

PANDAS: An Immune-Mediated Mental Illness

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PANDAS is an acronym for pediatric autoimmune neuropsychiatric disorders associated with streptococcus infections. It refers to a subset of children with obsessive-compulsive disorder (OCD) and/or a tic disorder who have presenting or worsening of symptoms following an infection with streptococcal bacteria.¹ The symptoms of PANDAS are not caused directly by the infection itself but rather by the body's abnormal immune response. The exact nature of the obsessions and compulsions can vary from child to child. Clinical cases of PANDAS are not readily identified in the medical community, nor is universal treatment agreed on. PANDAS is a novel syndrome, but the concept of an infectious agent causing neurologic and behavioral or emotional symptoms is not entirely new. Sydenham chorea and Lyme disease are 2 conditions that follow a similar pattern.

Diagnosing PANDAS

Criteria for diagnosis of PANDAS were established by Swedo and colleagues in a 1998 landmark article.² They listed the following 5 classic criteria: (1) presence of OCD and/or tic disorder, (2) pediatric



onset with symptoms at first onset between age 3 years and the beginning of puberty, (3) episodic nature of symptom course, (4) temporal relationship with group A beta β -hemolytic streptococcus infection, and (5) neurologic abnormalities during symptom exacerbation.

These children classically have a sudden onset of symptoms, including verbal and motor tics or chorea, obsessions

and compulsions, and emotional lability with inattentiveness, along with a recent history of streptococcal infection. History of symptom onset can be difficult to elicit because not all cases of streptococcal infections are symptomatic.³ In 1998, Swedo et al² identified early cases that fit the classic description. However, children may not always have the classic

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Susceptibility to Infections: How emotional, physical, and cellular factors contribute to immune response

EMILY CHAN, ND

The internal environment of the body highly affects susceptibility to infection. How can one person develop influenza, while a coworker in the next cubicle remains healthy, when both are exposed to the same office conditions? To reduce the likelihood of succumbing to infectious disease, it is important to understand the factors that contribute to infection and to promote the factors that support increased resistance to infection.

History of the Germ Theory

In the late 1800s, Louis Pasteur was credited with developing the germ theory, a hypothesis that proposes that microorganisms are responsible for the development of infectious diseases. Similarly, during the same period, Robert Koch proposed the theory of contagionism, which argues that disease is transmitted from person to person through inoculation, touch, proximity, and indirect transmission.¹ Primarily due to political and economic reasons of the times, the proposals by Koch for quarantine, dis-

infection, and boiling of water to prevent cholera were not well received because of the inconveniences that isolation had on manufacturing, trading, and exporting.¹ Despite the controversy he was met with, the germ theory has become a predominant cornerstone of modern medicine.

In a futile attempt to falsify the now-dominant germ theory, Max von Pettenkofer, a highly respected public health figure, swallowed the bacteria that allegedly caused cholera, proposing that

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representation, as demonstrated in the case study reviewed herein.

Symptoms may appear clinically as complaints of adventitious movements and fine motor function loss such as dysgraphia, as repetitive behaviors (eg, blinking or oral motor movements), or, as reported in the recent media, a child who began sneezing several thousand times per day. Other less frequent presenting OCD complaints include anorexia nervosa, specific phobias, compulsive hand washing, rituals such as opening and closing of doors, and abnormal bedtime routines.⁴

The streptococcal infection itself is not thought to be responsible for the symptoms of PANDAS. Rather, the etiopathogenesis is the body's abnormal reaction to the infection in a susceptible host. Results of related research suggest that antibodies from an infection may signal neuronal cells, triggering behavioral and movement disorders.⁵ In children with PANDAS, the streptococcal antigens penetrate the blood-brain barrier, and the immune reactions cross-react with neural cell tissue (antibrain and antibasal ganglia) that is involved in thought, movement, and emotion.⁶ This is similar to the molecular mimicry that occurs in glomerular nephritis and in rheumatic fever. Researchers have long known that OCD can be triggered by damage to the basal ganglia.⁷ In addition to the basal ganglia, specific regions in the brain that are associated with the symptoms of PANDAS are believed by Giedd and colleagues⁸ to be located in the caudate, putamen, and globus pallidus. Their research identified that these regions were all larger in a PANDAS group than in a comparison group. Just as rheumatic fever does not occur in all children who experience a streptococcal infection, neither will PANDAS. What appears to occur is diagramed as follows: streptococcus infection → a genetically susceptible host → abnormal immune response → PANDAS (OCD and/or tics).

PANDAS has been associated with other infectious agents such as *Mycoplasma* and *Borrelia* species, as well as viruses. This condition is referred to as PITANDS (pediatric infection-triggered autoimmune neuropsychiatric disorders) when the infectious trigger is not streptococcus. For the sake of simplicity, this article will focus only on streptococcus infections.

Testing

Because PANDAS is identified by clinical diagnosis, laboratory testing aids in confirming clinical judgment. Several tests are helpful in validating the clinical picture. I will discuss only the more commonly used laboratory tests and procedures, but further research on this topic will present a vast selection of less frequently used markers to help support evaluation and treatment decisions. Laboratory investigation should begin with a throat culture, especially in cases of recent symptom onset. This is often done incorrectly, especially in children. It is imperative that the sample should be collected properly from the back of the throat and around the tonsils. Next, a venous blood sample may be obtained for evaluation of antistreptolysin O (ASO) and antideoxyribonuclease serologic titers. Both of these markers are products

of a group A streptococcus infection, and elevations of these markers are seen in recent and recurrent infections. However, ASO titers can stay elevated for up to 6 months after exposure. In contrast, low ASO titers alone cannot rule out the diagnosis. Therefore, a single elevated laboratory value in concurrence with symptoms is insufficient to diagnose PANDAS. Follow-up studies performed monthly to check for falling serologic titers represent a good measure in congruence with symptom resolution.

Additional "second tier" testing for immunoglobulin subclass deficiencies and possibly food allergy profile testing are warranted if the clinical picture is supportive to evaluate immune burden. Immune profiles include IgA, IgE, IgM, and IgG, and subclasses can identify immune deficiencies or areas of over-

activation as sources contributing to immune system burden. Although less clinically helpful, magnetic resonance imaging can be used to aid diagnosis.⁸

Special Considerations and Lifestyle Issues

When working with a child with PANDAS, several special considerations must be made. Because asymptomatic family members can be common harbors of streptococcus bacteria, it is imperative that immediate family members of any patient with PANDAS should be evaluated if symptom resolution is not obtained in a timely manner. Other harbors or sources of reexposure to streptococcus are the skin (including perianal regions), impetigo skin infections, sinuses, tonsils, adenoids, and ear or urinary tract infections. Children with PANDAS have an

abnormal immune response, and clinical judgment should determine whether probiotics with strains of streptococcus bacteria should be avoided, although this is not published in the literature. Chronic exposure to oral streptococcus-containing probiotics may be one of multiple reexposure sources. Food allergy and immunologic panels may be helpful in evaluating immune system function. Food allergy profiles and appropriate elimination of identified foods can be helpful to decrease immune burden. Restrictive diets may be necessary based on individual circumstances and on clinical judgment.

Treatments

Once the etiology for a mental illness is found, the next step is to find effective treatments. The mainstay of treatment



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for PANDAS includes off-label use of common medications used in general pediatric practice. When discussing treatment, it should be considered that PANDAS is rarely a properly identified disorder; therefore, conventional treatment recommendations represent the work of a small group of clinicians who have researched the limited yet growing amount of information available. These

treatments include antibiotics, corticosteroids, selective serotonin reuptake inhibitors, and immunomodulatory therapies, although they are not universally agreed on. More novel therapies have received recent attention, including intravenous immunoglobulin (IVIG) and plasmapheresis, but these treatments are not options for everyone because of expense and lack of availability and are

being investigated. In research by Snider and colleagues,⁹ oral antibiotics administered once weekly were sufficient for symptom resolution in children studied for 1 year. Because reexposure is an ongoing concern, tonsillectomy has a role in the treatment of PANDAS. A literature review reveals several case studies supporting the removal of tonsils and adenoids to prevent reinfection in an individual or in family members.¹⁰ Intravenous immunoglobulin is an often used therapy when other treatments have failed or have not produced prolonged results. Intravenous immunoglobulin (1 g/kg of body weight over 2 days) should be administered by a physician who is knowledgeable about its use and about the immune system when the clinical picture and laboratory results are supportive of the disorder.¹¹ After treatment, magnetic resonance imaging should reveal improvement in the size of areas affected.⁸ Other investigations have shown positive results with IVIG in patients with Sydenham chorea.¹² In addition, cognitive behavior therapy is a safe and minimally invasive treatment that demonstrated improvement in OCD symptoms among a subgroup of patients with PANDAS in a small 3-week study.¹³ However, my experience, along with others in the field, is that PANDAS symptoms will resolve only when the infection is fully treated.

allergy identification and avoidance can have a role in decreasing the immune response. In addition, identifying yeast and other potential gastrointestinal infections that contribute to the immune response and treating those accordingly to decrease immune burden may have a further role in the treatment of some children with PANDAS. Anecdotally, immune-supportive therapies such as intravenous administration of selective nutrients with contents of vitamin C, zinc, and vitamin B complex should be considered as well to prevent recurrence.

Case Study

A postpubertal girl presented with 3-month history of sudden-onset motor tics involving her limbs, torso, and face occurring several times daily. Initially, she presented to the emergency department with complaints of sudden-onset "seizures." The imaging workup during her visit included electroencephalogram, magnetic resonance imaging, and computed tomography, which were all normal. The specialist's conclusion was essentially a suspicion of malingering. The patient went to another physician, who, after workup, treated her for yeast with pharmacotherapy. After 1 month, her symptoms did not improve. The patient and family presented to our clinic distraught and frustrated, as she was intending to drive soon, and this had been going on for approximately 3 months without an acceptable diagnosis or improvement. We performed an initial intake and were able to witness in the office what had been considered a seizure, which was quickly identified as an adventitious motor tic. Results of our ordered laboratory tests suggested possible PANDAS, with elevated ASO and antideoxyribonuclease titers that were 3 and

5 times the upper limits of reference ranges, respectively, and no known recent history of streptococcus infection. She was treated that same day in our office with a single dose of penicillin G benzathine (1.2 million U) administered intramuscularly in the upper gluteal region. At the 1-week follow-up visit, she had not had any return of symptoms, which she previously had been plagued with several times a day. She returned to my office 4 weeks after the initial visit with a sudden recurrence of symptoms. Again, we administered a single dose of penicillin G benzathine intramuscularly, and this time we added oral curcumin supplementation (150 mg, tapering up to 600 mg). The penultimate time I saw her, she was given a final dose of penicillin G benzathine intramuscularly, she was continuing oral curcumin supplementation, and we modified her yeast-free diet, as was indicated with gastrointestinal symptoms and fungal skin infection, to remove all possible yeast sources and fuel. We also added vitamin C daily (2000 mg) and a 5-day burst dose of oral prednisone (40 mg/d). Two months later at the most recent checkup, she had not had any return of symptoms.

Conclusions

As we try to bridge the gap between what we as physicians think and what we know, the hunt for effective therapies still continues, and we as holistic-minded physicians can provide that missing piece. Although not my first choice in the case study presented herein, antibiotics and oral corticosteroids are effective in restoring normalcy to a child's life quickly and effectively. The original symptom onset in our patient was after puberty, and there was no known history of recent streptococcus infection. In my experience, it is not uncommon that the clinical picture does not fit the strict criteria for PANDAS but rather represents a loose presentation that responds excellently to treatment. The intent of this discussion is not to guide treatment so much as to bring awareness and commence the thought process of how one goes about treating a child with PANDAS in the office setting. While a small group of experts in the field have concurred on the classic criteria of PANDAS, the definition of this newly discovered syndrome is likely to change. Knowledge of what PANDAS is and its pathogenesis will prepare you to make your own decision about what tools you are comfortable using and to spread the word when you find a new therapy that works. Clinicians and patients alike will thank you. ▾

Complementary Treatments and Supportive Interventions

In addition to what a very small group of medical doctors have identified as effective therapy, we as holistic physicians can get creative with our favorite and most effective treatments. Knowledge of the pathogenesis and etiology of this condition allows us to use safe, natural, and supportive therapies to treat this disorder that this difficult to manage and is rarely properly identified. This can quickly restore normalcy to families of children who are suddenly diagnosed as having this condition. By adhering to the principles of natural medicine, removing obstacles, replenishing what might be missing, and restoring the body's natural abilities, we can help children whose lives are devastated by this condition. Many natural therapeutics have not been explored to treat PANDAS. For example, damage to the central nervous system due to inflammation can be controlled with herbs such as curcumin.¹⁴ As mentioned earlier, food

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