 (21%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Elevated inflammatory markers ESR/CRP</td>
<td>3/43 (7%)</td>
<td>0/17 (0%)</td>
<td>3/26 (12%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Rheumatological/autoimmune markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA (&gt;1:160 titer)</td>
<td>7/43 (16%)</td>
<td>5/18 (28%)</td>
<td>2/25 (8%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Antihistone antibodies (&gt;1.0 Eliza)</td>
<td>6/41 (15%)</td>
<td>4/16 (25%)</td>
<td>2/25 (8%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Antithyroid antibodies</td>
<td>3/41 (7%)</td>
<td>2/16 (13%)</td>
<td>1/25 (4%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Tissue-transglutaminase antibodies</td>
<td>4/37 (11%)</td>
<td>1/14 (7%)</td>
<td>3/23 (13%)</td>
<td>0.38</td>
</tr>
<tr>
<td>More than one disease-associated autoantibody</td>
<td>7/44 (16%)</td>
<td>4/18 (22%)</td>
<td>3/26 (12%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Paraneoplastic/autoimmune encephalitis panel</td>
<td>1/16 (6%)</td>
<td>0/5 (0%)</td>
<td>1/3 (33%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Hematological abnormalities on at least one laboratory examination (presentation or flare)

<table>
<thead>
<tr>
<th>Medical evaluations</th>
<th>Fraction (%) of patients with medical finding (n=47)</th>
<th>Acute-onset (PANS group) (n=19)</th>
<th>Subacute/insidious-onset (not PANS group) (n=28)</th>
<th>Significance between PANS and not PANS groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytosis</td>
<td>20/47 (43%)</td>
<td>9/19 (47%)</td>
<td>11/28 (39%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>14/47 (30%)</td>
<td>8/19 (42%)</td>
<td>6/28 (21%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3/47 (6%)</td>
<td>2/19 (11%)</td>
<td>1/28 (4%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Anemia</td>
<td>7/47 (15%)</td>
<td>3/19 (16%)</td>
<td>4/28 (14%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Immunoglobulin (Ig) analyses

<table>
<thead>
<tr>
<th>Medical evaluations</th>
<th>Fraction (%) of patients with medical finding (n=47)</th>
<th>Acute-onset (PANS group) (n=19)</th>
<th>Subacute/insidious-onset (not PANS group) (n=28)</th>
<th>Significance between PANS and not PANS groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low IgG levels</td>
<td>6/21 (29%)</td>
<td>1/7 (14%)</td>
<td>5/14 (36%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Low IgA levels</td>
<td>5/21 (24%)</td>
<td>1/7 (14%)</td>
<td>4/14 (29%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Low IgM levels</td>
<td>6/21 (29%)</td>
<td>1/7 (14%)</td>
<td>5/14 (36%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any hypogammaglobulinemia above</td>
<td>11/23 (48%)</td>
<td>2/9 (22%)</td>
<td>9/14 (64%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Elevated IgE</td>
<td>2/14 (14%)</td>
<td>0/5 (0%)</td>
<td>2/9 (22%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Low vitamin D</td>
<td>4/42 (10%)</td>
<td>2/16 (13%)</td>
<td>2/26 (8%)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Tissue-transglutaminase antibodies.*

The prevalence of low IgG levels (14%) was higher than in healthy children (Marlow et al. 2004; Malleson et al. 2010; Satoh et al. 2012; Sperotto et al. 2014), but may have reflected recent infections. Although antihistone and antithyroid antibody titers were higher than those expected based on our laboratory’s reference ranges, these reference ranges were not age matched to our cohort; therefore, we cannot draw definitive conclusions from these data. As all laboratory blood tests were performed during presentation or relapse of disease, immunological and hematological abnormalities (Table 5) may have reflected aberrations secondary to recent infections. More research into specific and reproducible (through time) immunological and hematological deviations and presence of concurrent infections is necessary before drawing conclusions from these data.

In addition to the high reported prevalence of autoimmune disease in family members, psychiatric disorders were frequently reported in first-degree relatives. This “dual vulnerability” to autoimmune disease and psychiatric illness is not a novel finding, as it parallels prior reports in PANDAS, depression, Tourette’s syndrome, autism, schizophrenia, and other psychiatric disorders (Morin et al. 2008; Leckman and Vaccarino 2014; Stagi et al. 2014). Recent genetic findings in Tourette’s syndrome, autism, and schizophrenia may further support this dual vulnerability theory (Gesundheit et al. 2013; Postal and Appenzeller 2014; Stringer

fever and reactive arthritis) also follow a relapsing/remitting course with cumulative damage with each flare eventually leading to progressive disease in some cases (for example, cardiac valve damage in the case of acute rheumatic fever). Further research is needed to map the illness course in PANS patients, and correlate with infections and immunological phenotypes.

Autoimmune and other inflammatory diseases were reported to be prevalent in first-degree family members of our patients with and without PANS. This is consistent with what has been reported for family members of youth with PANDAS (Murphy et al. 2010). Both the PANS and non-PANS patients themselves frequently demonstrated coexisting autoimmune and/or inflammatory diseases, most commonly inflammatory back pain (21%), reactive or persistent arthritis (28%), and presumed celiac disease (11%). Patients with presumed celiac disease had high titers of TTG antibodies, and reported improvement of gastrointestinal symptoms on a gluten-free diet; however, these patients/families did not pursue confirmatory endoscopy/biopsy, because of the severity of the psychiatric illness. The rate of ANA positivity in our PANS cohort (28%) was higher than that reported in healthy children (Hilario et al. 2004; Malleson et al. 2010; Satoh et al. 2012; Sperotto et al. 2014), but may have reflected recent infections. Although antihistone and antithyroid antibody titers were higher than those expected based on our laboratory’s reference ranges, these reference ranges were not age matched to our cohort; therefore, we cannot draw definitive conclusions from these data. As all laboratory blood tests were performed during presentation or relapse of disease, immunological and hematological abnormalities (Table 5) may have reflected aberrations secondary to recent infections. More research into specific and reproducible (through time) immunological and hematological deviations and presence of concurrent infections is necessary before drawing conclusions from these data.

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et al. 2014). Families may share genes that lead to a propensity for immune dysfunction and psychiatric dysfunction, or to a mechanism that links the two. It is an intriguing possibility that relatives may have experienced an unrecognized PANS-like illness as youth, initiating their psychiatric illnesses, which are now seen as “garden variety” and idiopathic. Although this is speculation on our part, we feel that the presence of psychiatric illness in family members should not dissuade clinicians and researchers from considering the diagnosis of PANS.

Infections are postulated to be a trigger for PANS (Swedo et al. 2010). Except for GAS, no infections have been definitively linked to PANS. Our data set is limited, because of recall bias and limited workup surrounding the presentation and flares prior to coming to our PANS clinic. Therefore, we are not able to draw any conclusions, at this time, regarding the role of infections in triggering disease presentation and flares in either the PANS and/or the non-PANS group.

Based on parent inquiry, most parents reported that illnesses generally preceded neuropsychiatric deterioration in both groups. Although many had reported GAS pharyngitis, others had unknown or unclear illnesses. Workup for GAS infection was often not pursued at the initial presentation of OCD, presumably because of the lack of awareness and guidelines to help clinicians perform workups for medical illness at the onset of OCD. Additionally, GAS may be missed by using a rapid streptococcus test only, by using a throat culture that is improperly collected, or by failing to detect GAS in another location, such as the perianal area. Additionally, it was previously found that 27% of healthy children did not mount an ASO and anti-DNase B antibody response (Shet et al. 2003). As GAS infections in youth are common and possibly coincidental in this population, it is also difficult to establish causality in those patients who test positive. However, there has been a substantial body of literature linking GAS infections with OCD, eating restriction, and movement disorders including chorea and tics (Husby et al. 1976; Swedo et al. 1989, 1993, 1998; Mercadante et al. 2000; Leonard and Swedo 2001; Kirvan et al. 2003; Hoffman et al. 2004; Singer et al. 2004; Kirvan et al. 2006, 2007; Murphy et al. 2007; Yaddanapudi et al. 2010; Brimberg et al. 2012; Lotan et al. 2014; Toufexis et al. 2014; Williams and Swedo 2014).

We are not fully able to interpret our mycoplasma data, because IgM serology has poor positive predictive value (52%) (Chang et al. 2014); we hope to further explore this possible infectious trigger with more specific testing in the future (mycoplasma PCR). Mycoplasma has been reported to be a possible etiologic pathogen in striatal encephalitis, but not specifically acute-onset OCD (Candler and Dale 2004; Dale and Brilot 2012).

Although many parents report a possible association between infections and onset or flare of psychiatric symptoms, it is difficult to know if these infections are coincidental or are in the causal pathway. As discussed, we believe that there are adequate published data to support the connection between preceding GAS infections as an etiologic trigger for acute-onset OCD, certain movement abnormalities, and possibly eating restriction (Swedo et al. 1998; Leonard and Swedo 2001; Toufexis et al. 2014; Williams and Swedo 2014) but it is not known whether other infections are also in the causal pathway and whether GAS infections play a role for patients who are not described as having acute-onset symptoms. Well-designed prospective studies are needed to better explore connections between infections and psychiatric deterioration. In addition to acute rheumatic fever and reactive arthritis, the connection among infections, autoimmunity, and immune dysfunction is postulated in many autoimmune diseases including lupus (Esposito et al. 2014; Nelson et al. 2014) and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Sanders et al. 2004). The infection itself may not be the primary problem, but rather the inflammatory sequelae that develop after the infection is cleared.

Patients’ laboratory examinations revealed a high rate of hematological and immunological deviations (Table 5), including depressed immunoglobulins; the clinical significance remains unknown, however, and may be more relevant to preceding illnesses. Prospective studies are needed to determine the relevance of the immunophenotypes described in this report, with more detailed analysis including measurements repeated through time with correlation to infections and psychiatric symptom flares.

Patients in our cohort had severe and often life-impairing somatic symptoms including sleep disturbances, urinary symptoms (often extreme polyuria) not attributable to infections, sensory amplification (hyperacusis, photosensitivity, hyperosmia, sensitivity to touch), and generalized pain (Table 4). Corroboration with neuroimaging findings may help elucidate whether brain circuits involved in these symptoms overlap with brain circuits thought to be involved with OCD and eating restriction. Patient report of weakness and exercise intolerance may reflect general deconditioning or secondary effect of fatigue, pain, and depressed mood.

Although most of these patients did not report pain to their parents and/or primary care physicians, the results of our physical examination, clinical interview, and pain questionnaire demonstrate that most patients (68% in the PANS group and 64% in the non-PANS group) actually do experience pain, including “shooting pains,” limb pains, joint pain, and/or tender myofascial points. Many patients (26% of PANS group and 50% of the non-PANS group) reported neck, and/or back, and/or sacroiliac pain (Table 5). Furthermore, 21% of patients in both cohorts met criteria for the diagnosis of inflammatory back pain (age of onset <40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night that improved upon getting up and moving around) (Sieper et al. 2009). The diagnosis of inflammatory back pain clinically indicates the need for further work-up (including imaging, which is often, but not always, normal in early stages), anti-inflammatory medications, and monitoring by a rheumatologist.

Limitations

This study has several limitations. Potential limitations included reliance on parental history and recall, the small number of patients, possible missed infections (discussed previously), and ascertainment bias. In retrospective studies, recall bias and lack of detailed medical records surrounding the onset of illness may lead to misclassification of patients. Many patients presented to our clinic years after their initial symptom onset; therefore, the history was subject to recall bias, especially with regard to timing of onset and history of infections. Although reliance on parent recall is a potential weakness, we did obtain medical records to substantiate parent report. However, medical record documentation was sometimes vague with regard to the onset timing. Additionally, patients were not always evaluated by their pediatrician in the time period surrounding onset, and GAS screening was not performed in the majority of patients at presentation. Therefore, GAS infection and subsequent PANDAS are possibly underreported.

Future studies will attempt to use more stringent inclusion criteria to minimize the possibility of recall bias and, ideally, follow at-risk children prospectively. Although in our sample the
acute-onset group did not differ significantly from the subacute- or insidious-onset groups in this initial analysis of medical and psychiatric characteristics, this study may have been underpowered to find differences. Additionally, the immune function studies we performed were screening tests. Certainly more detailed immunophenotyping should be done in order to evaluate immune differences between these groups, which may or may not explain the differences in onset presentation (acute vs. subacute/insidious). Future larger studies with more detailed data correlated with more in-depth immunophenotyping may suggest differences that further distinguish the two types. Ascertainment bias may have followed from the tremendous impact of the illness on these children. These patients suffered from severe psychiatric, behavioral, and physical symptoms, which was reflected in the high impairment scores and the high degree of caregiver burden reported by the parents (Table 3). It is conceivable that medical health professionals and families caring for severely impaired patients sought medical attention at our clinic more readily than they did for more moderately or mildly impaired patients. As awareness of PANS grows, perhaps the profile of the population will change.

Conclusion

Patients presenting to our PANS clinic had grave psychosocial impairment assessed through the PANS Impairment Scale and the Caregiver Burden (both available in the online article at www.liebert.com/jcap), but only 40% of the patients met full PANS criteria by having symptoms starting abruptly. In addition to OCD, anxiety, mood disorder, cognitive deterioration, and the other symptoms previously described to comorbidity with PANS, patients coming to our clinic also had high rates of violence and psychosis. Due to the multidisciplinary nature of our clinic, patients had evaluations for pain, rheumatic conditions, and immunodeficiency. We cannot conclude definitely on the rates of these comorbid immune-related conditions since there is a strong ascertainment bias with regards to the patient population that chose to be evaluated in our clinic. Larger and more in-depth studies are needed to understand the immune system in patients with PANS and PANS-like illnesses.

Clinical Significance

Children presenting with acute-onset of OCD symptoms or restricted eating should be carefully evaluated for PANS, as they often have medical comorbidities and severe psychosocial impairment. Steps should be taken to evaluate for underlying infections and inflammatory illnesses per guidelines established by the 2013 PANS Consensus Conference (Chang et al. 2015). Caregivers may seek evaluation of PANS and/or PANDAS, but not all of these cases will meet the full PANS and PANDAS criteria requiring that symptoms develop and reach maximum intensity over a 24–36 hour period. Primary care and psychiatric professionals may be helped by knowing that some children with subacute or insidious onset of neuropsychiatric symptoms resemble those with *boca fide* PANDAS and PANS in many ways. If clinicians suspect a PANDAS or PANS-like illness, evaluation of infections, especially GAS, and inflammatory diseases may result in diagnostic insights that otherwise would not occur when encountering severe psychiatric symptoms.

Disclosures

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Disordered Eating and Food Restrictions in Children with PANDAS/PANS

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Abstract

Objective: Sudden onset clinically significant eating restrictions are a defining feature of the clinical presentation of some of the cases of pediatric acute-onset neuropsychiatric syndrome (PANS). Restrictions in food intake are typically fueled by contamination fears; fears of choking, vomiting, or swallowing; and/or sensory issues, such as texture, taste, or olfactory concerns. However, body image distortions may also be present. We investigate the clinical presentation of PANS disordered eating and compare it with that of other eating disorders.

Methods: We describe 29 patients who met diagnostic criteria for PANS. Most also exhibited evidence that the symptoms might be sequelae of infections with Group A streptococcal bacteria (the pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections [PANDAS] subgroup of PANS).

Results: The clinical presentations are remarkable for a male predominance (2:1 M:F), young age of the affected children (mean = 9 years; range 5–12 years), acuity of symptom onset, and comorbid neuropsychiatric symptoms.

Conclusions: The food refusal associated with PANS is compared with symptoms listed for the new Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) diagnosis of avoidant/restrictive food intake disorder (ARFID). Treatment implications are discussed, as well as directions for further research.

Introduction

In addition to the sudden overnight onset of classic obsessive-compulsive symptoms, the sudden onset of reduced and restricted food intake is one of the defining diagnostic symptoms of pediatric acute-onset neuropsychiatric syndrome (PANS) (Swedo et al. 2012). Multiple etiologies for PANS have been hypothesized, ranging from genetic and immunologic disorders to postinfectious sequelae. When the symptoms are preceded by a group A streptococcal (GAS) infection, the condition is referred to as “pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections” (PANDAS) (Swedo et al. 1998). In 1997, Sokol and Gray described the first cases of “PANDAS anorexia” (PANDAS-AN) in their eating disorders unit at the Menninger clinic (Sokol and Gray 1997). Notably, the PANDAS-AN patients described were prepubescent, feared weight gain as a result of body dysmorphic issues, and exhibited symptoms temporally related to a GAS infection. Additional reports document positive GAS cultures among youth with abrupt onset of choking fears and refusal to swallow (Henry et al. 1999). These observations contribute to a growing body of literature documenting that viral and bacterial infections can precipitate acute-onset food restriction (Patton et al. 1986; Park et al. 1995; Sokol and Gray 1997; Simon 1998; Sokol 2000, Watkins et al. 2001; Storch et al. 2004; Calkin and Carandang 2007). Systemic diseases, including autoimmune disorders such as systemic lupus erythematosus (Toulany et al. 2014), have also been reported to cause food restrictions via immune dysregulation. Anorexia nervosa (AN) has also been postulated to result when disease-related loss of appetite produces excessive weight loss (Dally 1969; Beumont et al. 1978) and subsequent development of body image distortions.

In youth with PANDAS, food restriction has been reported to occur in the context of obsessional fears about contamination, as well as in the context of the sudden onset of fears of swallowing, choking, or vomiting that are often associated with sensory phenomena (e.g., the perceived texture or appearance of the food). In rare instances, these fears lead to the child’s refusal to ingest anything orally including any liquids. Contamination fears may lead to dietary restriction of all or selected food items (Bernstein et al. 2010). For example, a child with PANDAS was reported to

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have a fear of choking and contamination that led to complete cessation of food consumption and loss of 10% of the subject’s body weight (Storch et al. 2004). Another report detailed the abrupt onset of obsessions about choking, accompanied by refusal to swallow, in association with a positive GAS culture (Henry et al. 1999). Restricted eating also has been reported to occur secondary to new onset of body image distortions of being “too fat” or not having a “six-pack” (Swedo et al. 2012). To date, little has been published on food restrictions in PANS. We report experience with 29 patients who met criteria for PANS and who also exhibited acute-onset food restriction.

Methods

The patients described in this series were participants in clinical trials at the National Institute of Mental Health (NIMH) or at the Rothman Center of Neuropsychiatry at the University of South Florida (USF). All subjects met criteria for PANDAS or PANS and reported new, abrupt onset of eating restrictions or food avoidance. Children participating in the NIMH trial (n = 16) were among a larger cohort enrolled in a study of intravenous immunoglobulin (IVIG) for the treatment of PANDAS (NCT01281969). This study was approved by the National Institutes of Health (NIH) Central Nervous System (CNS) institutional review board (IRB); parents provided informed consent and children provided assent for study participation. Children included from USF (n = 13) were from three studies, with most from a larger cohort of participants in a study investigating azithromycin as a PANS treatment (n = 10; NCT01617083, 6119-128500). These studies were approved by the USF-affiliated IRB; parents provided informed consent and children provided assent for study participation. All of the patients met full criteria for PANS; some also had evidence of preceding GAS infections and, therefore, met criteria for PANDAS. Pertinent subject data are summarized in Table 1.

Assessments

Symptom severity was measured using the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al. 1997) and Yale Global Tic Severity Scale (YGTSS) (Leckman et al. 1989). All assessments were conducted or reviewed by trained clinicians with experience in pediatric obsessive-compulsive disorder (OCD) and tic disorders. Comorbid symptom symptoms were collected at both sites using PANS/PANDAS checklists as well as symptoms deemed present in the clinical evaluation.

Laboratory tests for streptococcal infection included anti-DNase B and antistreptolysin O (ASO) titers. Because of differences in laboratory standardization, thresholds of elevation differed between sites. Thresholds used to designate groups into elevated or unevolved categories at each site were as follows: ASO > 160 IU/mL for ages 0–6 and > 200 IU/mL for ages 7–17 (USF); ages 5–17 years > 640 IU/mL (NIMH); anti-DNase B > 60 U/mL for ages 0–6 and > 170 U/mL for ages 7–17 (USF); > 375 U/mL (NIMH). Assays were performed by the USF clinical research laboratory, or for NIMH subjects, Mayo Medical Laboratories in Rochester, Minnesota.

Results

Twenty-nine children are the subjects of this report, including 20 males (69%) and nine females (31%), with mean age of 9 years (range 5–12 years). All children reported obsessive-compulsive symptoms, with an average CY-BOCS = 30.1 (± 5.2 SD). Eighteen children had tics, with an average YGTSS = 16.6 (± 7.9 SD) (see Table 1). Two thirds (n = 19) of the children (66%) reported that their food restrictions were secondary to contamination fears (see Table 2). Of those with contamination fears, 12 had fears involving germs, three had fears involving poison, and one each had fears of allergens, bleach, illicit drugs, or “the essence and personality of other people.” Others expressed fears of vomiting (28%, n = 8) or choking (21%, n = 6). In addition to food restriction, five patients (17.2%) refused to swallow their own saliva, and another five refused all food for several days or longer. Three children (10%) expressed concerns about weight or body shape. Mean change in weight (in pounds) was -4.21 (± 5.85 SD) and mean percent body weight change was -4.89% (1.91 kg ± 2.66 SD). In the USF sample, 12 out of 13 cases, and in the NIMH sample 14 out of 16 cases, had generalized OCD in addition to food restriction. Mean illness duration was 2.68 months (± 1.68 SD). For PANS neuropsychiatric symptoms, see Table 3.

Eighteen children (62%) were confirmed to have had a positive rapid GAS test or culture at or near the time of PANS onset (See Table 1). Six youth had been exposed to GAS. Mycoplasma pneumonia (MP) exposure or infection was evident in 4 of 12 children examined, 3 of whom (all male) had positive MP immunoglobulin (Ig) G and negative MP IgM, and 1 of whom (female) had positive MP IgG and IgM. A few children had more than one reported infectious trigger.

Selected cases

Patient 8. Patient 8 was an 8-year-old male who presented to USF 1 month following the sudden onset of severe acute-onset contamination fears, food refusal, and tics. Past medical history was significant for a viral infection (gastrointestinal [GI] symptoms) immediately preceding the PANS symptoms, and a lifetime history of frequent GAS infections leading to adenotonsilllectomy. Premorbid psychiatric history was notable for attention-deficit/ hyperactivity disorder (ADHD) and minor separation anxiety disorder (SAD). Physical examination was only remarkable for moderate livedo reticularis. The patient started having fears of dying suddenly while he and his family were at a restaurant. He thought he was having an allergic reaction, and despite efforts to assuage his anxiety, he began having a panic attack. Although he had no history of food allergies, he then developed contamination fears related to allergens in food, and he refused to eat most solid food. His mother reported that when she attempted to give him dry toast, he refused to eat it and began to dry heave. In addition to allergens, he expressed concern that “other people’s medications” were in his food. At evaluation 1 month post-onset, the parents reported that the child had lost 2 lb (3% of his body weight). All laboratory values were within normal limits, including streptococcal and mycoplasma titers. Out of a desperate desire to get him to eat, his mother began giving him fake allergy pills (i.e., Sweet Tarts), so that he would eat more. However, this measure soon failed, and the boy’s contamination fears generalized to the point where his intake was limited to clear liquids. He was started on azithromycin treatment and, within 1 month, his worries about allergens and medication poisoning were near remission, and he was eating and drinking normally.

Patient 12. Patient 12 was a 10-year-old male with a past history of ADHD, who presented at NIH with sudden-onset severe OCD and a specific fear that his hands and lips were contaminated with bleach cleaner. He had tested positive for GAS and had been
### Table 1. Patient Demographics, Premorbid History, Baseline Scores, and Laboratory Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at evaluation</th>
<th>Premorbid psychiatric history</th>
<th>Medical history</th>
<th>History of infection or exposure</th>
<th>CYBOCS</th>
<th>YGTSS</th>
<th>ASO</th>
<th>Anti-DNase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>5</td>
<td>-</td>
<td>Group T&amp;A</td>
<td>Exposure to viral meningitis</td>
<td>37</td>
<td>26</td>
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<td>NL</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>8</td>
<td>SAD (mild) skin picking age 2</td>
<td>-</td>
<td>Confirmed mycoplasma pneumonia</td>
<td>30</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Tics (mild)</td>
<td>Frequent GAS and URIs Eczema</td>
<td>Confirmed GAS</td>
<td>29</td>
<td>16</td>
<td>NL</td>
<td>↑</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>5</td>
<td>-</td>
<td>Frequent staphylococcal infections</td>
<td>Exposure to GAS</td>
<td>35</td>
<td>9</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>8</td>
<td>-</td>
<td>Frequent GAS Frequent URIs</td>
<td>Confirmed GAS</td>
<td>31</td>
<td>0</td>
<td>NL</td>
<td>↑</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>11</td>
<td>-</td>
<td>Frequent GAS</td>
<td>Confirmed GAS</td>
<td>13</td>
<td>0</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>12</td>
<td>Tics (mild)</td>
<td>Asthma</td>
<td>Exposure to GAS</td>
<td>33</td>
<td>16</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>9</td>
<td>ADHD SAD (mild)</td>
<td>Frequent GAS</td>
<td>Exposure to virus</td>
<td>31</td>
<td>9</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>9</td>
<td>-</td>
<td>Frequent GAS</td>
<td>Confirmed GAS</td>
<td>34</td>
<td>0</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
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<td>-</td>
<td>Frequent URIs</td>
<td>Confirmed mycoplasma pneumonia</td>
<td>37</td>
<td>0</td>
<td>↑</td>
<td>NL</td>
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<tr>
<td>11</td>
<td>M</td>
<td>12</td>
<td>Tics (mild)</td>
<td>-</td>
<td>Chronic URIs</td>
<td>29</td>
<td>34</td>
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<td>M</td>
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<td>Allergies</td>
<td>Confirmed GAS</td>
<td>31</td>
<td>9</td>
<td>NL</td>
<td>NL</td>
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<tr>
<td>13</td>
<td>F</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>Exposure to GAS (rapid antigen detection negative)</td>
<td>27</td>
<td>18</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>14</td>
<td>M</td>
<td>7</td>
<td>ADHD Sensory integration disorder Speech delay Tics (mild)</td>
<td>-</td>
<td>Confirmed GAS</td>
<td>27</td>
<td>4</td>
<td>NL</td>
<td>NL</td>
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<tr>
<td>15</td>
<td>M</td>
<td>12</td>
<td>-</td>
<td>Asthma Frequent GAS Asthma</td>
<td>Confirmed GAS</td>
<td>24</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
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<tr>
<td>16</td>
<td>M</td>
<td>11</td>
<td>Speech delay</td>
<td>-</td>
<td>Confirmed GAS</td>
<td>28</td>
<td>15</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>17</td>
<td>M</td>
<td>10</td>
<td>-</td>
<td>Frequent GAS</td>
<td>Confirmed GAS</td>
<td>28</td>
<td>12</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>7</td>
<td>-</td>
<td>Frequent GAS</td>
<td>Confirmed GAS</td>
<td>25</td>
<td>0</td>
<td>NL</td>
<td>↑</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>9</td>
<td>Anxiety</td>
<td>Asthma Borderline adrenal suppression (secondary to inhaled corticosteroids) Borderline hypothyroidism Frequent GAS Frequent otitis media PE tubes</td>
<td>Confirmed GAS</td>
<td>32</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
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<td>20</td>
<td>M</td>
<td>8</td>
<td>-</td>
<td>Frequent otitis media Scarlet fever</td>
<td>Confirmed GAS</td>
<td>37</td>
<td>0</td>
<td>↑</td>
<td>NL</td>
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<tr>
<td>21</td>
<td>F</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>Exposure to GAS (rapid antigen detection negative)</td>
<td>31</td>
<td>13</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>22</td>
<td>F</td>
<td>7</td>
<td>-</td>
<td>GERD</td>
<td>Exposure to GAS (rapid antigen detection negative)</td>
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<td>18</td>
<td>NL</td>
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<tr>
<td>23</td>
<td>M</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>Confirmed GAS</td>
<td>36</td>
<td>29</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>8</td>
<td>-</td>
<td>Asthma Food allergies</td>
<td>Exposure to GAS (rapid antigen detection negative)</td>
<td>31</td>
<td>21</td>
<td>NL</td>
<td>NL</td>
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</table>

(continued)
exposed to siblings who tested positive for GAS prior to his sudden onset of symptoms. The GAS infection was treated with a 5 day course of azithromycin. After the children’s GAS infections, their mother cleaned the house with bleach, and shortly afterwards, the patient developed an obsession that any food he touched would become contaminated with bleach, harming or killing him. Even when his mother removed all bleach from the house, he still believed she was “contaminated.” When his father performed yard work using fertilizer, the child believed that his father was also now “contaminated.” The child began to spit out or throw away any food that touched his hands or lips. He constantly sought reassurance from his parents by asking, “Is this bleach? Will bleach kill me?” In addition, he engaged in excessive showering, hand washing, and tooth brushing behaviors. He would only eat food that was cut into long “french fry” shapes so that he could pass the food into his mouth without it touching his lips, and eventually he refused to eat completely. This contamination fear generalized to the point that he would not swallow even his own saliva, and would instead hold his saliva in his mouth at school until he could go to the bathroom and spit it out. Because of intense contamination fears, the child had restricted his caloric intake to between 800 and 1000 calories daily, without expressed desire to lose weight or dissatisfaction with his weight. The child refused to eat or drink saliva in his mouth at school until he could go to the bathroom and spit it out. He also reported feeling hungry and was distressed by his inability to eat, even expressing suicidal ideation when frustrated.

Upon entering the NIH study, this child was prescribed penicillin or amoxicillin as prophylaxis against future GAS infections, and 2 g/kg of IVIG over a course of 2 days. Six weeks later, the patient and his parents reported a 90-95% improvement in his symptoms.

Patient 13. Patient 13 was an 8-year-old female who had a sudden onset of OCD symptoms including excessive confessing, concern with right and wrong, and contamination fears. She had been exposed to GAS at school, and she and her fraternal triplet sisters had flu-like symptoms, but she cultured negative for GAS pharyngitis. At her baseline visit at NIH, her ASO was 403 (normal for age), and anti-DNase B was elevated at 397. Historically the “healthiest” of her siblings, the patient experienced a drastic change in personality, with extreme perfectionism and concern with morals. She constantly confessed to doing something “wrong” or “bad” on purpose, when in fact she had done nothing. She constantly apologized and expressed guilt about supposed transgressions and would hit herself on the head or engage in other self-injurious behaviors.

At the time of presentation to NIH, the child’s overscrupulosity had escalated to the point that she felt she “did not deserve to eat” or do other pleasurable things such as watch television. She especially refused to eat foods that she considered “treats,” such as cookies and other foods with sugar. She insisted that her mother not pack treats in her lunch, and if her mother packed a treat anyway, the child refused to eat it and would bring it home or give it away to friends. During the structured interview, she admitted that she was somewhat preoccupied with her appearance and thought that an unrealistically thin doll represented an ideal to which to aspire.

This patient was prescribed a 2 week course of amoxicillin by an outside physician ~ 3 weeks after symptom onset. Two weeks later (and 4 weeks prior to study enrollment), amoxicillin-clavulanic acid was started by an outside physician for GAS prophylaxis; this medication was continued throughout the duration of NIH study participation as well. At NIH, this patient was treated with IVIG per protocol at baseline and 6 weeks, and made a full recovery with only slight residual generalized anxiety. Her parents reported that she was still a selective eater, but that her food intake was adequate.

Patient 24. Patient 24 was a 7-year-old girl with unremarkable premorbid medical or psychiatric history who presented to NIH with complaints of acute-onset OCD that began 9 months prior to evaluation. At that time, she abruptly displayed a compulsive need to carry a plastic bucket at all times secondary to fears of vomiting. She expressed fears of choking, and subsequently refused to eat for 3 consecutive days. She developed fear of contaminants and fear that harm might come to her. She also became characteristically irritable and aggressive, and she displayed severe separation anxiety, behavioral regression, inattentiveness, hyperactivity, and insomnia. A rapid GAS test performed at that time was negative, but was prescribed cephalexin. The cephalexin had no discernible therapeutic effect; therefore, 5 days later the child’s pediatrician discontinued cephalexin and prescribed a course of amoxicillin. Within 36 hours of starting amoxicillin, the child was described as “90% back to normal” according to her parents. Amoxicillin was continued for 6 weeks, then stopped for 5 days, but then resumed because of worsening behavior and anxiety, and then...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at evaluation</th>
<th>Food-related fears</th>
<th>Food-related behaviors</th>
<th>Δ Weight in kilograms (% body weight change)</th>
<th>Illness duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>5</td>
<td>Contamination fears: Germs; fear of vomiting</td>
<td>Restrictive eating</td>
<td>0</td>
<td>3 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>8</td>
<td>Fear of choking</td>
<td>Refusal of solid food; refusal to swallow saliva</td>
<td>+2.3 (4)</td>
<td>2 months</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Contamination fears: Germs; fear of vomiting</td>
<td>Refusal to eat unless father is present</td>
<td>0</td>
<td>1 month</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>5</td>
<td>Fear of choking or vomiting</td>
<td>Restrictive eating</td>
<td>−1.8 (9)</td>
<td>4 months</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>8</td>
<td>Contamination fears: Poison</td>
<td>Restrictive eating</td>
<td>0</td>
<td>1 month</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>11</td>
<td>Disgusted by smell and taste of food</td>
<td>Restrictive eating</td>
<td>−1.4 (4.6)</td>
<td>2 months</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>12</td>
<td>Contamination fears: Illicit drugs</td>
<td>Restrictive eating</td>
<td>−7.7 (14)</td>
<td>3 months</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>9</td>
<td>Contamination fears: Allergens</td>
<td>Restrictive eating</td>
<td>−0.9 (3)</td>
<td>6 months</td>
</tr>
<tr>
<td>9a</td>
<td>M</td>
<td>9</td>
<td>Contamination fears: Germs</td>
<td>Refusal to consume food that has been in his home</td>
<td>−1.8 (6)</td>
<td>1 month</td>
</tr>
<tr>
<td>10a</td>
<td>F</td>
<td>12</td>
<td>Contamination fears: Germs</td>
<td>Refused to eat or drink for 3 days; refusal to eat or drink unless preparing it herself</td>
<td>−5.9 (11)</td>
<td>2 months</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>12</td>
<td>Contamination fears: “Essence” of others in food</td>
<td>Restrictive eating; refusal to swallow saliva</td>
<td>−3.6 (8.3)</td>
<td>2 months</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>10</td>
<td>Contamination fears: Bleach</td>
<td>Would not allow food to touch his lips; eventual refusal of solid food; refusal to swallow saliva</td>
<td>Yes (value unavailable)</td>
<td>1 month</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>8</td>
<td>Feeling she didn’t deserve to eat or do pleasurable things, body image concerns</td>
<td>Restrictive eating</td>
<td>Yes (value unavailable)</td>
<td>2 months</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>7</td>
<td>Contamination fears: Poison</td>
<td>Restrictive eating; refusal to swallow saliva</td>
<td>Yes (value unavailable)</td>
<td>2.5 months</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>12</td>
<td>Contamination fears: Germs</td>
<td>Restrictive eating</td>
<td>0</td>
<td>5 months</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>11</td>
<td>Contamination fears: Poison</td>
<td>Refusal to eat for days</td>
<td>0</td>
<td>5 months</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>10</td>
<td>Contamination fears: Germs</td>
<td>Restrictive eating</td>
<td>0</td>
<td>8 months</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>7</td>
<td>One episode of fear of choking</td>
<td>Decrease in appetite</td>
<td>0</td>
<td>3 months</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>9</td>
<td>Contamination fears: Germs</td>
<td>Restrictive eating and drinking</td>
<td>−1.8 (4.5)</td>
<td>&lt;1 month</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>8</td>
<td>Contamination fears: Germs; fear of vomiting</td>
<td>Restrictive eating</td>
<td>0</td>
<td>3 months</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>6</td>
<td>Fear of choking</td>
<td>Restrictive eating</td>
<td>Yes (value unavailable)</td>
<td>3 months</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>7</td>
<td>Would not disclose; concerns about being overweight</td>
<td>Restrictive eating</td>
<td>Yes (value unavailable)</td>
<td>1 month</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>12</td>
<td>Contamination fears: Germs; fear of vomiting</td>
<td>Restrictive eating</td>
<td>−1.8 (4)</td>
<td>4 months</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>8</td>
<td>Contamination fears: Germs; fear of vomiting; fear of choking</td>
<td>Refusal to eat for 3 days</td>
<td>0</td>
<td>1.5 months</td>
</tr>
<tr>
<td>25a</td>
<td>M</td>
<td>12</td>
<td>Fear of vomiting</td>
<td>Refusal to eat for days</td>
<td>−5.9 (13)</td>
<td>2 months</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>9</td>
<td>Fear of vomiting</td>
<td>Restrictive eating</td>
<td>0</td>
<td>1 month</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>10</td>
<td>Fear of choking; Concerns of being overweight</td>
<td>Refusal to eat; refusal to swallow saliva</td>
<td>−7.7 (18)</td>
<td>3 months</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>6</td>
<td>Contamination: Germs</td>
<td>Restrictive eating; ritualized eating patterns</td>
<td>−4.5 (13)</td>
<td>1 month</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>9</td>
<td>Contamination: Germs; Concerns of being overweight</td>
<td>Restrictive eating</td>
<td>−0.9 (3)</td>
<td>2 months</td>
</tr>
</tbody>
</table>

*Indicates child was hospitalized secondary to dehydration.
continued for the next 5 months. Following exposure to a relative with a documented GAS infection, her symptoms suddenly returned and again included restricted eating secondary to contamination fears and obsessions about choking. Rapid GAS testing was negative, and a culture was not obtained. Amoxicillin was continued during this time, and a brief course of azithromycin was added by the child’s pediatrician. Amoxicillin was continued during NIH study enrollment, and in conjunction with a blinded infusion of sham IVIG/placebo, produced a similar reduction in symptom severity over the course of 8 weeks.

Discussion

The children in this case series displayed acute-onset food restriction, and concomitant obsessions about contamination, poisoning, vomiting, or choking. In some instances, disorders eating appeared secondary to sensory issues or body image distortions. In addition to restricted food intake, the children also reported compulsive ways of preparing food (e.g., cutting, smelling, arranging, and “decontaminating” food), restricting (e.g., avoiding foods bases on texture, color, smell), or refusing food. Two thirds of the children had obsessive fears about contaminated food or beverages, and five refused to swallow their saliva because of contamination concerns.

Eighteen of the 29 cases (62%) had documented GAS infections at or shortly prior to the onset of behavioral symptoms; the remaining 11 children had evidence of GAS exposure (n = 6) or had another infection (n = 5). Evidence of recent exposure to MP was demonstrated in one patient with a positive MP IgM (MP has been implicated in the development of neurologic sequelae [Yiğ et al. 2008]). Notably, MP has been considered in the pathogenesis of tic disorders (Müller et al. 2000, 2004) and is a proposed trigger for PANS (Swedo et al. 2012). Secondary symptoms such as enuresis, sleep disturbance, anxiety, and mood lability, as well as adventitious movements, are commonly associated with the onset of PANS (Bernstein et al. 2010) and were frequently present in these cases (see Table 3).

Molecular mimicry is one theory proposed in the etiology of PANDAS (Kirvan et al. 2006) and also has been postulated as a mediating factor in the development of restrictive eating disorders (Fetissov et al. 2005), as it is hypothesized that antibodies will cross the blood–brain barrier and provoke new onset psychiatric and neurological symptoms. Research has suggested that eating disorders may be associated with autoantibodies against z-melanocyte stimulating hormone, which is involved in appetite regulation, body weight, motivated behavior, and mood (Fetissov et al. 2005). Furthermore, animal models of antibodies to z-melanocyte stimulating hormones have been found to correlate with feeding behavior (Coquerel et al. 2012). OCD and anorexia are highly comorbid disorders, and structural and metabolic changes in the putamen and caudate have been found in both groups (Rubenstein et al. 1992; Harrison et al. 2009; Radua et al. 2010; Kaye et al. 2011; Rothenmund et al. 2011; Friederich et al. 2012). In addition, autoantibodies that have been discovered in children with OCD behaviors (Kirvan et al. 2006) and in adolescents with anorexia; serum positivity was found in 6 out of 22 subjects with AN, five of whom had comorbid OCD (Harel et al. 2001), suggesting there may be a role of autoantibodies and immune factors in AN.

Avoidant and restrictive food intake disorder (ARFID) is a new diagnosis in Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) (American Psychiatric Association 2013). Like other DSM-V disorders, the diagnostic criteria for ARFID describe a specific clinical presentation, without regard for etiology, response to treatment, comorbid symptoms, or even acuity of onset. The PANS cases described in this series met ARFID criteria, as there was a clear eating or feeding disturbance that led to inadequate food intake, accompanied by weight loss in some patients, and significant psychosocial dysfunction in all patients. Nearly all of the children in our series had a paralyzing fear of some adverse consequence of eating normally, as many felt food was poisoned or contaminated, or they had a fear they would vomit or choke. Only three children expressed concerns about body image or “getting fat,” but these obsessions developed later in the course of their symptoms. Because the children were so young, weight loss that would be trivial in an adult (e.g., 1–3 kg) may have been physiologically significant, and the children were at higher risk of dehydration and electrolyte disturbances. One child was hospitalized secondary to dramatic weight loss, and another required intravenous hydration.

As is shown in Table 4, ARFID would seem to capture the eating disturbances described previously more accurately than AN or another specified feeding or eating disorder. ARFID can be diagnosed with other psychiatric diagnoses such as OCD or pseudodystagia if the food restriction or avoidance is severe enough to be of clinical focus, or is an extreme characteristic of the comorbid disorder. In addition, psychiatric conditions, including food restriction secondary to reactive attachment disorder, autism spectrum disorder, trauma associated with choking, and specific phobia must be considered, as symptoms of ARFID can be attributed to these primary diagnoses alone (Kreipe and...
Eating disorders in children are on the rise, and the burden of these disorders on the healthcare system is high. Between 1999 and 2006, there was an 119% increase in eating disorder-related hospitalizations for children <12 years of age, per an analysis performed by the Agency for Healthcare Research and Quality (Rosen 2010). In particular, the steep rise in males with eating disorders is of concern (Carlat et al. 1997; Rosen 2003; Dominé et al. 2009). We hypothesize that the rise in eating disorders in young children, especially in males, as suggested by our cases, may be linked to a PANS presentation that could be missed by clinicians. It is noteworthy that there exists a preponderance of males with pediatric OCD (Geller and March 2012) as well as PANS (Swedo et al. 2012); the male preponderance seen in our sample may simply reflect what has been described for pediatric OCD. It is our hope that a PANS diagnosis will be considered in children who develop acute-onset food avoidance or restriction. The management and outcome of children with a PANS presentation differ from those for AN and ARFID, as treatment with antibiotics or immunomodulatory therapies is often curative (Perlmuter et al. 1999; Murphy and Pichichero 2002; Snider et al. 2005; Murphy et al. in press), as in the cases described above.

**Clinical Significance**

The cases described in this series demonstrate clinically important differences between the disordered eating of PANS and that of ARFID or AN. Acuity of onset, male prevalence, and young age at presentation are the most striking differences, and serve to distinguish the PANS patients from others with eating disorders. In the PANS group, environmental factors, particularly GAS infections, can lead to a cascade of immunological, psychological, and physical symptoms that result in abrupt restriction and/or aversion to food. Early appropriate diagnosis and treatment of PANS is essential, as prompt treatment with antibiotics or immunomodulatory therapies can produce dramatic symptom improvements. Further research is required to determine the best treatment practices for disordered eating in the PANDAS/PANS cohort.

**Disclosures**

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References


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Cefdinir for Recent-Onset Pediatric Neuropsychiatric Disorders: A Pilot Randomized Trial

Tanya K. Murphy, MD, MS,1,2 E. Carla Parker-Athill, PhD,3 Adam B. Lewin, PhD, ABPP,1,2,3 Eric A. Storch, PhD,1,2,3 and P. Jane Mutch, PhD1

Abstract

Objective: Previous studies suggest that the unexplained sudden and severe onset of obsessive-compulsive disorder (OCD) and/or tics may be infection or immune precipitated. Beta lactam antibiotics may be neuroprotective beyond their antimicrobial efficacy. We examine the preliminary safety and efficacy of cefdinir in reducing obsessive-compulsive and/or tic severity in children with new-onset symptoms.

Method: Twenty subjects were randomized to receive placebo or cefdinir for 30 days for the treatment of recent-onset OCD and/or tics. The placebo group received a comparable inactive treatment matched for taste, color, and consistency. The Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) and Yale Global Tic Severity Scale (YGTSS) were the primary outcome measures utilized.

Results: Subjects receiving cefdinir saw notable improvements in tic symptoms, with 44.4% showing at least a 25% reduction in YGTSS (mean decrease = 9.5) scores compared with 9.1% of the placebo group (mean decrease = 0.13). Despite improvements, significant group differences were not observed for YGTSS ($F[1, 13] = 4.03$, $p = 0.066$) although there were moderate differences between group treatment effects ($d = 0.72$). For OCD symptoms, subjects receiving cefdinir saw improvements in OCD symptoms, with 33.3% showing at least a 25% reduction in CY-BOCS scores (mean decrease = 7.8) compared with 27.3% of the placebo group (mean decrease = 4.7), but there were also no significant differences for CY-BOCS ($F[1, 13] = 0.385$, $p = 0.546$; $d = 0.24$).

Conclusions: Subjects assigned to cefdinir exhibited notable, albeit nonstatistically significant, improvements in tic symptoms, compared with the placebo group. There were also some improvements in OCD symptoms, although these were not significant. Overall, cefdinir was well tolerated. Given these preliminary results, a fully powered study is warranted to explore the efficacy of cefdinir as a therapeutic tool for new-onset pediatric neuropsychiatric symptoms, particularly those that appear to be precipitated by infection.

Introduction

Characterized by intrusive thoughts or impulses (obsessions), and repetitive behaviors or compulsions aimed at reducing distress, obsessive-compulsive disorder (OCD) often presents during childhood and early adolescence, with significant neuropsychiatric and neurological comorbidity. The etiology of OCD, like most neuropsychiatric disorders, remains largely unknown, although genetic predisposition and neurotransmitter dysfunction have been among the most prominent theories, with evidence of a familial association as well as abnormalities in serotonin, dopamine, and glutamate systems (Adams et al. 2005; Lazar et al. 2008; Pittenger et al. 2011).

Tic disorders, which also present during childhood with a predominantly prepubertal onset, have a particularly strong co-occurrence with OCD, with a reported 50% rate of comorbidity among those with the disorder (Bloch et al. 2006). Classified based on type (verbal and/or motor) and duration, tic disorders can range from provisional to chronic to Tourette’s disorder. In patients with comorbid OCD/tics, OCD symptom onset often occurs when tics are most severe, and often present with distinct features, including greater rates of symmetry obsessions; and counting, repeating, ordering, and arranging compulsions compared with OCD, which presents without comorbid tic symptoms (Leckman et al. 1994). Tic disorders often follow an intermittent course, with periods of symptom exacerbations/flare, or increased intensity and frequency.
of tics, followed by periods of symptom waning. The presentation or onset of symptoms in OCD and tic disorders, as well as their course, can vary significantly among patients. The inciting “trigger” may also significantly impact symptom onset and course characteristics. In some patients, the onset of symptoms can be “acute,” signifying a dramatic and abrupt onset of symptoms reaching a level of significant impairment within 24–48 hours, whereas in others the onset is insidious. The etiology of tic disorders, like OCD, is unclear and surrounded by significant debate, although genetics, neurochemical abnormalities, and basal ganglia dysfunction appear to be the most likely mechanisms (Jijun et al. 2010; Lerner et al. 2012; Moya et al. 2013).

Recently, the role of infection and resulting immunological disturbances has been implicated in the pathology of tic disorders and OCD. This theory has been strengthened by findings from animal models and clinical studies suggesting that early life immune challenges can lead to later neuropathology. In schizophrenia, for example, perinatal insults resulting in immune activation have been linked to the occurrence of the disorder, particularly the neuropathological, behavioral, and immune abnormalities observed in these patients (Patterson 2009; Winter et al. 2009; Brown 2012).

Perhaps most convincing, however, have been observations made in Sydenham’s chorea, a neurological disorder that occurs in a subset of individuals with rheumatic fever (RF), which presents with a high rate of OCD comorbidity (Swedo et al. 1989). Patients with Sydenham’s chorea experience involuntary movements and behavioral changes thought to be the result of streptococcal-induced autoimmune reaction targeted at the basal ganglia (Bronze and Dale 1993; Kirvan et al. 2006). Similarly, a subset of children were observed to present with tics following acute infection (Kiesling et al. 1993). Originally described in a group of 50 patients by Swedo et al., and termed “pediatric autoimmune neuropsychiatric disorders associated with streptococcus” (PANDAS), patients were noted as experiencing a sudden onset or exacerbation of symptoms of OCD and/or tics following group A streptococcus (GAS) infection (Swedo et al. 1998). Additionally, these patients presented with deterioration in their previous level of functioning, including academic difficulties, changes in personality, and severe mood disturbances (Lewin et al. 2011). More recently, the PANDAS classification has been expanded to include infections from other agents such as mycoplasma pneumonia, influenza, and Lyme infections following observations of influenza, and Lyme disease triggering OCD and/or tics (Allen et al. 1995; Muller et al. 2004). The term “pediatric acute-onset neuropsychiatric syndrome” (PANS) accommodates these other “triggers,” and now emphasizes the acute and severe onset of OCD or food refusal (Swedo et al. 2012).

Current treatments for OCD rely primarily on antidepressant and cognitive-behavioral interventions, whereas treatment of tic disorders rely on β2 agonists, antipsychotics, and behavioral intervention, although the presence of comorbid conditions often makes treatment response variable. Patients with OCD and comorbid tics, for example, are likely to be less responsive to serotonin reuptake inhibitor (SSRI) treatment than their counterparts without tics (March et al. 2007; Pallanti et al. 2011), and those with PANDAS may be more prone to behavioral activation with antidepressants (Murphy et al. 2006). In PANS/PANDAS patients with sudden onset OCD and/or tics, in whom infection has been clinically confirmed, preliminary studies have reported symptom improvements following antibiotic intervention (Murphy and Pichichero 2002; Murphy et al. 2012). Although the validity of the PANDAS/PANS diagnosis remains heavily debated (Murphy et al. 2010), symptom flares or continued symptoms may be caused by undetected and untreated infections, as previously observed in RF, making antibiotic intervention a potentially useful therapeutic tool (Lee et al. 2000).

Beta-lactam antibiotics, such as the penicillins and cephalosporins, are first line options for eliminating GAS infections, and possess low levels of GAS resistance, and with some studies suggesting that cephalosporins are more efficacious than the penicillins for GAS pharyngitis, with higher efficacy against β-lactamase producing bacteria (Casey and Pichichero 2004; Pichichero and Casey 2006). Recent studies have highlighted the neuroprotective properties of β-lactam antibiotics beyond their antimicrobial efficacy, when found to promote the expression of glutamate transporter GLT1, a neurotransmitter system also implicated in OCD and tic disorder (Rothstein et al. 2005).

In this study, we investigated the feasibility, tolerability, and preliminary efficacy of cefdinir, a third generation, broad-spectrum cephalosporin, in the treatment of children with new-onset OCD and/or tics. We hypothesized that children receiving antibiotics would show greater overall improvement in symptom severity than children receiving placebo.

Methods

Participants

Youth between 4 and 13 years of age with a history of recent (but not necessarily sudden and severe) onset of OCD and/or tics and symptom duration ≤6 months were included in the study. Subjects were recruited based on criteria previously described by Murphy et al. (2012). Briefly, all subjects met Diagnostic and Statistical Manual of Mental Disorders, 4th ed. criteria for OCD (American Psychiatric Association 1994), a tic disorder, or both, with diagnosis confirmed by clinical interview with the first author and a semi-structured diagnostic interview conducted by a trained clinician. Youth were excluded if any of the following were present: Active psychosis, mania, current suicidal intent, a diagnosis of intellectual deficiency, or other psychiatric conditions (based on clinical interview with a child psychiatrist) that would limit their ability to participate in study-related procedures. Youth who were nonresponders to prior trials with antibiotic(s) for OCD/tics were also excluded from the study. Those on stable doses of psychotropic medication for their condition were not excluded. Table 1 details sample characteristics. The presiding institutional review board approved all study procedures. Subjects were screened for study eligibility over the phone or at their clinic visit by either a research coordinator or a study investigator. After being given a description of the study and providing the appropriate written consent and assent, parents and youth were given a battery of assessments to complete at a scheduled study visit.

Clinical assessments

Assessments consisted of comprehensive parent, child, and clinical ratings for OCD, tics, and attention-deficit/hyperactivity disorder (ADHD); neurological/physical examinations; and assessments of medication tolerability. Medical record reviews were also completed. Maternal and paternal family histories were collected, including history of autoimmune disorders, chronic conditions, and psychiatric history. As this study focused on the efficacy of cefdinir in reducing the symptoms of OCD/tics and did not require evidence of an infectious trigger, laboratory assessment of streptococcal antibodies was not required, but was noted if available in medical records.

All assessments were conducted or reviewed by the first author or, for the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al. 1997), the Yale Global Tic Severity
CEFDINIR FOR RECENT ONSET NEUROPSYCHIATRIC DISORDERS

Table 1. Demographic Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>All (n = 20)</th>
<th>Placebo (n = 11)</th>
<th>Cefdinir (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>15 (75)</td>
<td>7 (64)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (25)</td>
<td>4 (36)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Age at evaluation, mean (SD)</td>
<td>7.55 (1.87)</td>
<td>7.36 (1.90)</td>
<td>7.79 (1.91)</td>
</tr>
<tr>
<td>Male</td>
<td>7.55 (1.82)</td>
<td>7.37 (1.68)</td>
<td>7.87 (2.02)</td>
</tr>
<tr>
<td>Female</td>
<td>7.29 (2.19)</td>
<td>7.33 (2.53)</td>
<td>7.14 (0)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCD only</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Tics only</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>OCD/tics</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Symptom course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute OCD</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Episodic course</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>New and not dramatic</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dramatic flares</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Wax/Wane w/illness</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stepwise progressive</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe onset tics</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infectious trigger</td>
<td>14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Recent URI</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Positive GAS (culture/rapid strep)</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No evidence of infectious trigger</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Comorbid diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Attention deficit/</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>hyperactivity disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous speech</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoidectomy</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myringotube tubes</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Frequent OM</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Frequent URI/GAS</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Allergy illness</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Perinatal complications</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

GAS, Group A Streptococcus; OCD, obsessive compulsive disorder; URI, upper respiratory infection; OM, otitis media.

Scale (YGTSS) (Leckman et al. 1989), and the Clinical Global Impressions Scale (CGI) (Busner and Targum 2007), by a trained clinician with experience in pediatric OCD and tic disorders. Raters with demonstrated reliability with all instruments were utilized in this study. All study personnel, except the study pharmacist, were blinded to group status. Parent ratings for inattention, impulsivity, hyperactivity, and oppositionality were assessed by the Swanson, Nolan, and Pelham–IV Parent Scale (SNAP-IV) (Swanson 1992), whereas mood, ADHD, OCD, and tics were assessed using the Tourette’s Disorder Scale (TODS), a parent-rated scale measuring symptom severity for irritability, motor and vocal tics, mood, and ADHD (Shytle et al. 2003).

For the CY-BOCS assessment, scores were analyzed for patients presenting with a clinical diagnosis of OCD or OCD/tics. Similarly, for the YGTSS assessment, scores were analyzed for patients presenting with a clinical diagnosis of tics or OCD/tics. Assessments were conducted at baseline to provide information on their utility in clinical practice and response prediction, and at the end of study to assess treatment efficacy. The onset and course characteristics (sudden and severe onset, recent but not sudden and severe onset, episodic, chronic), type of neuropsychiatric symptoms, and evidence of an infectious trigger were determined using a clinical interview and all available clinical documentation (see Table 1). Adverse events were carefully monitored. During the study, if a child developed a clinical infection that needed antibiotic therapy as recommended by the primary care provider, the study medication was held for the duration of that treatment, and study medication was resumed immediately upon completion of prescribed antibiotic.

Randomization and treatment

Subjects were randomized to the antibiotic group receiving 14 mg/kg per day in two daily doses (max 600 mg) or placebo for a total of 30 days. The placebo was matched for taste, color, and consistency to cefdinir suspension. Both cefdinir and placebo were dispensed in identical bottles, without manufacturer label or any other identifying information. For the purpose of this study, an important attribute of cefdinir was its increased palatability, with reports suggesting preferred taste and smell compared with other antibiotics, particularly for liquid formulations. As a large portion of our patients have difficulty swallowing tablets, necessitating the use of liquid formulations, the observed preference for cefdinir over other antibiotics makes this favorable in an effort to maintain the blinded nature of the study, avoiding the significant taste differences between cefdinir and placebo that may be encountered with other antibiotics.

Of the 24 subjects consenting, 21 met study inclusion criteria to be randomized to receive either placebo or a standard treatment dose of cefdinir. Once randomized, the study medications were dispensed in a double-blind manner, with randomization conducted by a research pharmacy using a computer program 1:1 ratio stratification of cefdinir or placebo according to primary tic disorder versus non-tic disorder. Ten were randomized to receive cefdinir treatment (9 actually began the study medicine as one subject withdrew prior to beginning treatment), and 11 to receive placebo (Fig. 1). Subjects returned every 2 weeks for assessment of study compliance, symptom improvement, and adverse events, and were instructed not discuss the specifics such as taste or color of study medication with anyone on the study team, except the pharmacist dispensing the medication.

Statistical analysis

Analysis of covariance (ANCOVA) was used to evaluate group differences in symptom severity between the cefdinir and placebo groups at posttreatment, controlling for the respective baseline variable. Cohen’s $d$ was used to determine within-group and between-group effect sizes, given the limited sample size employed in this study, with positive outcomes representative of symptom improvement. Cohen’s $d$ values of $0.2 < d < 0.5$ were considered representative of a small treatment effect, values of $0.5 < d < 0.8$ were considered representative of a moderate or medium effect, and values of $d > 0.8$ were considered representative of a large effect. SPSS statistical software was used to analyze all data, and an $\alpha$ of 0.05 was used to define statistical significance, given the pilot nature of this trial; no other statistical correction procedures were implemented.
Results

Enrolled subjects were predominantly male (75%), with an average age of 7.55 ± 1.87 years, with variable courses and co-occurring symptoms (Table 1). Notably, approximately one third had a prior speech disorder (phonological or stuttering or recovered delayed speech) and 55% had had adenoids and/or tonsils removed prior to onset.

Preliminary efficacy

To determine the effectiveness of cefdinir treatment on symptoms of OCD, CY-BOCS scores were analyzed by symptom groups (OCD or tics) as determined by the treating clinician as outlined earlier. Patients presenting with symptoms of OCD and randomized to the cefdinir group \((n=6)\), showed an average decrease in CY-BOCS score of 7.83 (Fig. 2). The placebo arm \((n=10)\) by comparison, showed a CY-BOCS decrease of 4.70 (Fig. 2). There were also large within-group treatment effects \((d=1.22)\) observed for the cefdinir group, compared with only moderate within-group effects for placebo treatment \((d=0.51)\). These differences were not significant between the cefdinir and placebo groups \((F[1,13]=0.546, d=0.24 [weak between-group effect]). Similarly, for OCD CGI-Severity (CGI-S) scores, there were no significant between-group differences \((F[1,13]=0.241, p=0.632; d=0.20)\) (Table 2).

Next, we examined the efficacy of cefdinir in reducing the intensity and frequency of phonic and/or motor tics in patients presenting with a clinical diagnosis of tics or OCD/tics. Patients randomized to receive cefdinir treatment, who presented with symptoms of phonic and/or motor tics \((n=8)\), showed improvement in tic symptoms relative to the placebo arm \((n=8)\), with the cefdinir group showing an average decrease in YGTSS scores of 9.50 (Fig. 3). By contrast, patients randomized to the placebo group demonstrated an overall average decrease in YGTSS scores of 0.13 (Fig. 3). There were also large within-group treatment effects \((d=0.97)\) observed for the cefdinir group, compared with very weak effect for placebo treatment \((d=0.01)\). Despite the improvements within the cefdinir group, and a moderate between-group treatment effect \((d=0.72)\), the between-group differences observed between cefdinir and placebo treatment were not statistically significant \((F[1,13]=4.030, p=0.066). Patients randomized to the cefdinir group who experienced symptoms of phonic and/or motor tics had reductions in tic CGI-S scores compared with those taking placebo, although between-group differences were not significant \((F[1,11]=2.890, p=0.117; d=0.53)\) (Table 2).

Although improvements in OCD and tic symptomology, as assessed by the CY-BOCS and YGTSS, were utilized as the main measures of cefdinir efficacy, we also employed additional neuropsychiatric measures to assess symptom improvement for symptoms of ADHD and mood. For ADHD, which is often observed within this population, two out of nine subjects randomized to the cefdinir group met criteria at baseline and at the end of 30 days treatment for SNAP-IV subscales of inattention and hyperactivity/impulsivity, and one also met criteria for oppositional defiant disorder (ODD). Among the placebo group, one subject met criteria for hyperactivity/impulsivity at baseline but not at 30 days, whereas another met criteria for ODD at the end of 30 days (but not at baseline). Although there were improvements in symptomology and decreased scores for the cefdinir group, there were no significant group differences in SNAP-IV ratings at post-treatment \((F[1,
groups. During the randomized controlled trial, two subjects in the placebo group were treated with antibiotics for infections (pneumonia and otitis, respectively) and one in the cefdinir group was treated (otitis). Neither of these subjects were the four with very much improved OCD and/or tics, who were described previously.

Discussion

Although the etiology of tic disorders and OCD remains unclear, research continues to suggest an infectious or immune-based etiology in a subset of individuals. Observations from disorders sharing similar clinical characteristics, such as Sydenham’s chorea, with evidence of antibody-mediated neuropathology, and clinical observations from patients presenting with abrupt symptom manifestations following acute infections, have all indicated aberrant immunological responses to infection as a key disease mechanism. Infection and the resulting immune responses are proposed to trigger a cascade of events, including antibody cross-reactivity, that culminates in the clinical presentation. Serological studies further support this theory, showing atypical streptococcal antibody responses from the sera of tic patients (Bombaci et al. 2009). In a study by Snider and colleagues, in which patients presenting with a sudden onset of OCD and/or tic symptom were giving prophylactic antibiotic treatment, a significant improvement in the frequency of neuropsychiatric flares was observed, further suggesting an infection-mediated and/or immune-related etiology (Snider et al. 2005).

In this pilot study, we aimed to determine the safety and efficacy of the antibiotic cefdinir in children with recent onset OCD/tics. This study did not require acute and severe onset of OCD/tics nor

### Table 2. Descriptive Statistics for Baseline and 30 Day Outcomes for Placebo and Cefdinir Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Cefdinir</th>
<th></th>
<th>Between-group d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>30 day</td>
<td>Baseline</td>
<td>30 day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td></td>
</tr>
<tr>
<td>CY-BOCS</td>
<td>18.60 (9.00)</td>
<td>13.90 (9.33)</td>
<td>22.67 (4.41)</td>
<td>14.83 (7.94)</td>
<td>1.22</td>
</tr>
<tr>
<td>YGTSS</td>
<td>13.50 (9.78)</td>
<td>13.38 (7.25)</td>
<td>20.38 (9.69)</td>
<td>10.88 (9.91)</td>
<td>0.97</td>
</tr>
<tr>
<td>CGI-S (OCD)</td>
<td>2.60 (0.97)</td>
<td>1.80 (1.14)</td>
<td>2.33 (0.82)</td>
<td>1.83 (0.98)</td>
<td>0.55</td>
</tr>
<tr>
<td>CGI-S (tic)</td>
<td>2.82 (1.25)</td>
<td>2.56 (1.13)</td>
<td>3.50 (1.38)</td>
<td>2.86 (0.69)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

**Cy-BOCS,** Children’s Yale-Brown Obsessive Compulsive Scale; **YGTSS,** Yale Global Tic Severity Scale; **CGI-S,** Clinical Global Impressions Scale – Severity; **OCD,** obsessive compulsive disorder.

Similarly, there were no significant group differences for symptoms of mood, tics, OCD, and ADHD, as assessed by the TODS rating scale ($F[1, 15]=0.234, p=0.635$) (Table 3).

**Post-hoc examination of youth showing large reduction in symptoms**

Two subjects in the cefdinir group had a large improvement (>50%) in OCD symptoms (average CY-BOCS change of 12.5), as did two subjects in the placebo group (average CY-BOCS change of 16.5). It is of note that one of the two subjects receiving cefdinir with large reductions in OCD severity presented with recent, but not dramatic, onset, and the other had an episodic course. One youth on placebo presented with an initial sudden and severe symptom onset, whereas another youth displayed episodic course. In addition, two subjects receiving cefdinir had dramatic improvements in tic severity (YGTSS average tic score improvement of 20); one had an onset that was not sudden and severe but with sudden and severe flare, and the other subject had episodic tics. All of these subjects with large symptom reductions had both OCD and tics, with one subject having large reductions in both OCD and tics.

**Safety**

There were few adverse events associated with cefdinir treatment, with most common adverse events being gastrointestinal disturbance such as abdominal pain and diarrhea. However, adverse events were reported in both cefdinir ($n=6$) and placebo groups ($n=8$) (Table 4). These events were transient and not serious. During the randomized controlled trial, two subjects in the placebo group were treated with antibiotics for infections (pneumonia and otitis, respectively) and one in the cefdinir group was treated (otitis). Neither of these subjects were the four with very much improved OCD and/or tics, who were described previously.

**FIG. 3.** Average change in Yale Global Tic Severity Scale (YGTSS) scores for subjects receiving placebo or cefdinir treatment. Delta scores represent changes in YGTSS scores taken at baseline and end of study. Negative signs denote an increase in scores.

**Table 3. Average Change in SNAP and TODS Scores for Subjects Receiving Placebo or Cefdinir Treatment**

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Placebo ($n=11$)</th>
<th>Cefdinir ($n=9$)</th>
<th>$F$ test</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP-IV</td>
<td></td>
<td></td>
<td>(1, 15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Inattention</td>
<td>0.14</td>
<td>2.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>0.14</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODD</td>
<td>0.17</td>
<td>−0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TODS</td>
<td></td>
<td></td>
<td>(1, 15)</td>
<td>0.23</td>
</tr>
<tr>
<td>Mood</td>
<td>1.71</td>
<td>−1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td>1.70</td>
<td>4.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCD</td>
<td>1.91</td>
<td>−0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>1.26</td>
<td>3.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SNAP-IV, Swanson, Nolan, and Pelham–IV Parent Scale; TODS, Tourette’s Disorder Scale; ODD, oppositional defiant disorder; OCD, obsessive compulsive disorder; ADHD, attention-deficit-hyperactivity disorder.
did it require evidence of infectious trigger, but rather focused on recent-onset pediatric neuropsychiatric disorder, as many children may have subclinical infections or non-GAS infections. In patients randomized to the cefdinir group, symptoms of OCD and tics improved following 30 day cefdinir treatment, with moderate treatment effects observed with tic symptoms, suggesting that cefdinir might be a useful therapeutic tool in treating the symptoms of OCD and tics for youth with recent onset of symptoms. Although we did not detect significant group differences between the cefdinir and placebo groups, we did observe large within-group treatment effects for the CY-BOCS and YGTSS for the cefdinir group but not the placebo group, suggesting improvement with cefdinir, especially for the youth with tics. Moderate-between-group treatment effects for YGTSS further supported the benefit for tic symptoms. With further investigation, including a fully powered study, we may also be able to identify certain characteristics such as age, duration of neuropsychiatric illness, symptom presentation, type of infection, immune risks, family history, and comorbid disorders that may influence treatment response. These factors may aid in defining persons who may respond optimally antibiotic intervention.

Cefdinir, like other cephalosporins, exerts its effects through disruption of bacterial protein synthesis. In addition to their antibacterial activity, this group of antibiotics has immunomodulatory effects, an attribute that may help explain its potential therapeutic effects (Ramos-Sevillano et al. 2012). Interestingly, other cephalosporins, such as ceftriaxone, have been shown to exhibit antidepressant properties, via increasing glutamate uptake in a mouse model of depression (Mineur et al. 2007; Thone-Reineke et al. 2008). Although the exact mechanism of action is still largely unknown, these properties may help explain the mechanism by which cefdinir may improve OCD and tics in the earliest stages of these disorders. Furthermore, it may help further support the possible link among infection, immune disruptions, and neurotransmitter systems that may influence treatment response. These factors may aid in defining persons who may respond optimally antibiotic intervention.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n = 11)</th>
<th>Cefdinir (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty sitting still</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dry lips</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moodiness/oppositional</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Limitations**

As mentioned, this study was a small pilot to investigate the use of cefdinir in the treatment of symptoms of recent onset OCD and tics. There are a few limitations of the current study that may impact the interpretation of outcomes. The most notable limitation was the small sample size utilized, which limits the amount of statistical significance that we can attribute to the study. Additionally, there were baseline differences in OCD and tic symptom severity; specifically, patients randomized to the cefdinir group presented with higher ratings, indicative of more severe symptomology. Although statistical analyses were performed to account for baseline differences, the potential exists for confounding the outcome. There were also limitations attributed to the study medication. Because of the liquid formulation of cefdinir, the integrity of the double blind may have been impacted more than would have been the case with tablet formulations, as taste, color, and consistency are more difficult to match to placebo. However, we were only aware of this occurring on one occasion. Additionally, subjects who had intercurrent infections requiring an antibiotic during the course of the study limited the total number of subjects receiving no antibiotics in the placebo arm during the course of the study. Lastly, the retrospective nature of parent report of initial symptom onset and course needs to be considered, because of the inherent recall bias associated with retrospective reporting.

**Clinical Significance**

Infections and immunological disruptions have recently gained momentum, with increasing evidence of the linkage between immune disruptions and neurological disturbances. Although other factors such as genetics, behavioral theory, and abnormalities in neurotransmitter systems should always be considered, the idea of an immune etiology opens the door for the utilization of known pharmaceuticals, including antibiotics.

**Conclusion**

In this study, we showed the potential for cephalosporin to reduce symptoms of OCD and tics in patients with a recent onset of symptoms. This study is preliminary, but results suggest that further investigation is warranted in order to establish relevance in standard clinical care. Additionally, this study highlights important areas in need of further investigation, in particular, the effects of comorbidity on treatment response, and potential predictors of disease course and treatment response. For example, because of this small sample size, it is unclear if those with symptoms with more dramatic onset fared better than those with a less dramatic onset of symptoms. Subjects with large symptom improvement did appear to have a dramatic onset, flares, or an episodic course. This was observed in the placebo arm as well, suggesting that some children with these types of courses may improve spontaneously. Armed with this information, we may be better able to improve diagnosis and treatment of these individuals by creating more tailored interventions that address their unique clinical presentations.

**Disclosures**

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Otsuka, Pfizer Pharmaceuticals, Roche Pharmaceuticals, Shire, Tourette Syndrome Association, and Transcept Pharmaceuticals, Inc. Dr. Murphy is on the Medical Advisory Board for Tourette Syndrome Association and on the Scientific Advisory Board for IOCDF. She receives a textbook honorarium from Lawrence Erlbaum. Dr. Ellisa C. Parker-Athill has no financial relationships to disclose. Dr. Eric Storch has received grant funding in the last 3 years from Agency for Healthcare Research and Quality, All Children’s Hospital Research Foundation, Centers for Disease Control, IOCDF, National Alliance for Research on Schizophrenia and Affective Disorders, the National Institutes of Health, Ortho McNeil Scientific Affairs, and Tourette Syndrome Association. He receives a textbook honorarium from American Psychological Association, Lawrence Erlbaum, and Springer publishers. Dr. Storch has been an educational consultant for Rogers Memorial Hospital. He is a consultant for CroNos, Inc. and Prophase, Inc., and is on the Speaker’s Bureau and Scientific Advisory Board for IOCDF. Dr. Adam Lewin receives grant funding from Agency for Healthcare Research and Quality, Centers for Disease Control, IOCDF, Joseph Brown Foundation, National Alliance for Research on Schizophrenia and Affective Disorders, National Institutes of Health, and University of South Florida Research Council. He is a consultant for Prophase, Inc., and has received speaker’s honoraria from the Tourette Syndrome Association. He received travel reimbursement from Roche Pharmaceuticals. P. Jane Mutch, Ph.D. has no financial relationships to disclose.

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Use of Intravenous Immunoglobulin in the Treatment of Twelve Youths with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections

Miro Kovacevic, MD,1 Paul Grant, MD,2 and Susan E. Swedo, MD2

Abstract
This is a case series describing 12 youths treated with intravenous immunoglobulin (IVIG) for pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS). Although it is a clinically based series, the case reports provide new information about the short-term benefits of IVIG therapy, and are the first descriptions of long-term outcome for PANDAS patients.

Introduction
Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) has been conceptualized as a forme fruste of Sydenham chorea (SC), the neurologic variant of rheumatic fever (Swedo et al. 2012). Both disorders are postulated to result from cross-reactive autoantibodies produced in response to molecular mimicry of Group A streptococcal (GAS) bacteria (Kiessling et al. 1993; Swedo et al. 1994; Garvey et al. 1998; Swedo et al. 1998). The proposed disease mechanism suggests that PANDAS and SC should respond to immunomodulatory therapies, such as oral steroids, intravenous immunoglobulin (IVIG), and therapeutic plasmapheresis. For SC, two controlled trials and a small case series document the efficacy of IVIG in reducing symptom severity and shortening the duration of illness (Garvey et al. 2005; van Immerzeel et al. 2010; Walker et al. 2012). Data for PANDAS are limited to a single randomized-entry controlled trial that compared IVIG against plasmapheresis and placebo (sham IVIG); at 1 month, neuropsychiatric symptom severity was reduced by 45% in the IVIG group, by 58% in the plasmapheresis group, and by 0% in the placebo group (Perlmutter et al. 1999). These treatment gains were maintained at 1 year follow-up evaluations, and appear to be related to the autoimmunity of PANDAS, as subsequent reports noted a lack of benefit for plasmapheresis for the treatment of non-PANDAS obsessive-compulsive disorder (OCD) (Nicolson et al. 2000). Similarly, IVIG administration was found to be without benefit for non-PANDAS tic disorders (Hoekstra et al. 2004).

To date, there have been no reports of the long-term outcome of PANDAS patients treated with IVIG. To address this issue, case files from a large clinical practice specializing in the treatment of PANDAS were reviewed by the treating physician (M.K.), and 12 patients with illustrative case histories were selected for this report. In addition to providing new information about the course of illness in PANDAS, these cases represent the first experience with 1.5 g/kg IVIG (divided into two daily doses of 750 mg/kg). The dosage was calculated from historical pediatric plasma exchange formulas that found that the optimum ratio of exogenous-to-endogenous IgG was 2:1, which translates to 1.496 g/kg of IVIG product (Graham 1963; Stoop et al. 1969).

Cases
Patient A
Patient A was a 7.5-year-old girl who had had an overnight onset of OCD symptoms 1 year previously. The symptoms began 2 weeks after she had completed treatment with azithromycin for a GAS-positive pharyngitis. Her initial OCD symptoms included intrusive thoughts, contamination fears (urine, saliva), repetitive compulsive behaviors (running in circles in response to thoughts, the need to remember what foods she ate looked like, and avoidance of foods she feared she would not remember), and reassurance seeking. Ancillary symptoms included tics, separation anxiety, irritability, emotional lability, difficulty concentrating, sensitivity to light, and enuresis. Over the course of the next year, she had a relapsing-remitting symptom course, with exacerbations reportedly occurring after illnesses treated with multiple courses of antibiotics (including azithromycin, amoxicillin, and amoxicillin-clavulanate). She had also undergone a tonsillectomy. Trials of sertraline and fluvoxamine were felt not to be...
helpful, but she had a “fair to good” response to a 6 month course of cognitive-behavior therapy (exposure and response prevention).

Shortly after experiencing severe, abrupt symptom exacerbation, the patient presented for initial evaluation. Her OCD symptoms were severe and disabling, occupying 9–11 hours a day. Symptoms improved during a 5 day steroid burst, but worsened following cessation of therapy. She was then treated with IVIG. Partial remission of symptoms occurred about 2 weeks following infusion, and a complete remission was achieved by 1 month post-IVIG. Follow-up evaluations at 3 and 6 months revealed continued improvement. Antibiotic prophylaxis was continued for 18 months. Nine months later (27 months after initial IVIG therapy), she experienced a minor symptom flare (symmetry concerns and counting compulsions) following an upper respiratory illness. A course of antibiotics was felt to be somewhat helpful, with symptoms resolving over the course of 1 month, and amoxicillin-clavulanate was continued as prophylaxis against GAS infections. Despite this, 3 months later, the patient developed a febrile illness with facial rash, chest and joint pain, and adventitious movements of her fingers. Several weeks later, she had another symptom recurrence with obsessional fears of dying and worries about harm(6,8),(995,990)

Patient B

Patient B was an 11-year-old boy who developed new-onset choreiform movements, as well as motor and phonic tics (including cough and whole body “shudder”) following a febrile illness that was treated with amoxicillin-clavulanate. A magnetic resonance imaging (MRI) scan of the brain, performed 1 month after symptom onset, showed decreased T2 signal in the basal ganglia. Tic severity was sufficient to warrant intervention, and ~4 months after symptom onset the patient was treated with a 5 day steroid burst (1 mg/kg/day prednisone, orally) followed by IVIG 1.5 mg/kg infusion. The interventions were reported to be beneficial, with complete resolution of his symptoms. One year later, the patient experienced an exacerbation of tics and received a second IVIG infusion. Recovery was again reported to be complete.

Patient C

Patient C was a 9-year-old girl who was first diagnosed with PANDAS at 6 years of age. At that time, she was treated with a 14 day course of amoxicillin-clavulanate, with nearly complete remission of symptoms. One month prior to evaluation in Hinsdale, the patient had a fainting episode at school and was evaluated at a local emergency department, where she was diagnosed with vasovagal syncope. The episode revealed that she had been experiencing a variety of behavioral symptoms, including obsessional fears, generalized and separation anxiety, insomnia, and urinary frequency with at least two episodes of nocturnal enuresis. She also complained of nonspecific abdominal discomfort and a related fear of “throwing up” after meals, which led to significantly restricted eating and a weight loss of 2–3 kg (7% of body weight) over the course of 1 month. Following treatment with steroids and IVIG, the patient experienced a rapid resolution of her symptoms, with complete remission by 4 weeks. She received azithromycin prophylaxis (250 mg twice weekly) for 1 year, and at a 4 year follow-up evaluation, she continued to be symptom free.

Patient D

Patient D was a 9.5-year-old boy who had sudden onset of contamination fears at 7 years of age following a documented GAS infection. Over the ensuing 18 months, he developed a variety of neuropsychiatric symptoms, including tics, agoraphobia, irritability, aggression, and sensivity to sounds. The diagnosis of PANDAS was made, and a therapeutic course of cefdinir had some beneficial effects. However, the patient subsequently developed a fear of choking and chronic abdominal pain, and the resultant food refusal led to a 4.5 kg (20%) weight loss, hospitalization, and tube feedings. These symptoms persisted for ~1 year prior to his evaluation and treatment at Hinsdale. A 5 day course of oral prednisone (1 mg/kg/day) had modest benefits. He was then treated with IVIG, which produced noticeable symptom improvements starting 2 weeks after infusion. He was maintained on prophylactic antibiotics for 1 year. Seven years later, a follow-up evaluation by telephone revealed that he continued to be in full remission.

Patient E

Patient E presented for evaluation at Hinsdale at 8 years of age, but his mother had first suspected that he had PANDAS when he was 3, when he had an abrupt onset of OCD symptoms that reportedly appeared as sequelae of a GAS infection and resolved following steroid treatment. Family history was notable for tics in the patient’s father and older brother. By 8 years of age, the patient had diagnoses of separation anxiety disorder, OCD, tic disorder, depression, and periodic limb movement disorder of sleep, with evidence of possible epileptiform activity that had been noted on overnight electroencephalogram (EEG) when he was 5 years of age. Trials of sertraline, mirtazapine, and escitalopram were somewhat helpful, but symptoms persisted. At the time of evaluation in Hinsdale, the patient’s symptoms included intrusive thoughts and contamination obsessions, symptom, checking, and repeating/reassurance-seeking compulsions; separation anxiety; temper tantrums and aggression; depression; school refusal; tics; and a decline in fine motor skills. Treatment with IVIG yielded an immediate response, with remission of his OCD symptoms and marked reduction in the frequency of tics. Four months later, his mother developed a GAS infection, and despite prophylactic antibiotics, the patient was noted to have increased school-related worries and “stuck” behaviors. The dosage of amoxicillin-clavulanate was increased, and 4 weeks later, the OCD symptoms had resolved, but motor and phonic tics remained. The patient’s OCD symptoms returned again 3 months later, and were once again improved by therapeutic doses of antibiotics. Long-term follow-up information is not available for this patient.

Patient F

Patient F was a 16-year-old boy who had been initially diagnosed with PANDAS at 9 years of age when he suddenly developed irrational fears, intrusive thoughts, and insomnia. He was treated with two consecutive 14 day courses of amoxicillin-clavulanate and became asymptomatic within 1 month. One brief relapse was noted later that year, but it resolved without intervention. At 16 years of age, the patient experienced a sudden, abrupt onset of severe and debilitating tics, including marked movements of the upper torso, arms, head, and neck. He was taken to the emergency department, where he was treated with diazepam; a brain MRI and EEG were reportedly normal. General anxiety and increased irritability were apparent at this time as well, but there were multiple
psychosocial stressors. The patient had not been ill, but his room-
mate had recently had an upper respiratory illness. Treatment with
amoxicillin-clavulanate produced only minimal improvements, but
a 5 day course of steroids resulted in complete, albeit temporary,
remission of the tics. The patient was then treated with IVIG, and a
“rocky” postinfusion course was noted, with increased tic severity
for the ensuing 2 weeks. The anxiety and tics continued to wax and
wane in severity over the next 6 months, with periods of symptom
improvement reported to occur in association with both increased
dosages of antibiotics and school holidays (e.g., summer vacation,
winter break). By 12 month follow-up, the patient was completely
asymptomatic, and these treatment gains were sustained for at least
6 months longer, when he was evaluated for the final time.

**Patient G**

Patient G was a 9-year-old boy who presented with a sudden
onset of debilitating separation anxiety, aggression, emotional la-
bility, urinary frequency, insomnia, and dysgraphia. Most signifi-
cantly, he developed compulsive, recurrent vomiting of all foods
and liquids, including water, leading to a 7 kg weight loss. He was
diagnosed with postinfectious gastroparesis, and fed exclusively
via nasojejunal tube. His past medical history was positive for an
episode of separation anxiety, tics, and OCD symptoms following a
brief illness at 7 years of age. He responded to a 5 day steroid burst,
with temporary symptomatic improvements. He had an immediate
and dramatic improvement following IVIG therapy, resuming
normal oral food intake, and his nasojejunal tube was removed.
Although there was a significant improvement in most of his
symptoms over the ensuing months, residual vomiting after meals
(without weight loss) continued to interfere with his return to
normal life. Eleven months following the initial IVIG treatment, he
received another course of IVIG, this time resulting in complete
remission of all symptoms. He remains asymptomatic 3 years later.

**Patient H**

Patient H was a 15-year-old boy with a history of reactive airway
disease and a 3 year history of “tic-like” behaviors, including
throat clearing and cough. The tics prompted consideration of a
PANDAS diagnosis, but acuity of the symptom onset and evidence
of preceding GAS infection were not documented. Subsequently,
the PANDAS diagnosis became more evident when the patient had
a sudden worsening of his tics, including the onset of coprolalia,
and acute onset of intrusive thoughts and compulsive praying, as
well as separation anxiety, temper tantrums, difficulty concentrat-
ing, and hyperactivity. The patient received two courses of IVIG,
separated by 4 months. Five weeks after the second infusion, the
patient’s tics had remitted, but his OCD symptoms had worsened
and were now associated with weight loss. It is unclear what
eventually led to symptom remission, as interim history is not
available, but a follow-up phone call 16 months after the second
IVIG infusion revealed that the patient was “almost 100% well.”

**Patient I**

Patient I was a 7-year-old girl who experienced the sudden onset
of multiple symptoms following an illness characterized by severe
sore throat. (The patient had had recent GAS exposure, but a throat
culture obtained during the illness was negative.) Her symptoms
included intrusive thoughts and a variety of obsessional fears, in-
cluding fear of being “fat,” as well as separation anxiety, temper
tantrums, immature behavior and baby talk, motoric hyperactivity,
inattention, aggressiveness, emotional lability, tics, mydriasis,
nighturnal enuresis, and multiple somatic complaints including joint
pain, chest pain, stomach pain, fatigue, and dizziness. A steroid
burst was helpful for a brief time and was followed by IVIG
infusion. Two weeks following IVIG infusion, the patient was re-
portedly “80% back to normal,” and by 6 weeks postinfusion she
had returned to 95% of her baseline. A few weeks later, she de-
veloped a GAS infection, and several symptoms returned, including
nocturnal enuresis. A second 5 day course of steroids secured re-
mission, and she was noted to be “100% well” 5 months following
initial IVIG treatment. Over the ensuing 18 months, she had a
relapsing-remitting symptom course with exacerbations occurring
in association with illnesses. (Relapses were not as severe as the
initial episode.) She received a second IVIG infusion and had a
complete remission of symptoms. Follow-up phone evaluation re-
vealed that she was continuing to do well > 12 months later.

**Patient J**

Patient J was a 12-year-old boy with a complex medical history
that included asthma, celiac disease (diagnosed at 9 years of age
because of significant growth failure), and eosinophilic esophagitis,
requiring gastroscopy and insertion of a feeding tube. It is of note
that his chief complaint at that time was “fear of choking,” not
dysphagia, as might be expected. At 10 years of age, the patient
developed severe OCD symptoms and debilitating generalized and
separation anxiety, possibly related to a GAS pharyngeal infection
that had occurred 6 weeks earlier (and was associated with elevated
antistreptococcal DNAase B titers), or a periorbital cellulitis, which
had occurred 1 month prior to symptom onset. Citalopram, ser-
traline, and finally risperidone were tried, without reported benefits.
The patient had a “positive” response to the steroid burst, but no
discernable improvements were noted for 11 weeks following IVIG
administration. Then, he had a sudden and dramatic remission of all
of his symptoms. His feeding tube was removed, and he returned to
normal activities. Eight months later (and despite adherence to the
prescribed regimen of prophylactic antibiotics), he had a recur-
cence of obsessions, compulsions, and generalized anxiety (without
eating restrictions). He was treated with IVIG and experienced an
almost immediate and lasting recovery. Follow-up evaluation
5.5 years later revealed that he continued to be asymptomatic and
functioning optimally.

**Patient K**

Patient K was an 11-year-old boy, who had a sudden onset of
OCD, anxiety, and tics at 6 years of age, following a GAS infection.
He was treated with psychiatric medications and behavior therapy,
with some benefits, but his therapist noted that symptom control
worsened following GAS exposure/infection. At the time of his
presentation to Hinsdale, his tics were severe and impairing to the
point that they interrupted sleep and had caused injury (by his biting
his tongue). The patient was receiving risperidone, fluvoxamine,
buspirone, and atomoxetine for diagnoses of Tourette Syndrome,
generalized anxiety disorder, OCD, and attention-deficit/hyperac-
tivity disorder. A steroid burst resulted in transient improvements
in his phonic tics. Both motor and phonic tics began to decrease in
intensity and frequency ~ 5 days following IVIG administration.
The tics continued to diminish over the next 2 weeks, and for the
first time in several years, the patient was tic-free for several days
at a time. Medications were, therefore, discontinued. Tics returned
~ 1 month following IVIG, and risperidone was restarted, but at a
lower dose. Six months following IVIG, the patient was noted to be
“tic free” and he continued to do well on low-dose risperidone over the next 2 years. When the patient was 13.5 years of age, tics returned “in full force” after the patient was exposed to a sibling with GAS. He was treated with a 10 day course of azithromycin, and placed on prophylactic antibiotics, and his tics resolved over the course of a few weeks. At follow-up, 6 years following IVIG treatment, the patient was noted to be tic free and doing well. Of particular note was that he had received a number of immunizations without difficulty, delivered his high school commencement speech, and had been awarded a scholarship to attend college.

**Patient L**

Patient L was an 8-year-old boy who suddenly developed debilitating OCD symptoms (excessive showering and hand washing, refusal to eat certain foods after making unreasonable excuses) 2 weeks after a GAS infection. Over the next 6 months, his OCD symptoms worsened and he also developed a coughing tic, anxiety, and a number of ill-defined abdominal complaints that prompted a gastroenterological evaluation (with negative results) and that eventually led to the patient’s complete refusal to eat. The patient lost nearly 25% of his body weight (declining from 22 kg to 17 kg) and was hospitalized numerous times for tube feedings and psychiatric interventions. Multiple selective serotonin reuptake inhibitors were tried, without appreciable benefit; a trial of lorazepam resulted in severe disinhibition; therefore, it was immediately discontinued. A consulting physician prescribed amoxicillin, which resulted in severe disinhibition; therefore, it was immediately discontinued.

**Discussion**

These 12 cases provide new information about the clinical features and course of PANDAS, as well as describing a variety of patterns of response to IVIG administration. The case series is limited by its selective nature, retrospective approach, and dependence on subjective reports from patients and their parents. The lack of a placebo control for the IVIG treatment is an additional shortcoming, as PANDAS is an episodic disorder that is expected to have periodic symptom remissions. However, all patients had failed prior therapies, suggesting that the immunomodulatory effects of IVIG were responsible for the symptomatic improvements.

All patients had an abrupt onset or exacerbation of severe OCD and comorbid neuropsychiatric symptoms as sequelae of GAS infections or exposures; therefore meeting diagnostic criteria for PANDAS (Swedo et al. 1998, 2004). Patients also met criteria for pediatric acute-onset neuropsychiatric disorder (PANS) because of the acuity of OCD onset and presence of multiple comorbid symptoms. The duration of illness and number of recurrences varied among individuals, but all patients benefited from IVIG administration, even when the neuropsychiatric symptoms had been present for several years prior to treatment.

Unlike typical autoimmune disorders, in which multiple doses of IVIG are required, PANDAS may respond to a single course of treatment. The neuropsychiatric symptoms appear to result from a misdirected immune response (triggered by the molecular mimics of GAS epitopes); therefore, inactivation of the cross-reactive antibodies with a single course of IVIG could be sufficient to produce lasting symptom improvement (Perlmuter et al. 1999). However, it is worth noting that 2 of the 12 patients received a second course of IVIG because of an inadequate response to the initial course of treatment, and 5 patients received a second IVIG treatment for a recurrence of symptoms. Further, all patients had received a 5 day course of oral steroids, administered as 1 mg/kg/day prednisone, followed by a 2 week observation period. The purpose of the “steroid burst” was to determine if long-lasting improvements could be produced by steroids alone, thus obviating the need for IVIG. A persistent response to steroids is unlikely in patients with PANDAS, as they produce only transient benefits in patients with SC (Garvey et al. 2005), and a similar etiopathogenesis is postulated for both disorders. In this case series, none of the children had persistent improvements following prednisone therapy or after antibiotic treatment (Murphy et al. 2014); therefore, IVIG was administered at a dose of 1.5 gm/kg (in two divided doses.)

**Conclusion**

This case series demonstrates the benefits of IVIG therapy for youths with PANDAS/PANS, including those who had been symptomatic for several years prior to treatment. Although the generalizability of this retrospective report is limited, the selected cases represent the breadth of symptom presentations in PANDAS/PANS, and provide additional evidence that IVIG may be useful in the management of children with moderate-severe symptoms.

**Clinical Significance**

IVIG was used as part of a multimodal therapeutic approach and demonstrated benefits for these 12 youths with moderate-severe symptoms of PANDAS/PANS. In addition to IVIG, patients received prophylactic antibiotics to prevent future infection-triggered symptom exacerbations. They also received standard psychiatric care, including use of anti-obsessional medications and cognitive-behavior therapy. For optimum symptom relief, it is necessary to utilize a combination of immunomodulatory therapy, antibiotic prophylaxis, and targeted symptom treatments, as described at the PANDAS Physicians Network (PPN) (www.pandasppn.org). The website presents a systematic graduated approach to treatment of PANDAS/PANS based on the “best practice” standards of expert clinicians from across the United States. In addition to providing suggestions for recognition and diagnosis of PANDAS/PANS, it also offers guidance in the management of patients with varying levels of severity.

**Disclosures**

No competing financial interests exist.

**References**


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Therapeutic Plasma Apheresis as a Treatment for 35 Severely Ill Children and Adolescents with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

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Abstract

Background: Because of its reported similarities to Sydenham chorea, therapeutic plasma apheresis (TPA) has been proposed as a potential treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). To date, support for the use of TPA has been limited to a few anecdotal reports and a small placebo-controlled trial demonstrating dramatic symptom improvements at 1 month and 1 year follow-up. To evaluate the safety and efficacy of TPA further, we undertook a retrospective review of all PANDAS patients treated with TPA at Georgetown University Hospital between August 2009 and October 2013.

Methods: Forty patients were identified, and sufficient information was available from medical records and telephone interview for 35 cases (88%). All 35 (23 boys; 12 girls) met diagnostic criteria for PANDAS (Swedo et al. 1998) and had severe symptoms. The TPA procedures were performed at Georgetown University Hospital using a protocol that processes a total of 4.5 blood volumes over 3–5 days (three treatments of 1.5 volumes each). Overall symptom improvements at 6 months post-TPA and long-term follow-up were estimated by parents, who also rated changes in individual symptoms to provide information about patterns of improvement.

Results: All patients were reported to have received at least some benefit from TPA, with average improvement of 65% at 6 months post-TPA and 78% at longer-term follow-up. A decrease in the number of reported symptoms also occurred, with particular improvements in obsessive-compulsive disorder (OCD), anxiety, tics, and somatic symptoms, including dysgraphia, sleep difficulties, and urinary urgency or frequency. Contrary to expectations, preceding duration of illness was not correlated with degree of improvement following TPA, suggesting that acuity of illness is not a factor affecting response. Only two adverse events were reported: both involved reopening of the site where the central line had been placed and resolved immediately following application of pressure and re-dressing of the puncture site.

Conclusions: Therapeutic plasma apheresis is an invasive medical intervention that should be reserved for treatment of children and adolescents who are severely affected by PANDAS. In such patients, it appears to be a safe, well-tolerated, and beneficial treatment option.

Introduction

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) has been reported to resemble Sydenham chorea (SC) in its etiology, pathophysiology, and response to treatment (Garvey et al. 1998; Swedo et al. 1998, 2012.) In both disorders, symptoms begin abruptly several weeks to months following prolonged infections with Group A streptococci (GAS), and are hypothesized to result from postinfectious autoimmunity mediated through cross-reactive antibodies, produced against molecular “mimics” or epitopes on the GAS cell wall that resemble host antigens (Swedo 1994; Kirvan et al. 2006a,b; Brimberg et al. 2012.) If the postulated disease mechanism is correct, then removal of the offending autoantibodies via therapeutic plasma apheresis (TPA) should produce symptomatic improvements (Perlmuter et al. 1999; Dale 2005). However, it is worth noting that TPA has a broad range of actions, and that the mechanism of therapeutic benefit is not known for any disorder, including PANDAS and SC (Weinstein 2008). For SC, a randomized comparison of TPA against oral prednisone or intravenous immunoglobulin (IVIG) demonstrated that TPA produced greater, longer-lasting improvements than the other two immunomodulatory treatments.
therapies; however, the sample size was small \( n = 8 \) for the TPA group (Garvey et al. 2005). For PANDAS, two anecdotal case reports and a single clinical trial suggest that TPA is beneficial in reducing obsessive-compulsive disorder (OCD), tics, and associated neuropsychiatric symptoms (Tucker et al. 1996; Perlmutter et al. 1999; Elia et al. 2005).

A double-blind, randomized entry clinical trial compared five single-volume apheresis treatments \( n = 10 \) against 2 g/kg IVIG \( n = 9 \) or sham IVIG placebo \( n = 10 \), and demonstrated that obsessive-compulsive symptoms were reduced by an average of 65% in the TPA group (compared with 42% in the IVIG group and no response in the placebo group) (Perlmutter et al. 1999). Treatment gains were maintained at 12 month follow-up, suggesting that a single course of TPA might be effective in producing long-lasting remission of symptoms (Perlmutter et al. 1999). Five patients with non-PANDAS OCD had no improvement following open-label treatment with TPA, providing indirect support for its postulated mechanism of action in PANDAS (Nicolson et al. 2000). Further evidence is provided by investigations that showed reduced titers of cross-reactive antibodies following TPA (Kirvan et al. 2006).

The American Society for Apheresis considers the controlled trials and published case reports sufficient to recommend TPA as first-line treatment for PANDAS (and SC) (Szczepiorkowski et al. 2007a,b; Weinstein 2008). However, when members of the American Academy of Neurology (AAN) examined the same literature, they concluded that “there is insufficient evidence to support or refute the use of plasmapheresis for PANDAS’’ (and SC) (Cortese et al. 2011). The conflicting treatment guidelines not only caused confusion for clinicians, but also created barriers to care for children and adolescents with PANDAS. In an attempt to obtain additional controlled-trial data, a sham-apheresis trial was designed, received institutional review board (IRB) approval, and was initiated at the National Institute of Mental Health (NIMH) in the early 2000s. Only three subjects were enrolled before the principal investigator (S.E.S.) stopped the protocol because of ethical concerns related to central line placement and hospitalization of children for nontherapeutic (placebo) interventions. Consequently, questions about the utility of TPA must be answered by additional clinical experience, such as this report of 35 children and adolescents receiving TPA for PANDAS.

**Methods**

Between January 2009 and October 2013, 40 patients (25 boys, 15 girls) were referred by M.E.L. to Georgetown University Hospital for treatment with TPA. Follow-up information was available for 23 boys and 12 girls \( n = 35, 88\% \). All patients met diagnostic criteria for PANDAS (Swedo et al. 1998, 2004) and had severe symptoms, with marked impairments of functioning at home, at school, and with peers. Additional indications for TPA included aggressive, violent behavior or danger to the patient or others; severe restrictions of food and/or fluid intake; or minimal or no response to prior treatment with oral steroids \( n = 5, 14\% \) or IVIG \( n = 17, 48\% \). All subjects had received therapeutic doses of antibiotics without relief of symptoms, but all were maintained on antibiotic prophylaxis throughout the treatment period. Ten of the 35 patients \( 29\% \) described here are also included in a report of clinical characteristics of a larger sample \( n = 40 \) of children and adolescents with PANDAS (Swedo et al., 2015).

The TPA procedures were performed at Georgetown University Hospital Department of Pediatrics, Division of Hematology and Oncology, using the Georgetown TPA protocol for PANDAS/pediatric acute-onset neuropsychiatric syndrome (PANS). In brief, this protocol involves insertion of a central line (usually in the femoral vein) and administration of three 1.5 volume therapeutic exchanges over the course of 3–5 days.

Data for this retrospective report were collected from several sources including the child’s pediatric records, consultation notes, and medical records from the child’s admission to Georgetown University Hospital. Additional clinical information was provided by parents’ responses on a questionnaire assessing symptoms of PANS, which had been administered at initial evaluation, and by a follow-up telephone call conducted by a bachelor’s level research assistant (N.L., J.S.) under the supervision of the treating physician (M.E.L.). The information gathered was used to confirm and expand upon the medical records, and included specific queries about adverse events, presence and severity of symptoms at baseline and post-TPA treatment, and estimates of improvement at 6 months post-TPA and long-term follow-up. The duration of the long-term follow-up varied from 6 months to 5.4 years \( \text{mean} = 3 \text{years} \pm 1.5 \).

**Results**

The mean age at TPA was 11.5 years \( \pm 3.6; \) range 4–18.75; mean age at symptom onset was 7.6 years \( \pm 3.5; \) range 2–14.5; and average duration of illness was 4.2 years \( \pm 3.7. \) At baseline, all patients were described by their parents as “severely” or “extremely” ill and had OCD, tics, separation anxiety, sleep difficulties and other neuropsychiatric symptoms (see Table 1). Six months after TPA, parents reported that their child’s symptoms had improved by 65% on average \( \pm 28; \) range 5–100%. Two subjects appeared to have only minimal response to TPA \( \% \) and 20%, respectively); however, this appears to have been the result of an infection-triggered relapse (GAS and mycoplasma), rather than a lack of response to the intervention. At long-term follow-up, all subjects were reported to be improved from baseline, with average reduction in symptom severity of 78% \( \pm 23.2; \) range 20–100% and seven patients reported to be in complete symptom remission. Three illustrative cases are described.

**Case 1**

A 10.5-year-old girl developed emotional lability, irritability, and sensory issues a few weeks after receiving antibiotics for GAS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline ( n = 35 )</th>
<th>( \leq 6 \text{ Months} ) Post-TPA ( n = 35 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>34 (97)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Tics</td>
<td>22 (63)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>27 (77)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Frequent urination</td>
<td>17 (49)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Irritability and aggression</td>
<td>24 (69)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>8 (23)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dysgraphia</td>
<td>19 (54)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>8 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Initial insomnia, interrupted sleep</td>
<td>20 (57)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>20 (57)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Choreaform movements</td>
<td>12 (34)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>11 (31)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Behavioral regression</td>
<td>14 (40)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
pharyngitis. Within 48–72 hours, her symptoms had escalated to include OCD, separation anxiety, initial insomnia, interrupted sleep, and rage episodes. She returned to the pediatrician and again tested positive for GAS, which was treated with a second course of antibiotics. She also received oral steroids, which relieved her symptoms for a few months.

Without obvious reinfection, the child experienced an abrupt recurrence of OCD, depression (crying in her room every night), and separation anxiety. She refused to shower, left her room with greatly reluctance, and developed an obsession with matches, lighting them repeatedly as she stood over the kitchen sink in the evenings. Her parents were concerned that she would start a fire, as she had had significant sleep interruptions and often woke in the night to light and relight matches (sometimes in her room).

The patient received three 1.5 volume TPA procedures over 4 days, and began to improve within 1 week. By the end of 4 weeks, she was completely symptom free. The patient did well for 4 months and then had an abrupt onset of food restriction. This time, she was treated with 2 g/kg IVIG (over 2 days) and a course of cognitive-behavior therapy. Symptoms remitted once again, and she has remained symptom free for the past 3 years.

Case 2

This 7-year-old boy developed sudden onset of severe inattention and impulsivity, and received a diagnosis of attention-deficit/hyperactivity disorder (ADHD), despite an early developmental history that was devoid of behavioral problems. He was started on a stimulant and quickly developed episodes of uncontrollable rage; therefore, the medication was discontinued. Over the next few days, he developed OCD (fears that a man would kill his family), severe separation anxiety, generalized anxiety, emotional lability, initial insomnia, sleep interruptions, and bed wetting. The severity of the irritability, temper tantrums and “out of control” behavior prompted a diagnosis of bipolar disorder, rather than PANDAS. However, a throat culture revealed GAS; therefore, he received a 10 day course of antibiotics. He had developed dysgraphia, and an infectious diseases specialist recommended continued treatment with antibiotics. A trial of oral steroids produced an increase in symptoms, but this may have been the result of a recurrent GAS infection, as a throat culture was positive during this interval (while the patient was on antibiotics). Because of the recurrent GAS infections, he was referred for a tonsillectomy, which neither improved nor exacerbated his symptoms. Similarly, treatment with 2 g/kg IVIG had no discernible benefits. The patient continued to provoke the irritability, temper tantrums and “out of control” behavior prompt a diagnosis of bipolar disorder, rather than PANDAS. She received 2 g/kg IVIG, which produced 70% reduction in symptom severity, but she failed to return to her premorbid baseline. Two years later, this patient developed eating restrictions, which led to weight loss >20% of her body weight, and extreme malnutrition, as evidenced by bradycardia (resting heart rate of 40). The patient received TPA (1.5 volumes/procedure × 3) and slowly improved. At long-term follow-up, she also was reported to be doing well.

Interestingly, the index patient (X) has a sister who is 3 years younger. Two years after the onset of X’s symptoms, her younger sibling presented with an abrupt onset of separation anxiety, OCD (contamination fears), impulsivity, irritability, aggression, sleep disorder, frequent urination, dysgraphia, and behavioral regression. The rages/impulsive episodes were so severe that the child had broken all of the family’s dishes, put her fist through all of the artwork in the house, and attempted to jump from a moving car. Her father’s throat culture was positive for GAS, but the patient’s culture was negative. A course of antibiotics produced no improvement, and steroids were not a viable option because of the behavioral symptoms. She received 2 g/kg IVIG, which produced 70% reduction in symptom severity, but she failed to return to her premorbid baseline. Two years later, this patient developed eating restrictions, which led to weight loss >20% of her body weight, and extreme malnutrition, as evidenced by bradycardia (resting heart rate of 40). The patient received TPA (1.5 volumes/procedure × 3) and slowly improved. At long-term follow-up, she also was reported to be doing well.

Summary of cases

All individual symptoms had decreased in frequency by 6 months, as shown in Table 1. Importantly, some of the most worrisome symptoms had dropped to negligible levels, including a reduction in psychosis (from 23% to 3% of patients); eating restrictions (from 20% to 3%), and suicidality (from 23% to 0%).

Based on TPA’s theorized mechanisms of action, we expected that children and adolescents with chronic symptoms would have a less robust response to the immunomodulatory treatment. However, there was no correlation between symptom duration and degree of improvement following TPA, as is shown in Figure 1. A number of transient adverse events can occur during TPA, ranging from tingling of the lips caused by calcium fluxes, to more serious vasovagal reactions (e.g., Perlmutter et al. 1999). None of these were severe enough to be noted in the TPA procedure records. The only notation was for a midprocedure line change in one patient. Similarly, post-TPA complications were rare, and clinically nonsignificant. Two subjects experienced bleeding at the site of central line insertion shortly after being discharged from the hospital (possibly because of failure to apply pressure at the site for the instructed period of time). One subject returned to Georgetown, and the other reported to an urgent care center for...
application of pressure and a new dressing. No further bleeding occurred, and the puncture wound healed in both subjects without further incident.

Discussion

This case series demonstrates that TPA is both safe and effective for treatment of severely ill children and adolescents with PANDAS. Data were available for 35 of 40 consecutively treated subjects, and revealed that TPA administration was associated with an average decrease in symptoms of 65% at 6 months and 78% at long-term evaluation. Comparable improvements were reported for the number and severity of individual PANDAS symptoms. Complications of TPA were limited to two minor episodes of post-discharge bleeding at the central line insertion site.

Although these cases represent the largest treatment series reported to date for PANDAS, the study was limited by its retrospective design. The information that could be gleaned from the medical records was limited to recorded, clinically relevant data, and the parent reports may have been subject to recall bias. In addition, there was significant variation in the duration of the “long-term” outcomes, as the telephone interviews were conducted from May through August 2014 and subjects had been treated between January 2009 and October 2013. However, these potential limitations are mitigated by the fact that the retrospective review included 35 of 40 consecutively treated patients (88%) and multiple sources of information. Further, the average improvement observed in this case series is equal to that demonstrated in the placebo-controlled trial of TPA conducted by Perlmutter and colleagues (1999), with symptoms reduced by 65% in both the research and clinical settings. Importantly, these striking short-term improvements were maintained for extended periods of time when subjects received adequate prophylaxis against symptom-triggering infections.

It is worth noting that all patients in this series were severely ill at the time of treatment, despite treatment with standard psychiatric interventions, as well as antibiotics and steroids or IVIG. Further, the average duration of illness prior to TPA was greater than 4 years, indicating that this was the “treatment of last resort” for many patients. Fortunately, duration of illness was not correlated with degree of symptom improvement, which allows clinicians to employ a systematic, graduated approach to treatment of PANDAS.

It is generally accepted that less invasive treatments such as antibiotics (Murphy et al., 2014), and possibly oral steroids, should be the initial consideration for all PANDAS patients. TPA and IVIG should be reserved for subjects who remain severely symptomatic after treatment with the less-invasive therapies. There are two potential exceptions to this graduated treatment approach: Subjects with life-threatening suicidality or aggressive behaviors, and those with severe restrictions of food and/or fluid intake. Examples of violent behaviors in this series included a child who was found in his younger sibling’s bedroom with a knife posed over the sleeping child’s chest; two children who attempted to jump from a moving vehicle; and a child who was rescued from a rooftop where he intended to jump to his death, because he “didn’t deserve to live.” Eating restrictions that might prompt use of TPA include those leading to a weight loss of >10–15% of the subject’s starting body weight, and those requiring tube feedings to maintain adequate nutrition and hydration.

It is also important to note that the patients in this series were not treated with TPA alone. All received psychiatric treatment, including supportive therapy, anti-obsessional medications and/or cognitive-behavior therapy to address obsessive-compulsive symptoms, and a variety of psychotropic medications for relief of comorbid neuropsychiatric symptoms. All subjects also received antibiotics; initially at therapeutic doses (Murphy et al. 2002; Murphy et al., 2014), and then at dosages that would provide prophylaxis against GAS infections (Garvey et al. 1999; Snider et al. 2005). Despite these interventions, these patients remained severely ill until receiving TPA, when they experienced dramatic, long-lasting reductions in the number and severity of symptoms. Importantly, none of the subjects experienced a worsening of symptoms following TPA administration, and the treatments were particularly beneficial for the most concerning symptoms of suicidality, violent/aggressive behaviors, and eating restrictions. Although a retrospective case series cannot provide definitive proof that the symptomatic improvements were directly related to TPA, these cases clearly demonstrate that inclusion of TPA in a multifaceted treatment approach has potential benefits for children and adolescents with severe symptoms of PANDAS.

Conclusion

In this series of 35 youths with severe symptoms of PANDAS, TPA was found to produce dramatic clinical benefits, with reported
improvements averaging 65% and 78% at six months and long-term, respectively. Only two patients failed to respond to TPA and both had intercurrent infections that may have mitigated against response. Adverse effects of TPA were minor and limited to temporary discomforts associated with central line placement and the apheresis procedures. Thus, it appears that TPA provides a safe, efficacious treatment option for severely ill pediatric patients.

**Clinical Significance**

This large case series confirms and extends the findings of Perlmutter et al. (1999) by demonstrating that TPA is safe and efficacious in the treatment of PANDAS symptoms. Both studies found that TPA produced dramatic, long-lasting benefits, with an average reduction of 65% in the severity of obsessions, compulsions, anxiety, and other symptoms. It is worth noting the current series utilized three 1.5-volume apheresis procedures over 4–5 days, rather than five single-volume exchanges over 8–10 days. Since therapeutic benefits appear to be comparable for the two regimens, the shorter treatment protocol is preferable, as it requires fewer hospitalization days, decreases the risks of infection and other complications, and (for larger youths) permits use of peripheral intravenous catheters rather than a central line.

The case series also emphasizes the importance of preventing future infection-triggered recurrences through the use of appropriate hygienic controls and prophylactic antibiotics. For patients who remained infection free, a single course of TPA was sufficient to produce long-lasting remissions of symptoms, while those suffering from intercurrent infections were noted to have post-infectious relapses. Thus prevention of post-TPA infections should be a high priority in the treatment of children with PANDAS.

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**Disclosures**

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**References**


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Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and Obsessive-Compulsive Disorder

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Abstract

Background and objective: Antineuronal antibodies have been implicated in tic and obsessive compulsive disorders (OCD) associated with group A streptococcal infections. We investigated antineuronal autoantibody levels as well as antibody-mediated neuronal cell signaling activity, as previously reported for Sydenham chorea and pediatric autoimmune neuropsychiatric disorder associated with streptococci (PANDAS), to determine immunological profiles for a large cohort of children with tics and/or OCD.

Methods: Study participants (n = 311; ages 4–27 years, 66% male) were selected from a larger group of individuals with self-reported neuropsychiatric symptoms (n = 742) and included only those with accurate knowledge of group A streptococcal infection status, except for four individuals in whom streptococcal infection status was unknown. Healthy control samples (n = 16; ages 5–14 years, 81% male), came from the National Institute of Mental Health and Yale University. In addition to serum donations, participants and/or legal guardians provided neuropsychiatric and related medical histories of symptoms that had lasted >1 year. Antineuronal immunoglobulin G (IgG) titers were measured by standard enzyme-linked immunosorbent assay (ELISA) and compared with mean titers of normal age-matched sera against lysoganglioside, tubulin, and dopamine receptors (D1R and D2R). Antibody-mediated signaling of calcium calmodulin dependent protein kinase II (CaMKII) activity in a human neuronal cell line (SK-N-SH) was tested in serum.

Results: Of 311 individuals, 222 (71%) had evidence of group A streptococcal infection, which was associated with tics and/or OCD (p = 0.0087). Sera from individuals with tics and/or OCD (n = 261) had evidence of elevated serum IgG antibodies against human D1R (p < 0.0001) and lysoganglioside (p = 0.0001), and higher serum activation of CaMKII activity (p < 0.0001) in a human neuronal cell line compared with healthy controls (n = 16). Furthermore, patients with tics and OCD had significantly increased activation of CaMKII activity compared with patients with only tics or only OCD (p < 0.033 for each).

Conclusion: Our study suggested a significant correlation of streptococcal-associated tics and OCD with elevated anti-D1R and antilysoganglioside antineuronal antibodies in serum concomitant with higher activation of CaMKII in human neuronal cells. Youth and young adults with chronic tics and OCD may have underlying infectious/immunologic etiology.

Introduction

In the last few decades, there has been a growing interest in the association of infections, autoimmunity, and behavioral changes, and their impact on the genesis of neuropsychiatric disorders (Murphy et al. 2012). In 1998, a link between obsessive-compulsive disorder (OCD) and group A streptococcal infections was identified by Swedo at the National Institute for Mental Health (NIMH) (Swedo et al. 1998). These disorders may be identified as pediatric autoimmune neuropsychiatric disorder associated with streptococci (PANDAS) Research Fund, University of Oklahoma; Pepsi/Global Giving; and National Institute of Mental Health (NIMH) Bench to Bedside Grant. The work of Dr. Julie Stoner was supported in part by a grant from the National Institutes of Health, National Institute of General Medical Sciences, grant 1 U54 GM104938-01A1.

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strep (PANDAS) (Swedo et al. 1998) or pediatric acute-onset neuropsychiatric syndrome (PANS) in the presence of other causes, including infections (Swedo et al. 2012). This discovery was a result of two parallel studies conducted at the NIMH, including investigation of children with OCD and tics and investigation of children with Sydenham chorea (SC), the major neurological manifestation of acute rheumatic fever (ARF), which presents with involuntary movements and neuropsychiatric disturbances, including obsessive-compulsive symptoms, hyperactivity, and emotional lability (Marques-Dias et al. 1997). Swedo and coworkers identified a cohort of patients who experienced a sudden acute onset of obsessions and compulsions that followed a relapsing–remitting symptom course. Five diagnostic criteria emerged from careful observation of these patients: 1) Presence of OCD (by Diagnostic and Statistical Manual of Mental Disorders IV criteria) or a tic disorder, 2) symptom onset between 3 years of age and puberty, 3) episodic course of illness, with abrupt and substantial symptom exacerbations, 4) symptom onset and exacerbations associated temporally with group A streptococcal infections, and 5) presence of neurological abnormalities, including choreiform movements during symptom exacerbations (Swedo et al. 1998).

Murphy also describes neurological symptoms in acute onset OCD/tic patients, including severe hyperactivity, loss of fine motor skills (handwriting deterioration), or adventitious movements, such as choreiform movements (Murphy et al. 2012). Psychiatric symptoms as described by Murphy et al. included irritability, frequent mood changes, separation anxiety, hyperactivity, late-onset attention problems, personality change, oppositional behaviors, sleep disturbances, and deterioration in mathematical skills. Although streptococcal infections have been closely associated with a PANDAS onset, there is debate in the literature whether group A streptococcal infections are coincidental or causal. Historical accounts from the first 50 cases of PANDAS indicate that at least some cases of PANDAS occurred immediately following or during a group A streptococcal infection (Swedo et al. 1998). Whether PANDAS is a variant of ARF is still debated (Kurlan et al. 2008). Although there is still discussion as to the exact mechanism of PANDAS, current PANDAS criteria cite that a history of RF is exclusionary for a PANDAS diagnosis. However, controversy does exist among some neurologists regarding the validity of PANDAS as a subset of OCD/tics versus its being a forme fruste of RF (SC). In SC, neuropsychiatric symptoms predate choreoathetoid movements. PANDAS is described as including choreiform piano-playing movements of the fingers and toes (Swedo et al. 1998).

Since the initial identification of the PANDAS subgroup, it has been proposed that the disorder may develop as a result of postinfectious autoimmune processes (Swedo et al. 1998; Kirvan et al. 2006b). We hypothesize that antistreptococcal antibodies produced in response to group A streptococcal infection cross-react with neuronal targets of susceptible hosts through the process of molecular mimicry (Kirvan et al. 2003). We suggest that the pathogenesis of PANDAS could be similar to that of SC, which was delineated by studying human monoclonal antibodies (mAbs) derived from an SC patient. Three human mAbs reacted with the surface of neuronal cells and demonstrated antibody cross-reactivity with the group A carbohydrate epitope N-acetyl-β-D-glucosamine (GlcNAc) and lysoganglioside. mAb 24, one of these mAbs, possessed the highest avidity for lysoganglioside, and also induced elevated calcium calmodulin dependent protein kinase II (CaMKII) levels in SK-N-SH, a human neuronal cell line. Subsequent studies of acute and convalescent sera from SC patients demonstrated that antibodies in the acute sera had immunoglobulin G (IgG) reactivity profiles similar to that of mAb 24 (Kirvan et al. 2003). Autoantibodies against tubulin and lysosomglioside were also present in PANDAS (Kirvan et al. 2006b). Additionally, both SC and PANDAS sera stimulated neuronal cells in culture in an IgG-dependent reaction, leading to activation of CaMKII.

Mouse and rat animal models lend support to the streptococcal autoimmune hypothesis. Group A streptococcal-immunized mice were found to have serum immunoreactivity to deep cerebellar nuclei (DCN) and increased IgG deposits in DCN (Hoffman et al. 2004). Streptococcal immunized mice with anti-DCN antibodies developed distinct motoric and behavioral disturbances that correlated with level of immunoreactivity to the DCN (Hoffman et al. 2004). The validity of the autoimmune hypothesis in the murine model was further demonstrated through passive transfer of antistreptococcal sera from immunized mice to naïve mice (concomitant with lipopolysaccharide [LPS] to break the blood–brain barrier) (Yaddanapudi et al. 2010). It was also found that passive serum antibody transfer recipients developed motor and behavioral disturbances. Repetitive behaviors in both Group A β-hemolytic streptococci (GABHS) donor and passive transfer mice are reminiscent of tics, obsessions, and compulsions (Yaddanapudi et al. 2010).

In an investigation of the specific neural and immune characteristics in a Lewis rat model, Brimberg et al. reported that exposure of male Lewis rats to GABHS antigens led to OCD/tic-like behavior, as well as immunological and neural characteristics similar to those of SC and PANDAS (Brimberg et al. 2012). Behaviorally, streptococcal-exposed rats were impaired in manipulating food and in traversing a narrow, but not a wide, beam. Serum studies of the immunized rats to GABHS led to antibodies that activated CaMKII signaling, and sera from GABHS rats reacted more significantly with human D1 and D2 dopamine receptor membrane antigens than that from control rats. The reactivity of the GABHS rat sera with the D1 and D2 receptor antigen was confirmed by Western immunoblot. Impaired food manipulation and increased induced grooming in GABHS-exposed rats were alleviated by the administration of the D2 blocker haloperidol, which is used to treat motor and compulsive symptoms in SC and PANDAS (Brimberg et al. 2012).

Evidence for autoantibodies in PANDAS and SC includes several studies that have demonstrated significantly higher concentrations of antineuronal antibodies in patients with SC, OCD, and Tourette’s syndrome compared with healthy controls. (Husby et al. 1976; Kiessling et al. 1993, 1994; Singer et al. 1998); however, further studies did not replicate these results (Black et al. 1998). In further support of autoantibodies and the autoimmune hypothesis, there are several reports of immunosuppressive treatments (e.g. plasmapheresis, intravenous immunoglobulin [IVIG], and prednisone) resulting in immediate and strong suppression of acute childhood OCD and Tourette’s syndrome (Kondo and Kabasawa, 1978; Matarasso 1992; Swedo 1994; Allen et al. 1995; Perlmuter et al. 1999).

Autoantibody detection and the identification of their neuronal targets in SC and PANDAS has been the object of scrutiny for some time (Husby et al. 1976; Church et al. 2002; Kirvan et al. 2003; Singer et al. 2005; Dale et al. 2006; Brilot et al. 2011; Dale et al. 2012; Mohammad et al. 2013; Pathmanandavel et al. 2013; Ramamathan et al. 2013). The autoantibody hypothesis has been debated in the literature with inconsistent results, that is, with both positive (Church et al. 2003; Kirvan et al. 2006b; Pavone et al. 2006) and negative findings (Singer et al. 2005; Morris et al. 2009). There are several challenges associated with the investigation into
these autoantibodies, including clinical distinction of PANDAS from other presentations of OCD or tics (Murphy et al. 2012), and there is a lack of prospective studies examining any temporal relation between antecedent bona fide GABHS infections and the onset or exacerbation of tics and obsessive-compulsive symptoms (Leckman et al. 2011). Most recently, autoantibodies against the D1 and D2 receptors were confirmed in SC by an independent study in which the ratio of anti-D1/anti-D2 receptor antibodies correlated with symptoms (Ben-Pazi et al. 2013) and another study of SC mAb and serum from youth with SC and PANDAS that demonstrated reaction with the D2R and the chorea-derived human mAb targeted dopaminergic neurons in transgenic (Tg) mice (Cox et al. 2013).

The purpose of this study was to determine if our previous findings applied to a large cohort of patients from the general community with self-reported neuropsychiatric symptoms. We hypothesized that youth with OCD and/or tics would have higher rates of GABHS infection history than those without, and higher levels of lysoganglioside, tubulin, dopamine D1 receptor, and dopamine D2 receptor antineuronal autoantibodies than healthy controls. Additionally, we hypothesized that serum activation of CaMKII levels in youth with OCD and/or tics would be elevated and be correlated with a positive GABHS infection history.

**Methods**

Our investigation \( (n=742) \) was conducted to evaluate the presence of elevated antineuronal autoantibodies in patients with tics and/or OCD. This study included data from the subset of the 311 in the current report (see consort diagram, Fig. 1). The study inclusion criteria were a report of a tic disorder, OCD, or both, by parent and/or physician. Recruitment was weighted toward subjects with a detailed history of streptococcal infection, either positive or negative for cultures or antistreptococcal antibody titers (antistreptolysin O [ASO] or anti-deoxyribonuclease B [anti-DNAs B]). Patients on psychotropic medication, antibiotics, or steroids for their condition were not excluded. Additionally, patients who had previously received intravenous immunoglobulin or plasma exchange in the past but were experiencing symptoms were not excluded. Only patients with accurate group A streptococcal infection information \( (n=311) \) were included in this study. Of the 311, all but 4 were categorized with or without history of streptococcal infection. There were 261 patients who had tics/OCD, and the remaining had other neuropsychiatric symptoms and were not included in the analysis (see Fig. 1). Sixteen healthy controls selected at the National Institute of Mental Health and Yale University had normal physical examination findings; no lifetime personal history for the participant or any first degree relative with a

![FIG. 1. Consort diagram depicting recruitment of study subjects.](image-url)
Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM IV) diagnosis of a tic disorder, Tourette syndrome, OCD, or attention-deficit/hyperactivity disorder (ADHD); and had ASO titers ranging between 70 and 513 (Todd units) (American Psychiatric Association 1994). Figure 1 is a consort diagram depicting recruitment of study subjects.

Study procedures

Our study was conducted at the University of Oklahoma Health Sciences Center. This study was approved by the University of Oklahoma Health Sciences Center human subjects institutional review board. Although the study was not formally advertised, parents were informed about the study from initial participants who had contacted our research laboratory about research studies for PANDAS. Before participation, parents or legal guardians gave written consent for subjects years of age. Oral assent was given by youth ≥7 years, and when age appropriate (≥13 years), subjects gave written assent. Subjects >18 years of age gave informed consent. Blood samples were collected and the samples and consent forms were returned overnight to the research laboratory from areas throughout the United States.

Streptococcal infection status

The status of streptococcal infection was determined for 311 patients: 222 (72%) were streptococcus positive, 85 (28%) were streptococcus negative, and 4 (1%) had undetermined status. The streptococcal infection status was determined using either throat culture, ASO antibody assay, or anti-DNAse B antibody assay, or a combination of the three tests. When the age of the participant was known and either ASO and anti-DNAse B antibody assays were available, their thresholds were age adjusted as previously described. (Kaplan et al. 1998). Where ages were unavailable, thresholds used were ≥200 for ASO and ≥240 for anti-DNAse B (Murphy et al. 2012).

Antineuronal antibody titers in the enzyme-linked immunosorbent assay (ELISA)

Ninety-six well Immunolon-4 microtiter plates (Dynatech Laboratories) were coated with antigen: lysoganglioside (Sigma, 20 μg/mL), tubulin (MP Biomedical, 10 μg/mL), human dopamine receptor D1 antigen (Perkin Elmer, 10 μg/mL), and human dopamine receptor D2L antigen (Perkin Elmer, 10 μg/mL), and incubated overnight at 4°C. ELISA was performed on patient and control sera as previously described (Cox et al. 2012).

Calcium calmodulin (CaM) kinase assay

Cell culture. SK-N-SH human neuroblastoma cells obtained from American Type Culture Collection (ATCC) were treated with serum after growth in F12-Dulbecco’s Modified Eagle Medium (DMEM) (complete with 10% fetal bovine sera and Pen/Strep) as previously described (Kirvan et al. 2003). Cell extracts were centrifuged at 15,000 rpm for 20 minutes at 4°C. Protein concentrations of the cell lysates were determined by Bradford assay (Bio-Rad Protein Assay Kit II #500-0002).

CaM KII activity assay. Protein kinase activity was measured using CaM kinase assay system (signa-TECT CaM Kinase assay kit, Promega) according to the manufacturer’s instructions. In brief, 5 μL of cell lysate was incubated with 50 μM peptide substrate and [γ-32P] adenosine triphosphate (ATP) for 2 minutes at 30°C as previously described (Kirvan et al. 2003). Sera were tested at 1:100 (Brimberg et al. 2012; Cox et al. 2013).

Discussion

We found that subjects with chronic tics and/or OCD had elevated serum levels of several antineuronal antibodies, and
increased induction of CaMKII, similar to those with SC and PANDAS. In this group, subjects with a positive history of GABHS infection were also more likely to have both tics and OCD. Therefore, it may be that several categories of movement and behavioral disorders are triggered by infection, and are associated with increased CaMKII activity, as shown in Fig. 3. CaMKII enzyme activation levels are shown as percent above basal level plus basal level at 100%. The mean % CaMKII activation for the three groups (tics only, OCD only, and tics-OCD) is compared to healthy control subjects.

Table 1. Demographic and Symptom Characteristics for 311 Participants: Comparison of Males versus Females (Distribution Was Not Significant)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=311)</th>
<th>Male (n=206)</th>
<th>Female (n=105)</th>
<th>p value*</th>
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<tbody>
<tr>
<td>Age (years, mean [± standard deviation])</td>
<td>9.91 (±3.95)</td>
<td>9.70 (±3.95)</td>
<td>10.29 (±3.95)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sex (male, count [%])</td>
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<td>—</td>
<td>—</td>
<td>0.16</td>
</tr>
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<td>Race/Ethnicity (count [%])</td>
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</tr>
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<td>African American</td>
<td>5 (3%)</td>
<td>3 (2%)</td>
<td>2 (3%)</td>
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</tr>
<tr>
<td>Asian/Pacific Islander</td>
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<td>9 (7%)</td>
<td>0</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>169 (90%)</td>
<td>111 (87%)</td>
<td>58 (95%)</td>
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<tr>
<td>Hispanic</td>
<td>4 (2%)</td>
<td>3 (2%)</td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>Native American</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity unknown (count [%])</td>
<td>123 (40%)</td>
<td>79 (38%)</td>
<td>44 (42%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Symptoms (count [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tics only</td>
<td>53 (20%)</td>
<td>35 (20%)</td>
<td>18 (20%)</td>
<td></td>
</tr>
<tr>
<td>OCD only</td>
<td>91 (35%)</td>
<td>57 (33%)</td>
<td>33 (37%)</td>
<td></td>
</tr>
<tr>
<td>Tics and OCD</td>
<td>117 (44%)</td>
<td>79 (46%)</td>
<td>38 (43%)</td>
<td></td>
</tr>
<tr>
<td>No tics and no OCD</td>
<td>2 (&lt;1%)</td>
<td>2 (1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other neurological symptoms (count [%])</td>
<td>48 (15%)</td>
<td>33 (16%)</td>
<td>16 (15%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Group A streptococcal infection (307/311 participants) (count [%])</td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Positive</td>
<td>222 (72%)</td>
<td>148 (73%)</td>
<td>74 (72%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>85 (28%)</td>
<td>55 (27%)</td>
<td>29 (28%)</td>
<td></td>
</tr>
<tr>
<td>Group A streptococcal infection status unknown (count [%])</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*p value comparing distribution between males and females was not significant. Two-sample t test was used to compare the means from continuous measures and Fisher’s exact test was used for comparison of the distribution of categorical measures between males and females.

OCD, obsessive-compulsive disorder.

FIG. 2. The presence of obsessive-compulsive disorder (OCD) and tics was significantly associated with streptococcal infection status (overall \( \chi^2 \) test \( p=0.0087 \). After adjustment for multiple pairwise comparisons, subjects who were positive for streptococcus were more likely to have both tics and OCD (51%) than those who were negative for streptococcus (30%) (adjusted \( p=0.0063 \)). Percent of 311 minus 4 indeterminate = 307 (see Fig. 1 and Table 1). Of the 307/311 patients, 222 were streptococcus positive – 72% – (See Table 1) and 85 were streptococcus negative (28%). The four who were indeterminate (1%) were not considered in the streptococcal evaluated cohort. See Table 1 under “group A streptococcal infection.” However, only 184 streptococcus positive and 76 streptococcus negative (from tics/OCD group, \( n=261 \)) are compared here.

FIG. 3. CaM kinase II (CaMKII) activation is associated with obsessive-compulsive disorder (OCD) and tics (\( p=0.0008 \)). CaMKII enzyme activation levels shown are percent above basal level plus basal level at 100%. Normal % CaMKII activation mean: 94–100. All CaMKII activity is calculated as enzyme activity in pmol/min/μg protein (\( p=0.0008 \)). (p value refers to comparison overall among the three groups – tics only, OCD only, and tics-OCD – not comparison with healthy control subjects.)
with elevated antineuronal antibodies. Our previous work has supported this idea by demonstrating antistreptococcal/antineuronal antibody binding, including human monoclonal antibodies, to human neuronal cells and activation of CaMKII by sera IgG from SC and PANDAS patients (Kirvan et al. 2003, 2006a,b, 2007; Brimberg et al. 2012; Ben Pazi et al. 2013; Cox et al. 2013). We previously reported that antibody titers against neuronal antigens, lysoganglioside, and tubulin were significantly elevated in acute SC sera compared with convalescent sera. Lysoganglioside competitively inhibited antigen–antibody interaction of SC acute sera with GlcNAc, the dominant epitope of the GABHS carbohydrate (Kirvan et al. 2003; Kirvan et al. 2006b). Additionally, SC acute sera were found to have higher tubulin-specific Ab titers than matched convalescent sera or sera from ARF without chorea (Kirvan et al. 2007). In 2006, sera IgG from acute PANDAS cases were tested in a competitive inhibition ELISA, and, similarly to SC sera, it was found that lysoganglioside specifically inhibited antigen-antibody interaction of SC acute sera with GlcNAc, the dominant epitope of the GABHS carbohydrate (Kirvan et al. 2006b). When the sera of 261 patients diagnosed with OCD, tics, or both were found to react in a direct ELISA with lysoganglioside as the antigen, sera IgG had statistically significantly higher titers than those from healthy controls (median values of 320 vs. 100, respectively, \( p = 0.0001 \)) (Table 2, Fig. 5). The direct ELISA with tubulin as the antigen did not show a statistically significant difference between sera and tics, OCD, or both, versus the sera from healthy controls (Table 2).

In 2012, Brimberg et al. reported that the sera from GABHS immunized rats reacted more significantly with human D1 and D2 receptor antigens than the sera from control rats in direct ELISA and Western blot. To draw a comparison to human disease, reactivity of acute PANDAS and SC sera IgG was tested in direct ELISA, and SC sera reacted more significantly with the dopamine D2 receptor membrane antigen compared with the sera from healthy controls, and the PANDAS sera reacted more significantly with both the D1 and D2 receptor antigens when compared with the sera from healthy controls. Our current study shows that sera IgG

![Graph](image1.png)

**Fig. 4.** Analysis of 261/307 individuals demonstrates significantly elevated neuronal cell signaling (CaM kinase II [CaMKII]) among patients with obsessive-compulsive disorders and/or tics compared with healthy controls. CaMKII enzyme activation levels shown are percent above basal level plus the basal level at 100%. All CaMKII activity is calculated as enzyme activity in pmol/min/\( \mu \)g protein. Normal % CaMKII activation mean: 94–100.

![Graph](image2.png)

**Fig. 5.** Analysis of 261/307 individuals demonstrates significantly elevated antilyso ganglioside immunoglobulin G (IgG) antibody titers among patients with obsessive-compulsive disorders and/or tics compared with healthy controls.

**Table 2. Antineuronal Antibody Titers in Participants with Tics and/or Chronic Obsessive-Compulsive Disorder versus Healthy Control Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with tics and/or OCD (n = 261)</th>
<th>Healthy control subjects (n = 16)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaM kinase II activation</td>
<td>Median 157, P25 137, P75 173.5</td>
<td>Median 94, P25 90, P75 99</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-D1R IgG titer</td>
<td>2000, 1000, 4000</td>
<td>1000, 500, 1000</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-D2R IgG titer</td>
<td>4000, 2000, 8000</td>
<td>4000, 2000, 8000</td>
<td>0.66</td>
</tr>
<tr>
<td>Antilyso ganglioside IgG titer</td>
<td>320, 160, 320</td>
<td>100, 80, 160</td>
<td>0.0001</td>
</tr>
<tr>
<td>Antitubulin IgG titer</td>
<td>500, 500, 1000</td>
<td>500, 500, 1000</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Titers were determined as described in the Methods section.

*p value comparing distribution between patients with tics/OCD and healthy controls using the Wilcoxon rank sum test.

OCD, obsessive-compulsive disorder; P25, 25th percentile; P75, 75th percentile; D1R, dopamine D1 receptor antigen; D2R, dopamine D2L receptor antigen (L refers to long isoform of dopamine D2 receptor); IgG, immunoglobulin G titers specific for each antigen listed.
from subjects with more chronic OCD, tics, or both reacted more significantly with human D1 receptor antigen compared with the sera from healthy controls in direct ELISA (median value of 2000 vs. 1000, respectively, \( p \leq 0.0001 \)) (Table 2, Fig. 6). However, these subjects did not have significant antibody levels against the D2 receptor, in contrast with our previous findings in PANDAS. As our current group consisted of subjects who had been reporting tics and OCD for \( >1 \) year, with many reporting tics and OCD for several years, they may represent a different phenotype than the original PANDAS cohort, which exhibited acute onset OCD and/or tics along with fine piano-playing choreiform movements. It is possible that different phenotypes may map with different neuronal receptor antibodies.

We also demonstrated increased CaMKII signaling in subjects with OCD and/or tics, particularly in those with both OCD and tics. CaMKII is a multifunctional enzyme highly concentrated in the brain, which mediates many different learning, memory, and developmental cell pathways, and has broad substrate specificity dependent on concentration, intracellular localization, and intracellular calcium levels (De Koninck and Schulman 1998; Bejar et al. 2002; Menegon et al. 2002; Tsui et al. 2005). In preliminary testing of acute SC sera \( (n=5) \) and matched convalescent sera \( (n=3) \), there was an increase in CaMKII activation in the acute sera (Kirvan et al. 2003). In a subsequent investigation that included PANDAS sera, 75% of acute PANDAS sera induced

![FIG. 6.](image)

Analysis of 261/307 individuals demonstrates significantly elevated anti-D1R antibody titers among patients with obsessive-compulsive disorders and/or tics compared with healthy controls.

![FIG. 7.](image)

Analysis of sera from the complete registry (742 individuals) demonstrates significantly elevated (A) neuronal cell signaling (CaM kinase II), (B) anti-D1R, and (C) antilyso-ganglioside immunoglobulin G (IgG) titers, \( p < 0.0001 \).
antibody-mediated activation of CaMKII to significantly higher levels than did matched convalescent sera \((p=0.001)\) (Kirvan et al. 2006b). The present study reveals two important correlations involving CaMKII activation by serum: 1) The presence of OCD and/or tics was positively associated with antibody-mediated CaMKII activation \((n=261, p=0.0088)\); and 2) antibody-mediated CaMKII activation was elevated for patients with OCD and/or tics \((n=261)\), with median percentile increase values ranging from 149 to 162, whereas it remained unaffected in healthy controls, with a median of the 94th percentile \((n=16, p<0.0001)\). The difference in the median value for CaMKII activation between patient samples and healthy controls is similar to what was found for PANDAS sera and non-PANDAS sera in previous studies (Kirvan et al. 2006b).

In addition to these immunological findings, we found that the presence of OCD and/or tics was associated with positive streptococcal infection history \((p=0.0087)\) (Fig. 2). There have been both negative and positive reports on the association of streptococcal infections with tics or OCD (Murphy and Pichichero 2002; Luo et al. 2004; Murphy et al. 2004, 2007; Kurlan et al. 2008; Leckman et al. 2011; Martino et al. 2011; Murphy et al. 2012). It is sometimes difficult to detect the streptococcal infection associated with exacerbations of tics and OCD, because infections can precede symptoms by several months, or can be representative of a chronic carrier state. It has been suggested in previous studies that to accurately determine an association with streptococcal infection, longitudinal samples are required rather than a single time point (Leckman et al. 2011). This is the first report finding that streptococcal infections may be more prevalent in subjects who have combined tics and OCD.

We also found that subjects who had a positive history of streptococcal infection were more likely to have both OCD and tics (51%) than those who were negative for streptococcal infections (30%), whereas there was no significant association with infection history when tics or OCD were considered alone. Therefore, it is possible that patients who present with both OCD and tics are more likely to have had streptococcal infections in their history. As there may be various etiologies for obsessive-compulsive symptoms and tics, it may be that a streptococcal etiology may represent a more “virulent” cause that disrupts the basal ganglia in a more widespread fashion, leading to multiple neuropsychiatric symptoms. Presentations of OCD and tics alone may be less likely to be manifestations of disorders associated with GABHS, but still may have similar pathogenic mechanisms.

Study strengths include a generalized community sample and the use of factual medical records when available. However, a diagnosis of a tic disorder, OCD, or both was based on the parents’ report when a physician’s report was not available. The parents’ report may not have been accurate, and may have resulted in misclassification of cases. Given the nature of data reporting from multiple sources, not all variables (e.g., age, ethnicity) are complete. Missing data may result in information bias if those with available data are not representative of the target population of youth and young adults with a tic disorder, OCD, or both. Limitations of the study included lack of severity measures (e.g., Yale–Brown Obsessive Compulsive Scale [YBOCS], TGSS), the small sample size of the control cohort, and the self-report nature of neuropsychiatric symptoms. Furthermore, we do not have reports of associated neuropsychiatric symptoms that the patients may have experienced, such as anxiety, depression, irritability, or cognitive impairment, all of which have been reported in youth with PANDAS.

**Conclusions**

Our study suggested a significant correlation of streptococcal- associated tics and OCD with elevated anti-D1R and antilyso- ganglioside antineuronal antibodies in serum concomitant with higher activation of CaMKII in human neuronal cells. Youth and young adults in OCD and/or tics appeared to have higher rates of GABHS infection history than those without OCD and/or tics. Analysis of sera from the complete registry of individuals \((742)\) demonstrated significantly elevated neuronal cell signaling through CaMKII, as well as anti-D1R and antilyso-ganglioside IgG titers. Youth and young adults with chronic tics and OCD may have underlying infectious/immunologic etiology.

**Clinical Significance**

The statistically significant correlation between a history of tics and OCD with antineuronal antibodies against D1R and lyso-ganglioside and functional activation of CaMKII suggests that pediatric neuropsychiatric disorders outside of PANDAS may also be associated with autoimmunity against the brain. The functional activity of the autoantibodies to signal CaMKII in human neuronal cells suggests that antibodies could target receptors in the brain and alter dopamine neurotransmission, leading to neuropsychiatric symptoms of tics and/or OCD. Furthermore, youth presenting with OCD and/or tics, regardless of acuteness of onset, should be screened for GABHS infection. Treatment of these youth, however, extends beyond the scope of these findings. Clearly, additional studies are needed in youth with chronic tics and OCD to determine best evaluation and treatment approaches. By understanding the immunological and physiological factors associated with GABHS infection related chronic OCD and tic disorders, clinicians will eventually be able to more accurately identify, diagnose, and target treatment to better manage chronic symptoms to improve outcomes in this population.

**Acknowledgment**

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**Disclosures**

Dr. Amir Zuccolo, Dr. Julie Stoner, and Erica Edwards have no conflict of interest to declare. Dr. Kiki Chang has received research funding from GlaxoSmithKline and Merck, is on the Data and Safety Monitoring Board (DSMB) for Sunovion, and is an unpaid consultant for Bristol Myers-Squibb, GlaxoSmithKline, and Lilly. Dr. Carol Cox, Adita Mascaro-Blanco, and Kathy Alvarez declare financial interest in Moleculera Labs, a commercial laboratory for diagnostic testing of autoantibodies against the heart and brain. Dr. Madeleine Cunningham is chief scientific officer and co-founder with financial interest in Moleculera Labs.

**References**


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Cytokine Correlations in Youth with Tic Disorders

E. Carla Parker-Athill, PhD¹; Jared Ehrhart, PhD²; Jun Tan, PhD, MD²,³ and Tanya K. Murphy, MD, MS¹,³

Abstract

Background: Studies have noted immunological disruptions in patients with tic disorders, including increased serum cytokine levels. This study aimed to determine whether or not cytokine levels could be correlated with tic symptom severity in patients with a diagnosed tic disorder.

Methods: Twenty-one patients, ages 4–17 years (average 10.63 ± 2.34 years, 13 males), with a clinical diagnosis of Tourette’s syndrome (TS) or chronic tic disorder (CTD), were selected based on having clinic visits that coincided with a tic symptom exacerbation and a remission. Ratings of tic severity were assessed using the Yale Global Tic Severity Scale (YGTSS) and serum cytokine levels (interleukin [IL]-2, IL-4, IL-5, IL-10, IL-12p70, IL-13, interferon [IFN]-γ, tumor necrosis factor [TNF]-α, and granulocyte macrophage-colony stimulating factor [GM-CSF]) were measured using Luminex xMAP technology.

Results: During tic symptom exacerbation, patients had higher median serum TNF-α levels ($z = -1.962$, $p = 0.05$), particularly those on antipsychotics ($U = 9.00$, $p = 0.033$). Increased IL-13 was also associated with antipsychotic use during exacerbation ($U = 4.00$, $p = 0.043$) despite being negatively correlated to tic severity scores ($p = -0.599$, $p = 0.018$), whereas increased IL-5 was associated with antibiotic use ($U = 6.5$, $p = 0.035$). During tic symptom remission, increased serum IL-4 levels were associated with antipsychotic ($U = 6.00$, $p = 0.047$) and antibiotic ($U = 1.00$, $p = 0.016$) use, whereas increased IL-12p70 ($U = 4.00$, $p = 0.037$) was associated with antibiotic use.

Conclusions: These findings suggest a role for cytokine dysregulation in the pathogenesis of tic disorders. It also points toward the mechanistic involvement and potential diagnostic utility of cytokine monitoring, particularly TNF-α levels. Larger, systematic studies are necessary to further delineate the role of cytokines and medication influences on immunological profiling in tic disorders.

Introduction

Tic disorders have been shown to have a strong genetic component, with observations of common polymorphisms and a high degree of hereditability among patients (Chou et al. 2010; Liu et al. 2011). These polymorphisms, although they are potential diagnostic markers, do not fully explain the pathological mechanism, the heterogeneous symptoms, or the unpredictable course characterized by periods of symptom waxing and waning that is seen in patients with tic disorders. Similarly, evidence of neurochemical abnormalities in dopamine, serotonin, and γ-aminobutyric acid (GABA) systems, although an important component of the mechanism of tic disorders and related to aspects of motor dysfunction, does not fully explain the etiology of tic disorders (Lijun et al. 2010; Lerner et al. 2012). The infectious etiology of neurological and neuropsychiatric disorders has gained increasing attention as a result of observations correlating prenatal and early childhood infections (Brown et al. 2004; Winter et al. 2009; Khandaker et al. 2014) and immunological abnormalities (Ashwood et al. 2011) to the occurrence of schizophrenia and autism. Despite rekindled interest, however, infection and immunological dysfunction have long been hypothesized as central components of tic disorders, partly as a result of observations of infection-triggered symptomology, cytokine and other immune abnormalities, and strong similarities to Sydenham’s chorea (SC), the prototype infection-triggered neurological disorder (Swedo 1994). Cytokines in particular have been shown to be an important part of the pathological mechanism of these disorders, with increasing evidence of genetic polymorphisms and abnormal serum expression being associated with disease course (Leckman et al. 2005; Chou et al. 2010). In SC, a group A streptococcal (GAS) mediated disorder occurring in a subset of individuals with rheumatic fever (RF), patients experience involuntary movements and a manifestation of neuropsychiatric symptoms including obsessions/compulsions and

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anxiety, which are thought to be the result antistreptococcal anti-

bodies targeting structures in the basal ganglia, dopamine receptors,

and neuronal proteins (Kirvan et al. 2003; Dale et al. 2012; Ben-Pazi

et al. 2013). There has also been increasing evidence to support an

equally important role for cytokines in disease pathology, given

observations of increased serum cytokine levels in patients with

cytokine-related neuropathology in similar movement disorders

(Church et al. 2003; Lewitius et al. 2014). These pathologies,

particularly increases in serum cytokine levels, have also been ob-

served in patients with tic disorders, along with abnormal immu-

nological responses to GAS and basal ganglia pathologies (Giedd


Given the increasing awareness of the role of immune dysre-

gulation in tic disorders, we aimed to determine if serum cytokine

levels differed during periods of tic symptom exacerbation and

remission in patients with a diagnosis of chronic tic disorder (CTD)

or Tourette syndrome (TS). We hypothesized that inflammatory

cytokine levels would be positively correlated with tic symptom

severity. Understanding the role of these cytokines in tic pathology

may be an important step in understanding the mechanism of tic

disorders and the involvement of the immune system.

Methods

Participants

Twenty-one patients with CTD or TS, ages 4–17 years, were

selected from a larger prospective cohort recruited to investigate

neuropsychiatric phenomena with temporal association to strepto-

coccal pharyngitis (Murphy et al. 2012). Briefly, participants were

selected for the current study based on meeting Diagnostic and

Statistical Manual of Mental Disorders, 4th ed. (text revision)

(American Psychiatric Association 2000) criteria for a tic disorder

(TS or CTD) confirmed by clinical interview and a semistructured

diagnostic interview with a trained clinician. Participants with ac-

tive psychosis, mania, current suicidal intent, a diagnosis of intel-

lectual deficiency, or autism (based on clinical interview with a

trained clinician) were excluded from the study. Those on stable

doses of psychotropic medications were not excluded. Participants

were also required to have a documented exacerbation/flare and a

remission episode of tic symptoms during the course of the larger

cohort study, to be included in the present study. The average time

between an exacerbation and remission cycle was 8.7 months.

Study procedures were approved by the institutional review board,

and parental consent and participant assent when applicable (>7

years) was obtained prior to enrollment.

Clinical assessments

Assessments were conducted by T.K.M. or by a trained clinician

with experience in pediatric tic disorders, and consisted of com-

prehensive parent, child, and clinical ratings for tic disorders and

obsessive-compulsive disorder (OCD), as well as comprehensive

neurological/physical examinations and medical record reviews.

Assessments included the clinician-rated Yale Global Tic Severity

Scale (YGTSS) for tic disorders (Leckman et al. 1989), and the

clinician rated Children’s Yale-Brown Obsessive Compulsive

Scale (CY-BOCS) for OCD (Scahill et al. 1997). For the present

study, tic symptoms were considered to be in an exacerbated state

when the current visit’s YGTSS Total Severity Score was ≥15

points and exceeded the previous visit’s score by ≥5 points. Sim-

ilarly, OCD symptoms were considered to be in an exacerbated

state when the current visit’s CY-BOCS Total Score was ≥15

points and exceeded the previous visit’s score by ≥5 points. For

remission, tic or OCD symptoms were considered remitted if the

current visit’s YGTSS or CYBOCS score was <5.

Cytokine analysis

In addition to the clinical assessments, serum samples were

collected during visits coinciding with an exacerbation of tic

symptoms, and again during a visit coinciding to symptom remis-

sion. In short, peripheral blood was collected in silicone-coated

tubes (BD Bioscience, CA), centrifuged at 2500 rpm for 15 minutes

and serum collected, aliquoted, and stored at –80 until analysis.

Serum levels of cytokines were measured using human multi-

plexing bead immunoassays and Luminex-xMAP fluorescent bead-

based technology. The standard curve was derived using Bio-Plex

software and manufacturer-supplied reference cytokine levels, and

a five parameter model used to calculate final concentration. Nine

cytokines (interleukin [IL]-2, IL-4, IL-5, IL-10, IL-12p70, IL-13,

interferon (IFN)-γ), tumor necrosis factor (TNF)-α, and granulo-

cyte macrophage-colony stimulating factor (GM-CSF) were mea-

sured per manufacturer’s instructions (BioRad, CA).

Statistical analysis

The Wilcoxon signed rank test was used to evaluate differences

in serum cytokine levels during periods of symptom exacerbation

and remission. Mann-Whitney test was used to determine

between-group differences in patients presenting with exacerbation–

remission of only their tic symptoms, and those who experienced

exacerbation–remission of OCD/tic symptoms. Data were reported

as medians unless otherwise specified. Spearman rank correla-

tion coefficients were used to test for associations between cyto-

kine levels and symptom severity. SPSS statistical software was

used to analyze all data with an α of 0.05 defining statistical

significance.

Results

Participant demographics and clinical characteristics

Four participants with CTD (n = 4) and 17 with TS (n = 17) were

selected for this study (mean age = 10.63 ± 2.34 years, 62% male).

The average age of tic onset was 6.56 ± 2.54 years, and average

duration of symptoms was 3.02 ± 2.09 years. During periods of tic

symptom exacerbation, average YGTSS Total Tic Severity scores

were 23.81 ± 7.20 compared with 0.62 ± 1.56 during tic symptom

remission. Ninety percent of patients also presented with comorbid

OCD (n = 19), with an average age of OCD onset of 6.95 ± 2.57

years and an average duration of 2.89 ± 2.21 years. For those with

comorbid OCD, the average CY-BOCS score during periods of tic

symptom exacerbation was 17.37 ± 10.77, compared with 11.42 ±

10.69 during periods of tic remission (Table 1).

Do serum cytokine levels differ during periods of tic symptom exacerbation and remission?

The level of nine cytokines was analyzed in the serum of patients with a clinical diagnosis of CTD or TS when their tic symptoms were in an exacerbated or flared state, and again when they had remitted, irrespective of OCD symptom status (Table 2). Of the 13 patients having detectable serum TNF-α levels, 77% (n = 10) showed higher plasma concentrations of TNF-α during periods of tic symptom exacer-

boration whereas 15% (n = 2) had a higher serum concentration
during tic symptom remission. One patient showed no change in
TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS BASED ON TIC/ODC SYMPTOM COMORBIDITY DURING SYMPTOM EXACERBATION AND REMISSION

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Tic only (n=10)</th>
<th>OCD/tic (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>8 (80.0)</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>10.67 ± 2.39</td>
<td>10.58 ± 2.41</td>
</tr>
<tr>
<td>YGTSS ex, a ± SD</td>
<td>23.50 ± 7.41</td>
<td>24.09 ± 7.35</td>
</tr>
<tr>
<td>YGTSS rem, b ± SD</td>
<td>0.90 ± 1.91</td>
<td>0.36 ± 1.21</td>
</tr>
<tr>
<td>Age onset</td>
<td>5.88 ± 2.33</td>
<td>7.18 ± 2.68</td>
</tr>
<tr>
<td>Duration</td>
<td>3.49 ± 2.35</td>
<td>2.59 ± 1.83</td>
</tr>
<tr>
<td>CY-BOCS ex, c ± SD</td>
<td>6.75 ± 5.75</td>
<td>25.09 ± 5.45</td>
</tr>
<tr>
<td>CY-BOCS rem, d ± SD</td>
<td>7.75 ± 7.36</td>
<td>14.09 ± 12.21</td>
</tr>
<tr>
<td>Age onset</td>
<td>7.13 ± 2.18</td>
<td>6.82 ± 2.93</td>
</tr>
<tr>
<td>Duration</td>
<td>2.71 ± 2.17</td>
<td>3.01 ± 2.35</td>
</tr>
<tr>
<td>Combined ex, e ± SD</td>
<td>14.45 ± 5.62</td>
<td>24.59 ± 4.75</td>
</tr>
<tr>
<td>Combined rem, f ± SD</td>
<td>3.55 ± 3.32</td>
<td>7.23 ± 6.31</td>
</tr>
<tr>
<td>Medications, ex/rem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>5/4</td>
<td>10/9</td>
</tr>
<tr>
<td>Antibiotics</td>
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<td>2/4</td>
</tr>
<tr>
<td>Other</td>
<td>9/9</td>
<td>11/10</td>
</tr>
</tbody>
</table>

Data represent patients experiencing an exacerbation–remission cycle of their tic symptoms only, “tic only,” and those experiencing an exacerbation and/or remission cycle of both OCD and tic symptoms, “ODC/tics.”

TABLE 2. SERUM CYTOKINE LEVELS DURING TIC SYMPTOM EXACERBATION AND REMISSION

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Exacerbation</th>
<th>Remission</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>0.07 (0.00–1.59)</td>
<td>0.05 (0.01–1.67)</td>
<td>−0.04</td>
<td>0.97</td>
</tr>
<tr>
<td>IL-5</td>
<td>0.79 (0.00–0.58)</td>
<td>0.59 (0.03–1.88)</td>
<td>−0.05</td>
<td>0.96</td>
</tr>
<tr>
<td>IL-10</td>
<td>2.76 (0.32–3.02)</td>
<td>1.73 (0.00–20.64)</td>
<td>−0.07</td>
<td>0.94</td>
</tr>
<tr>
<td>IL-12p70</td>
<td>28.20 (10.10–1.47)</td>
<td>0.00 (0.08–2.32)</td>
<td>−0.87</td>
<td>0.38</td>
</tr>
<tr>
<td>IL-13</td>
<td>0.81 (0.15–6.76)</td>
<td>0.45 (0.15–7.49)</td>
<td>−0.22</td>
<td>0.83</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>15.53 (0.88–48.75)</td>
<td>12.35 (2.16–51.51)</td>
<td>−1.29</td>
<td>0.20</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.06 (0.00–0.60)</td>
<td>0.03 (0.00–0.34)</td>
<td>−1.96</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

Data represent results of the Wilcoxon sign rank test. Cytokine levels are measured in pg/mL and are expressed as medians and ranges. Levels for IL-2 and GMC-SF were below lowest detectable limit.

Does OCD comorbidity impact the level of serum cytokines during a tic exacerbation–remission cycle?

We also examined whether cytokine levels during periods of tic symptom exacerbation and remission differed in patients experiencing an exacerbation–remission cycle of only their tic symptoms, (tic only), compared with those experiencing an exacerbation–remission cycle of both OCD and tic symptoms (OCD/tics). Of the 19 patients presenting with a diagnosis of comorbid OCD and tics, 11 experienced an exacerbation and subsequent remission of both OCD and tic symptoms (Table 1). There were no significant differences in serum cytokine levels between tic only patients and OCD/tic patients. We also examined differences in patients presenting with a CTD versus those presenting with TS. Again we found no significant differences between these two groups, nor did we find any significant differences associated with attention-deficit/hyperactivity disorder (ADHD) or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) comorbidity.

Does medication status affect cytokine level?

All patients enrolled in this study were receiving some form of medication, either prescribed or over the counter, during periods of tic symptom exacerbation and remission. Sixty-two percent of patients receiving an antipsychotic medication, and 14% were receiving an antibiotic. Ninety-five percent were receiving an over the counter medication during periods of tic symptom exacerbation whereas 91% received similar medications during symptom remission (Table 1). We also examined the effect of medication use on serum cytokine levels during periods of tic exacerbation and remission. During periods of tic symptom exacerbation, median serum cytokine level for TNF-α (U=9.00, p=0.033) and IL-13 (U=4.00, p=0.043) were significantly elevated in patients taking antipsychotics, whereas IL-5 (U=6.5, p=0.035) was significantly elevated in those taking antibiotics (Table 3). During periods of symptom remission, median IL-4 was significantly elevated in those taking antipsyhtics (U=6.00, p=0.047) and antibiotics (U=1.00, p=0.016), whereas IL12p70 was significantly elevated in those taking antibiotics (U=4.00, p=0.037) (Table 4).

Does symptom severity, as measured by the YGTSS and CY-BOCS correlate with cytokine level?

We examined whether there was a correlation between symptom severity, as reflected by the YGTSS Total Severity and CY-BOCS...
activating T-cells, and inducing immunological responses to infection, as a potent regulator of the immunological tool. The pathogenesis of tic disorders, while providing an important diagnostic tool, may suggest an important role for this cytokine in the understanding of tic disorders. In the present study, we sought to examine the relationship between serum cytokine levels and tic symptom severity in patients with a clinical diagnosis of CTD or TS. Seventy-seven percent of patients expressed significantly higher levels of serum cytokines and other immune mediators during infection (Kuhweide et al. 1990; Kim et al. 2006). Like many other cytokines, TNF-α also plays an equally important role in the regulation of the central nervous system (CNS), both physiological and pathological. Recent studies in neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) have highlighted the pathological aspects of this relationship, showing evidence of increased serum TNF-α levels preceding clinical presentations of motor dysfunction (Tolosa et al. 2011). Although the exact mechanism is still unknown, oxidative stress and resultant motor neuron cell death, which are the consequences of neuroinflammation, have been proposed. However, several studies have pointed toward excitotoxicity from TNF-α induced modulation of glutamate signaling as well as GABA and glutamate receptors expression (Lewitus et al. 2014; Olmos and Llado 2014). The actions of TNF-α in ALS may shed light on its role in tic disorders given the comparable clinical observations, including the association of increased TNF-α levels and symptom severity and the involvement of the GABA systems (Jijun et al. 2010; Lerner et al. 2012).

Although there appears to be a significant role for TNF-α in tic disorders, other cytokines such as IL-13 may also be important in understanding the underlying role of the immune system in this disorder. IL-13, which we found to be negatively correlated to tic symptom severity, displays anti-inflammatory properties, and has been shown to regulate immunoglobulin E (IgE) antibody production, which has also been shown to correlate negatively with YGTSS scores (Hoshino et al. 1999; Wynn 2003; Hajoui et al. 2014). The role of IL-13 in tic disorders may be less characterized; however, several studies have found evidence suggesting immune abnormalities in patients with tic disorders, supporting the hypothesis that infection and abnormal immunological responses to infection may be central to the underlying pathological mechanism of tic disorders. In the present study, we sought to examine the relationship between serum cytokine levels and tic symptom severity in patients with a clinical diagnosis of CTD or TS. Seventy-seven percent of patients expressed significantly higher levels of serum cytokines and other immune mediators during infection (Kuhweide et al. 1990; Kim et al. 2006). Like many other cytokines, TNF-α also plays an equally important role in the regulation of the central nervous system (CNS), both physiological and pathological. Recent studies in neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) have highlighted the pathological aspects of this relationship, showing evidence of increased serum TNF-α levels preceding clinical presentations of motor dysfunction (Tolosa et al. 2011). Although the exact mechanism is still unknown, oxidative stress and resultant motor neuron cell death, which are the consequences of neuroinflammation, have been proposed. However, several studies have pointed toward excitotoxicity from TNF-α induced modulation of glutamate signaling as well as GABA and glutamate receptors expression (Lewitus et al. 2014; Olmos and Llado 2014). The actions of TNF-α in ALS may shed light on its role in tic disorders given the comparable clinical observations, including the association of increased TNF-α levels and symptom severity and the involvement of the GABA systems (Jijun et al. 2010; Lerner et al. 2012).

**Table 3. Impact of Medications on Cytokine Expression During Tic Symptom Exacerbation**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Statistic</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-10</th>
<th>IL-12p70</th>
<th>IL-13</th>
<th>IFN-γ</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Yes</td>
<td>6.40</td>
<td>12.23</td>
<td>9.31</td>
<td>8.31</td>
<td>9.17</td>
<td>7.90</td>
<td>10.18</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.00</td>
<td>7.92</td>
<td>8.00</td>
<td>6.00</td>
<td>3.33</td>
<td>8.80</td>
<td>4.80</td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>1.00</td>
<td>26.50</td>
<td>22.00</td>
<td>9.00</td>
<td>4.00</td>
<td>21.00</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.21</td>
<td>0.15</td>
<td>0.65</td>
<td>0.50</td>
<td>0.04*</td>
<td>0.62</td>
<td>0.03*</td>
<td></td>
</tr>
</tbody>
</table>

Total scores, and serum cytokine level. During periods of tic symptom exacerbation, serum levels of IL-13 showed a moderate negative correlation to YGTSS Total Severity scores (r = -0.599, p = 0.018), particularly symptoms of motor tics (r = -0.655, p = 0.008). However, this correlation was not observed during symptom remission. There were no significant correlations observed between serum cytokine levels and CY-BOCS scores.

**Table 4. Impact of Medications on Cytokine Level During Tic Symptom Remission**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Statistic</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-10</th>
<th>IL-12p70</th>
<th>IL-13</th>
<th>IFN-γ</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic Yes</td>
<td>8.90</td>
<td>11.93</td>
<td>10.57</td>
<td>8.58</td>
<td>9.23</td>
<td>8.31</td>
<td>7.62</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4.00</td>
<td>8.67</td>
<td>8.40</td>
<td>8.25</td>
<td>5.33</td>
<td>6.42</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>6.00</td>
<td>31.00</td>
<td>27.00</td>
<td>23.00</td>
<td>10.00</td>
<td>17.50</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.05*</td>
<td>0.27</td>
<td>0.46</td>
<td>0.90</td>
<td>0.20</td>
<td>0.40</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>

Data represent results of the Mann–Whitney U Test. Cytokine levels are measured in pg/mL and are expressed as medians. Levels for IL-2 and GMC-SF were below lowest detectable limit.

IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; GMC-SF, granulocyte macrophage-colony stimulating factor.

*Statistically significant result.
however, its role in immune regulation and its correlation with autoimmune disorders suggest that it may be a promising target along with TNF-α for explaining the mechanism of tic disorders. Moreover, IL-13 and TNF-α have been shown to display bidirectional regulation with IL-13 downregulating the expression of TNF-α and TNF-α potentially downregulating IL-13 (Cosentino et al. 1995; Albanesi et al. 2007). With increasing evidence of a role for immune dysregulation in the pathogenesis of tic disorders, cytokines such as TNF-α and IL-13 may be an important link in understanding the pathological mechanism driving this disorder.

In addition to explaining aspects of disease mechanism, the ability to correlate cytokine levels to disease state and symptom severity may be an important diagnostic asset, particularly in a pediatric setting where significant emphasis must be placed on parental recall because of a lack of biological markers. Although only TNF-α and IL-13 showed significant associations with tic severity in our study, with TNF-α being increased during exacerbations and IL-13 correlating negatively to severity scores, we observed increases in the level of several other cytokines in patients receiving antibiotic/antipsychotic medications. TNF-α and IL-13 levels were increased during tic symptom exacerbation in patients taking antipsychotics, whereas IL-5 was increased in patients taking antibiotics. We also observed increased levels of anti-inflammatory cytokine IL-4 in patients on antibiotic and/or antipsychotic medications during tic symptom remission.

These observations suggest that cytokine levels may be impacted by medication status, as antipsychotics and antibiotics have been shown to have immune modulating effects, with studies showing increased IL-4 levels following antipsychotic treatment and decreased TNF-α levels with macrolides (Morikawa et al. 2002; Himmerich et al. 2011; Al-Amin et al. 2013). The impact of antipsychotic drugs on the immune system and cytokine expression may highlight a potentially important aspect of their therapeutic mechanism. With increasing evidence of the immune irregularities, including cytokine disruption, in neurological disorders such as tic disorders, the ability of antipsychotics to modulate cytokine expression and potentially normalize the immune system may be, at least in part, key to their therapeutic efficacy (Al-Amin et al. 2013). In the case of antibiotics, their impact on the immune system has been well documented and may be indirectly related to their mechanism of action (Morikawa et al. 2002; Williams et al. 2005). It is important to remember, however, that these interactions may not be therapeutically beneficial, as seen from the more deleterious side effects attributable to antipsychotic and antibiotic use. Particularly in the case of antibiotics, the inability of these agents to differentiate between resident gastrointestinal microbial constituents, known to participate in immune regulation, and invading pathogenic species, can result in modulation of the immune system, with little therapeutic value (Jakobsson et al. 2010).

It is also noteworthy to remember that these observations may not be causative, as patients experiencing a more severe symptom exacerbation are more likely to require pharmacological intervention. Conversely, the association with increased cytokine levels during antibiotic or antipsychotic treatment may be coincidental, with increases in proinflammatory cytokines such as TNF-α, and anti-inflammatory cytokines IL-4 correlating to changes in tic severity. Regardless, this association is one that requires further investigation.

**Conclusion**

Despite our findings, some disagreement still exists among studies investigating immune irregularities, particularly cytokine levels, within the tic population. Some groups, for example, have noted no correlations between TNF-α level and tic disorder (Gabbay et al. 2009), whereas others have found reduced levels of TNF-α level in patients with tic disorders (Matz et al. 2012). These discrepancies may be the result of methodological differences in study design, including inherent differences within the patient populations chosen for each study. Although in most studies patients were enrolled based on a diagnosis of a tic disorder, the presence of comorbid disorders and differences in criteria for defining flared versus remitted states may lead to differences in study outcomes. Psychotropic and antibiotic medications pose another confounding factor, although other studies reported no significant effects of medications, despite both of these medication categories having been shown to modulate cytokine level (Obregon et al. 2012). However, the mounting evidence supports that cytokine measurement may be an important clinical tool in determining susceptibility, diagnosis, symptom monitoring, and, perhaps, therapeutic intervention, and more work is necessary to determine the exact role of cytokines in tic etiology.

**Limitations**

Although this study supports the hypothesis of an infection and/or immune-mediated etiology of tic disorders, there were several limitations that further necessitate the need for larger systematic analyses of immune function in tic disorders. These included a limited sample size, the presence of comorbid disorders within our cohort, and a significant percentage of patients on psychotropic and antibiotic medications, which are known to have immunological effects.

**Clinical Significance**

Despite the limitations, this study supports previous findings by other groups citing cytokine dysregulation in patients with tic disorders. Furthermore, it identifies TNF-α as an important target for investigating cytokine dysregulation and immunological abnormalities within the tic population. Understanding the role of immune abnormalities in the pathogenesis of tic disorders may not only aid in our understanding the mechanism driving this disorder but may also provide biological markers that can be utilized clinically in diagnosis, the determination of symptom severity, and therapeutic intervention.

**Disclosures**

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