



PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection

A review of clinical presentation, diagnosis, and treatment.

ABSTRACT: If undiagnosed and untreated, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) can suddenly and drastically disrupt the lives of previously healthy children and their families. The key to prompt diagnosis of PANDAS and its appropriate treatment is provider awareness that streptococcal infection may present with neuropsychiatric symptoms. The authors discuss the signs and symptoms that characterize PANDAS, as well as its presumed pathogenesis, and illustrate, through a composite case history, a symptom presentation, diagnostic journey, treatment course, and recovery that is representative of many PANDAS cases.

Keywords: group A streptococcus, obsessive–compulsive disorder, PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, strep throat, tics, Tourette syndrome

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) was identified in 1998 as a syndrome that described the sudden and dramatic pediatric onset of symptoms that mimic obsessive–compulsive disorder (OCD) or tic disorders characteristic of Tourette syndrome following infection with group A streptococcus (GAS).¹ In 2012, PANDAS was retrospectively classified as a subset of a new,

broader clinical syndrome, pediatric acute-onset neuropsychiatric syndrome (PANS). PANS is similar to PANDAS in clinical presentation, but unlike PANDAS, which by definition is etiologically rooted in a documented GAS infection, PANS has no single, specific etiology.² In PANDAS, it's hypothesized that the GAS infection triggers an autoimmune response that targets neurons in the brain's basal ganglia, thereby causing healthy children with no

prior history of neurologic disorders to experience a rapid onset of neuropsychiatric symptoms.³

ASSOCIATED RISK FACTORS

In addition to GAS infection, some data suggest that PANDAS may be associated with maternal autoimmune disease.⁴ Sex and age may also play a role in susceptibility to PANDAS. In the initial report describing working diagnostic criteria, the overall ratio of boys to girls with PANDAS was 2.6 to 1, and among children under eight years of age, the ratio of boys to girls was 4.7 to 1.¹ Although 75% of those diagnosed with PANDAS were male, the reason for increased vulnerability among boys was not determined. The reduced frequency of PANDAS during the postpubertal years may be due to a natural decline in cross-reactive autoimmunity in adolescence and to the fact that incidence of GAS infections declines substantially at age 12 when most children have developed antibodies against all GAS strains.¹

PREVALENCE AMONG CHILDREN WITH OCD OR TIC DISORDERS

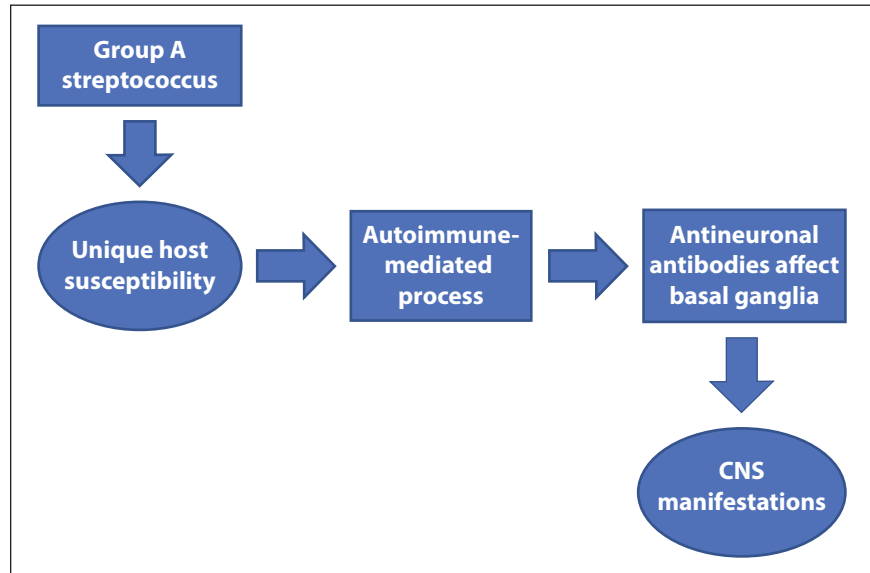
In the United States, approximately 500,000 children (one in 200) have been diagnosed with OCD⁵ and roughly 138,000 (one in 360) have been diagnosed with Tourette syndrome.⁶ According to the National Institutes of Health (NIH) Genetic and Rare Diseases Information Center (GARD), the prevalence of PANDAS among these children is unknown, though some researchers suggest that PANDAS may account for more than 10%.^{7,8}

PANDAS PATHOPHYSIOLOGY

The basal ganglia are a cluster of neurons that lie deep within the cerebral hemisphere. Since they process and control motor, limbic, sensory, and associative information through direct and indirect pathways, the basal ganglia are essential for healthy brain function, movement, and behavior.⁹

As far back as 1998, Swedo and colleagues suggested that the etiology of PANDAS may parallel that of Sydenham chorea or rheumatic fever, in which autoantibodies attack neuronal cells in the basal ganglia causing neuropsychiatric and movement disorders.¹ This hypothesis is consistent with subsequent animal studies in which researchers produced symptoms resembling Sydenham chorea and PANDAS in rodents to determine the pathological

Figure 1. Possible PANDAS Pathogenesis



In a small number of children, infection with Group A streptococcus (sometimes asymptomatic) seems to trigger an autoimmune process in which antineuronal antibodies attack host cells rather than the streptococcus itself. These antibodies affect pathways in the basal ganglia, resulting in symptoms of obsessive-compulsive disorder, tics, or other central nervous system (CNS) changes.

basis of the symptoms. Based on such studies, it's theorized that in children who develop PANDAS, the streptococcal bacteria attempt to hide from the immune system through a process called molecular mimicry in which the bacteria mimic the molecular structure of the host's tissue, igniting an autoimmune reaction that triggers the production of antineuronal antibodies, which attack host cells rather than the intended streptococcal bacteria, disturbing neurotransmitters (principally dopamine), disrupting basal ganglia pathways, and ultimately triggering OCD and tic disorders (see Figure 1).³

CLINICAL PRESENTATION

Children with PANDAS have a sudden onset or worsening of OCD symptoms or tics that occurs either simultaneously with a GAS infection or shortly thereafter, followed by a relapsing-remitting episodic course, which may be accompanied by a variety of other symptoms and comorbidities.^{1,10} (See *Common Accompanying Symptoms and Comorbidities in PANDAS*.^{1,10}) Children may or may not present with pharyngitis or other typical strep throat symptoms.¹ Onset of OCD symptoms in PANDAS is atypical in that it is sudden and dramatic. Whereas OCD usually develops over months or years, behavioral changes in children who develop PANDAS can

often be pinpointed by the child's parents to a particular day.¹¹ In a three-year prospective study of 12 school-age children with new-onset PANDAS, all symptoms related to OCD, anxiety, and tics were resolved, on average, 14 days after appropriate antibiotic treatment of the GAS infection was initiated.¹¹ In this study, in every case in which PANDAS behavior recurred, this behavior was associated with a new GAS infection requiring further antibiotic treatment.¹¹ This finding is consistent with the initial PANDAS cohort described by Swedo and colleagues, in which 77% of 144 symptom exacerbations were associated with confirmed new GAS infection or a known repeat exposure.¹ For this reason, long-term streptococcal prophylaxis may be prescribed for children with very severe symptoms to reduce the risk of long-term neuropsychiatric sequelae.¹²

DIAGNOSING PANDAS

There are five specific diagnostic criteria for PANDAS (see *PANDAS Diagnostic Criteria*^{13,14}). Most of these can be determined through nursing assessment, a thorough patient history, and physical examination.

Testing to confirm a temporal association with a GAS infection may include a throat or perianal culture, which would identify current streptococcal infection or carriage, or a blood test for antibodies that would verify a recent streptococcal infection, such as antistreptolysin O (ASO) antibody for suspected infection within the past one to four weeks, or antideoxyribonuclease B (Anti-DNase B) antibody for suspected infection within the past six to eight weeks.¹⁴

Common Accompanying Symptoms and Comorbidities in PANDAS^{1, 10}

- Severe separation anxiety and other anxiety disorders
- Motor hyperactivity
- Abnormal movements
- Restlessness
- Sleep disturbances
- Sensory irregularities
- Hallucinations
- Urinary frequency and urgency
- Difficulty concentrating
- Mood swings
- Irritability
- Major depression
- Developmental regression (bed-wetting, tantrums, baby talk)
- Loss of academic abilities (predominantly math and handwriting)

Unfortunately, many health care providers are unfamiliar with PANDAS or have no experience diagnosing or treating the condition. Parents often see multiple providers before receiving an accurate diagnosis. Once diagnosed, appropriate treatment may involve a number of specialists, including a pediatrician, neurologist, rheumatologist, infectious disease specialist, immunologist, psychologist, psychiatrist, or a PANDAS specialist.

Some children develop PANDAS following asymptomatic GAS infections.

TREATMENT AND PROGNOSIS

Depending on the child's presentation, PANDAS intervention often involves a three-pronged approach¹⁵:

- antimicrobial therapy to resolve the GAS infection
- psychoactive medication and behavioral therapy to relieve neuropsychiatric symptoms
- nonsteroidal antiinflammatory drugs (NSAIDs) or steroids and immunomodulatory therapy (plasmapheresis) to address immune system dysfunction.

Whereas one patient with PANDAS may require only antimicrobial therapy, another may also require antidepressants, NSAIDs, steroids, plasmapheresis, or all of the above.

Most children with PANDAS can recover completely with early antibiotic treatment, though some, despite early treatment, develop persistent neuropsychiatric symptoms requiring long-term treatment that includes antimicrobial prophylaxis.^{12,16} It is essential to prevent reinfection, as neuropsychiatric symptoms can worsen with subsequent streptococcal infections.¹⁶ Patients with recurrent GAS-associated exacerbations may require prophylactic antibiotic treatment beyond age 18, depending on the frequency and severity of the exacerbations and the risk of repeated GAS exposure.¹² Untreated or unrecognized PANDAS increases the risk of having OCD and tic disorders into adulthood.

A COMPOSITE CASE HISTORY

After returning from a weeklong summer camp, eight-year-old Elizabeth started behaving in a way that troubled her mother. (This case is a composite based on our experience.) During the days, Elizabeth seemed withdrawn; at night, she frequently woke and asked to sleep with her mother, who found the behavior alarming and worried that her daughter may have experienced sexual abuse at

camp. Although Elizabeth's mother asked her daughter many questions, she was able to determine only that Elizabeth had been fatigued at camp. Elizabeth's separation anxiety soon passed, and she seemed to be "back to normal."

A few weeks later, however, Elizabeth began to withdraw from activities she had formerly enjoyed, such as going to dance class and bike riding with friends. Eventually, she reached a point where she expressed a wish to die. She told her mother she was afraid she was going to hurt herself and pleaded with her parents to let her sleep with them every night. Elizabeth also began to engage in repetitive behaviors, such as watching the same video for hours, and to display tic-like movements. Shortly thereafter, Elizabeth's mother received a call from Elizabeth's teacher that Elizabeth had become notably inattentive, and that both her handwriting and mathematical ability had sharply declined.

A questionable diagnosis. Elizabeth's parents arranged for their daughter to see a psychologist, who diagnosed Elizabeth with OCD and recommended treatment with antipsychotic medications and behavioral therapy. Skeptical of the diagnosis and feeling hopeless, Elizabeth's mother mentioned her concerns to a friend who was a pediatric nurse.

PANDAS Diagnostic Criteria^{13, 14}

- Presence of obsessive-compulsive disorder, tics, or both
- Prepubertal emergence in children at least three years of age
- Abrupt onset with a relapsing-remitting course
- Temporal association with group A streptococcus infection
- Neurologic abnormalities

it, this pediatrician was aware of the syndrome and ordered the ASO and Anti-DNase B titers to determine whether Elizabeth had a prior GAS infection and, if so, the probable time at which it had occurred.

Elizabeth's mother took her daughter for the tests, but was further frustrated by the fact that the laboratory personnel were unfamiliar with PANDAS and didn't know how to code it for their billing. Three days later, Elizabeth's pediatrician reported that Elizabeth's titers demonstrated evidence of a prior streptococcal infection despite having no pharyngeal symptoms.

Treatment considerations. Although antipsychotics are an appropriate treatment for OCD and

Behavioral changes in children who develop PANDAS can often be pinpointed by the child's parents to a particular day.

A potential explanation. The nurse suggested that Elizabeth's symptoms may be explained by PANDAS, a rare neuropsychiatric complication of a GAS infection. Elizabeth's mother remembered that shortly before the change in Elizabeth's behavior, Elizabeth's younger sister had been diagnosed with strep throat. Although Elizabeth's mother was intrigued by the possibility that Elizabeth's symptoms might be explained by PANDAS, she thought it was unlikely since Elizabeth, who had a tonsillectomy at age five, did not develop a sore throat during the time her sister was ill. However, when the nurse told her that some children develop PANDAS following asymptomatic GAS infections,^{1, 12} Elizabeth's mother called her daughter's pediatrician, explained Elizabeth's behavioral changes and her suspicion that they may signify PANDAS, and asked if Elizabeth could be tested for a streptococcal infection.

Testing and results. Although PANDAS is relatively rare and many providers have never heard of

are often prescribed as an adjunct treatment for PANDAS, the majority of children with recent-onset PANDAS experience a reduction in neuropsychiatric symptoms within weeks of receiving antimicrobial treatment.¹² Early in the disease process, Elizabeth's psychologist had prescribed antipsychotics, which Elizabeth never took because her mother was skeptical of the OCD diagnosis. She felt that Elizabeth's "overnight" behavioral changes warranted further medical investigation. Had Elizabeth's mother not investigated her daughter's symptoms further, it would have led to misdiagnosis, treatment failure, and lifelong complications.

Therapy varies according to the child's specific needs, with some children experiencing dramatic improvement with antibiotic and immunomodulatory treatments and others requiring supportive and behavioral therapies or psychoactive medications.¹⁷ While psychoactive medications may reduce the neuropsychiatric symptoms, they have no effect on

the underlying GAS infection, which PANDAS treatment must address.

PANDAS management and outcome. With the laboratory results in hand, the pediatrician prescribed amoxicillin for Elizabeth and referred her

agement. When discussing potential complications of streptococcal infections, it is good nursing practice to inform families of the signs and symptoms of PANDAS, though this complication is considered rare.

Taking a patient history is important in uncovering PANDAS, as it may reveal a recent streptococcal infection that could account for a sudden change in behavior.

to a pediatric neurologist, who rejected the possibility of PANDAS, suggesting that Elizabeth's long-term treatment should consist of standard OCD therapies, not antibiotics. Ultimately, Elizabeth met with a pediatric infectious disease specialist who firmly supported her diagnosis of PANDAS. The specialist recommended that Elizabeth continue to take amoxicillin for one year. The family subsequently sought out a physician who specialized in PANDAS. The PANDAS specialist and the family were very pleased that, after taking amoxicillin for only a few days, Elizabeth experienced a significant reduction in neuropsychiatric symptoms. The PANDAS specialist also felt that, so long as her symptoms remained at bay, Elizabeth would need no other treatment modalities.

Although other patients with PANDAS may require psychiatric, antiinflammatory, or immunomodulatory therapies in addition to antibiotics, Elizabeth completed her yearlong antibiotic therapy shortly after her ninth birthday without any recurrence of neuropsychiatric symptoms. Following an accurate diagnosis and appropriate pharmacological treatment, Elizabeth experienced a complete recovery.

NURSING IMPLICATIONS

Nurses play an important role in establishing a rapport with patients and gaining their trust. While taking a patient's history, nurses can help patients and their family members identify potential signs and symptoms of PANDAS and feel comfortable disclosing psychiatric symptoms. While taking a patient history is always a vital part of the nursing process, it may be particularly important in uncovering PANDAS, as it may reveal a recent streptococcal exposure or infection that could account for a sudden change in behavior. Nurses' knowledge of PANDAS can promote proper testing, prompt diagnosis, and appropriate patient and family teaching regarding disease progression and man-

TEACHING POINTS FOR PARENTS AND PATIENTS

Nurses should teach parents about the following strep throat prevention strategies:

- sterilization or replacement of toothbrushes two to three days after antibiotic initiation and upon antibiotic completion
- no sharing of food or drinks
- good hygiene
- avoiding known streptococcal exposures
- testing for streptococcal carriers in family members, if indicated

In the event of a known family streptococcal infection, parents should be instructed to report any new behaviors in any child between the ages of three and puberty, especially if the behaviors do not quickly resolve. If PANDAS is diagnosed, the regimen may involve antibiotics, antipsychotics, antiinflammatory drugs, and immunomodulatory therapies, and strict medication management is critical.

Patient education must include the need to

- take antibiotics as prescribed.
- take probiotics to prevent secondary infections associated with long-term antibiotic use.
- avoid abrupt withdrawal of antipsychotic medications.
- take antiinflammatory medications with meals and a full glass of water.
- keep follow-up appointments, as repeat laboratory tests may be necessary to ensure that the streptococcal infection has resolved.

Urge parents to inquire about school accommodations (individualized education programs, or IEPs) as appropriate and to seek behavioral and mental health care for their child as needed. Inform them of PANDAS research, resources, and services, such as those listed on the PANDAS webpage of the NIH GARD (https://rarediseases.info.nih.gov/diseases/7312/pediatric-autoimmune-neuropsychiatric-disorders-associated-with-streptococcus-infections#ref_11819), the Family Resources webpage of the

PANDAS Physicians Network (www.pandasppn.org/parent-information), and the National Partners webpage of the National Institute of Mental Health (www.nimh.nih.gov/outreach/partnership-program/national-partners.shtml).

Encourage parents to share this information with other family members, caregivers, teachers, and school nurses. Such open communication is crucial to both recovery and prevention of PANDAS recurrence, because understanding this disorder enables everyone concerned to better address the needs of children who have the condition and to realize events that should prompt parental notification, such as behavioral changes, academic decline, or possible streptococcal exposure. ▼

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