

A photograph showing a woman with long brown hair, wearing a yellow t-shirt and jeans, smiling as she stands behind a young boy. The boy is wearing a blue and green plaid shirt and is looking towards a doctor. The doctor, seen from the back, has voluminous curly brown hair and is wearing blue scrubs. The doctor's hands are gently holding the boy's chin, examining his throat. The background consists of light-colored vertical blinds.

Treating PANDAS

By Rodney P. Lusk, MD

Current treatments for PANDAS have been shown to be relatively effective, but could surgical treatments such as tonsillectomy and adenoidectomy offer more effective results?

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC disorders associated with streptococcal infections (PANDAS) is a relatively new diagnosis thought to be associated with one in 2,000 children with strep infections. It was originally based on 50 cases reported in 1998 in which 77 percent of children had a preceding group A streptococcal (GAS) infection.¹ In this initial report, PANDAS is characterized with the acute onset of obsessive compulsive disorder (OCD)-type symptoms that include aggressive behavior, compulsive handwashing, compulsive cleaning and frequent checking of locks on doors or windows. Muscular tics are also characteristic, with audible tics noted in some children. Other symptoms that are variably expressed include urinary urgency, hyperactivity, impulsivity, deterioration in handwriting, separation anxiety and decline in school performance. Handwriting deterioration appears to be an early hallmark of the disorder. Anorexia is another psychiatric illness that can be comorbid in PANDAS and has less to do with body image and more with the sensation of texture, taste of food or fear of choking.

A closely related disorder is Sydenham chorea, which is associated with rheumatic fever. PANDAS, however, is not associated with any symptoms of rheumatic fever — specifically fever, arthritis or carditis. And, PANDAS is not considered a “milder form” of Sydenham chorea. Recently, the term pediatric acute-onset neuropsychiatric syndrome (PANS) has been used to describe the acute onset of neuropsychiatric conditions similar to PANDAS but with a broader range of potential etiologies. A key diagnostic feature of PANS is the acute dramatic onset of an obsessive compulsive disorder or severely restricted food intake. Sensory issues are thought to be more common in PANS and can manifest themselves as sensitivity to light, food texture (anorexia), olfactory hallucinations, tactile issues with clothing, shoes and socks, and frequent urge to urinate but without the physiological need. Another classification of similar disorder is called childhood acute neuropsychiatric symptoms (CANS). Each classification has its advocates, and there is certainly significant overlap in symptoms. This article will not focus further on this debate other than to say that there is significant overlap in the symptoms and underlying etiology. Current treatment protocols are similar for all three.

Pathophysiology of PANDAS

It is interesting to note that GAS is not the only infectious agent thought to result in a neurological disease. Mycoplasma pneumonia is implicated in Tourette syndrome,² with 59 percent of Tourette syndrome patients having elevated antibody titers. Lyme disease is also thought to be a trigger for PANS, with

OCD symptoms being prominent. And, there is a large body of knowledge indicating that *Toxoplasma gondii*, from infected cat feces, may be associated with schizophrenia.³ The mechanisms of these infectious processes with the neurological system is likely varied, but as we learn more, a common immunological pathway may be implicated.

The underlying pathophysiology of PANDAS is important when considering possible treatment modalities. The pathophysiology of PANDAS is thought to be based on molecular mimicry of GAS antibodies that target brain proteins leading to the clinical manifestations of PANDAS. GAS antibodies may directly stimulate or block receptors of the basal ganglia (a region of the base of the brain that is responsible for involuntary movements), or affect immune complexes that lead to inflammation of the basal ganglia. PANDAS children have also been found to have significantly higher levels of antibodies that trigger calcium-calmodulin-dependent protein kinase II (CaM kinase II) production. These cross-reactive antibodies may interfere with neuronal signals by increasing CaM kinase II production in the basal ganglia, eventually leading to dopamine dysregulation. This dysregulation may subsequently lead to the clinical presentation characteristic of PANDAS. Animal models are being developed to further define the underlying pathophysiology of this disorder.⁴

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PANDAS Diagnosis

Definitive laboratory tests for the diagnosis of PANDAS are lacking; however, certain tests are useful. Identifying strep through cultures is important. As many as 85 percent of patients are positive with one serology test, and 95 percent are positive when multiple tests such as ASO and anti-DNase B titers are used. These two tests are clinically useful and routinely obtained.

Antibodies to human brain enolase (AE), neural tissue and anti-streptococcal antibodies have been shown to be significantly elevated in patients with the early onset of psychiatric disorders. The use of neuroimaging (MRI) has been used, but it is nonspecific. An MRI most commonly shows inflammation and enlargement of the basal ganglion. With progressive decrease in antineuronal antibody titers, the inflammation in the basal ganglion has been shown to progressively decrease.

SINCE STREPTOCOCCAL INFECTIONS ARE ASSOCIATED WITH PANDAS, PROMPT ANTIBIOTIC INTERVENTION REMAINS THE PRIMARY COURSE OF MEDICAL MANAGEMENT, ESPECIALLY IN THE ACUTE PHASE.

Current PANDAS Treatment

Since streptococcal infections are associated with PANDAS, prompt antibiotic intervention remains the primary course of medical management, especially in the acute phase. The primary antibiotics include penicillins (amoxicillin or amoxicillin plus clavulanic acid) or cephalosporins. Other forms of medical management include sporadic reports of successful management with steroids and nonsteroidal anti-inflammatory drugs, which are thought to reduce inflammation of neurological tissue, especially in the basal ganglion. The effects of these mostly appear in case reports, and no general conclusions regarding their effectiveness can be provided.

Two other forms of management, immunotherapy and therapeutic plasma exchange (TPE), have been shown to be somewhat encouraging in small case series. Immunotherapy is based on providing a large number of intravenous immune globulin (IVIG) antibodies pooled from adult blood donors. It is thought that providing a large number of antibodies against bacteria and viruses will result in a greater ability to fight the infection.

However, this treatment is not without significant side effects, which include chills, low-grade fever and headache, and rare serious side effects such as difficulty breathing, chest pain, seizures and severe anaphylactic reactions.

TPE is a process by which whole blood is removed from the patient, the plasma is removed from the blood, and then the red blood cells are returned to the patient. TPE is thought to exert benefits by removing autoantibodies and antigen-antibody complexes, which potentially reduces the inflammation. The method seems to be the direct opposite of immunotherapy. The treatment is often provided in an inpatient setting, and requires either a central or femoral catheter. It is also associated with adverse effects that are frequent and can be serious.

While both immunotherapy and TPE have been shown to be effective, they are expensive and require hospitalization. Therefore, it would be advantageous if less expensive therapies with fewer possible adverse effects could be found.

Treating PANDAS with Tonsillectomy and Adenoidectomy

Because of the presumed infectiousness of strep, it would seem logical to remove tissue that is a likely source of strep infections, namely the tonsils and adenoids, as a possible PANDAS treatment. However, reports in the literature have been mixed. Early case reports were encouraging, showing improvement and, in some cases, resolution of symptoms. These were all case or small series reports, so it is difficult to know the true role of tonsillectomy and adenoidectomy.

Recently, a study of 114 patients with PANDAS⁵ was conducted to determine whether tonsillectomy and/or adenoidectomy might improve a child's neuropsychiatric course. Patients were divided into two groups: those who had surgery and those who didn't. The researchers found that, because ASO titers (a blood test to measure antibodies against streptolysin O) were not different between the two groups, tonsillectomy and/or adenoidectomy does not prevent PANDAS. They also found that surgery did not result in reduced OCD or tic severity compared with the non-surgery group. In addition, the researchers noted that the symptoms of PANDAS were not different between the two groups. There are, however, problems with this study. First, it had only 20 patients who had previous surgery and subsequently developed PANDAS. Second, tonsillectomy and adenoidectomy were lumped together. This is a problem because both tissues need to be surgically addressed. The researchers acknowledge shortcomings in their study. The patients who had

tonsillectomies and/or adenoidectomies had the procedure prior to onset of their neuropsychiatric disorders. None of the patients had their procedure during or shortly after the acute onset of their symptoms. Further, the researchers acknowledged that: “All of our subjects had existing OCD and/or tics at study entry. If a subset of youth did have OCD/tic remission after the surgical procedure, our study would not have detected those.” Therefore, the question remains: Does tonsillectomy and/or adenoidectomy have a role in the treatment of PANDAS during the first few months or years of the onset of neuropsychiatric symptoms?

Similarly, a multi-institutional study in Italy⁶ showed that tonsillectomy had no effect on the symptomatology, progression, streptococcal and neuronal antibody titers, or the clinical severity of neuropsychiatric symptoms in children with PANDAS. The researchers concluded that the clinical progression, antibody production and neuropsychiatric symptom severity did not differ with surgical intervention.

Contrary to these results is unpublished data (with a manuscript in review) that shows tonsillectomy and adenoidectomy in children with symptoms of PANDAS. We⁸ examined 12 children with PANDAS/PANS who underwent tonsillectomy and adenoidectomy (one out of the 12 had adenoidectomy alone) during a relatively acute phase of their disease. The majority of parents kept a daily symptoms diary before and after surgical intervention. There was significant improvement in symptoms (tics, OCD, anxiety, regressive behavior) in nine of the 12 children who had surgery. Of the nine who were improved, three reported excellent results, were symptom-free and off all medications. The remaining six were markedly improved but still required intermittent antibiotics during upper respiratory tract infections. The three who did not improve were treated with IVIG. One markedly improved and is symptom-free, another is improved but has relapses and the third continues with symptoms and has ongoing IVIG treatments with ongoing symptoms.

We⁸ concluded that tonsillectomy and adenoidectomy appear to have remarkable improvement (resolution) in some children, improvement with intermittent relapses in others and no significant improvement in about a quarter of the patients. The cause of the variable responses is unclear, but it could be secondary to genetic predisposition or duration of symptoms. Admittedly, these numbers are very small. But as a pilot study, the results indicate that tonsillectomy and adenoidectomy in the relatively acute phase of disease warrant further study. At this time, however, we would not recommend routine tonsillectomy and adenoidectomy in children with PANDAS/PANS.

These results are supported by other reports in the literature. One multi-institutional study⁷ compared nine patients who were treated with tonsillectomy with 10 patients treated with antibiotics. Four of the nine patients had complete resolution of their symptoms after tonsillectomy. The researchers concluded that PANDAS patients who did not respond to antibiotics may have significant benefit from tonsillectomy. There are several other case reports showing resolution of symptoms after tonsillectomy.⁹

If antibody complexes indeed cause inflammation of neural tissue, it would seem that the greater intensity and duration of inflammation, the greater the damage to the neural tissue. This, in turn, may be associated with less responsiveness to any therapeutic intervention. As such, it's possible that tonsillectomy and adenoidectomy are less effective in children with longer duration of symptoms.

Better Studies Are Needed

Investigations to date of successfully treating and resolving PANDAS are woefully inadequate of good prospective data that take into account accurate diagnosis and duration of symptoms. This important data can be gathered only through routine, even daily, assessment of patient symptoms prior to and after any intervention, either medical or surgical. And, adequate numbers for investigation can only be accomplished through a multi-institutional study with data acquired through a central database repository. It is hoped that continued and more accurate and thorough research will find better treatments for this puzzling disorder. ■

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