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Review of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections

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Abstract

During the past decade, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) has become the topic of numerous debates, sparking research on its presentation, existence, and treatment. As the awareness of PANDAS has increased among the general community, health care providers have been forced to increase their knowledge of this controversial disease state. This article will review the background information, diagnostic criteria, treatment, and contentious issues related to PANDAS.

Keywords: pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, PANDAS, GABHS

Background

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) refers to a subset of individuals who develop an abrupt onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms following a group A beta-hemolytic streptococci (GABHS) infection. In some instances, initial presentation may be delayed by several days or weeks. Diagnosis is restricted by the temporal association between the infection and sudden exacerbation of OCD or tic disorder symptoms and the lack of definitive diagnostic laboratory studies. Although the exact prevalence of PANDAS is unknown, it is suspected to be low. The limited ability to definitely diagnose PANDAS along with the restricted pediatric prepubertal age range contributes to this reported low prevalence. The following information presented will review the diagnostic criteria, pathophysiology, clinical course, treatment, and some of the controversy associated with PANDAS.

Diagnostic Criteria

The diagnostic criteria for PANDAS were first established by Swedo et al[1] in 1998. The term refers to a group of neuropsychiatric disorders with a proposed autoimmune basis and a temporal relationship to GABHS infection. PANDAS was developed when investigators identified patients who did not meet the criteria for Sydenham chorea (SC) following a streptococcal infection. SC manifests from rheumatic fever and is an autoimmune disorder resulting in neuropsychiatric symptoms, such as choreiform movements, hyperactivity, and tic exacerbations. Although there are some similarities between SC and PANDAS, some differences between them include the presence of rheumatic fever and choreiform movements for SC, and GABHS infection for PANDAS.[2] Other symptoms associated with SC include hypotonia, behavioral problems, and emotional fragility. The clinical course of SC is often subacute and self-limited.[3]

The diagnostic criteria for PANDAS include the following[1]:

- Presence of OCD and/or a tic disorder
- Onset after age 3 years to the beginning of puberty

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- Episodic course of symptom severity characterized by abrupt onset of symptoms or by a pattern of recurrent symptom exacerbations and remissions
- Temporal relationship with GABHS infection
- Association with neurologic abnormalities (eg, hyperactivity, tics, or choreiform)

Psychiatric comorbidities frequently include emotional lability, separation anxiety, nighttime fears, oppositional behaviors, and school performance deterioration. PANDAS should not be diagnosed based on a single GABHS infection, because streptococcal infections are very common in children, especially between September and April, when the rate of infection is the highest.[4] Some researchers are in favor of diagnosis following two or more GABHS infections associated with symptom exacerbation.

Diagnosis of streptococcal infections using laboratory values is complicated because PANDAS is by definition a postinfectious condition. The pediatric standard is to determine direct confirmation of GABHS infection using rapid strep tests and throat cultures; however, although PANDAS symptoms occur abruptly as opposed to insidiously, the actual onset may not occur for weeks or months after the GABHS infection has occurred, been treated, and resolved. Antistreptococcal antibody titers, such as antistreptolysin O and deoxyribonuclease B, are much more indicative of a recent GABHS infection and may be the preferred method of confirmation. Single point in time testing of antibody titers does not indicate clinical symptoms; therefore, serial antibody titers are more useful, because serial increases up to 2-fold may more accurately define a streptococcal infection. The diagnosis of PANDAS is unlikely if both antibody titers are low.

There are a few factors that may complicate the diagnosis of PANDAS using laboratory studies. First, negative throat cultures do not eliminate the possibility of an individual being a streptococcal carrier. Second, antibody titers may remain elevated for several months following an acute infection, and a streptococcal carrier's antibody levels may remain elevated, limiting their applicability in aiding in the diagnosis of an acute or recent streptococcal infection that may be associated with PANDAS. To alleviate these complications, the combination of antibody titers and throat cultures should be used, because the combination is more accurate than either test alone.

Pathophysiology

The precise pathophysiology of PANDAS is unclear, but it is believed that a GABHS infection is the inciting event. It is theorized that PANDAS results from the body's developing immune response to the streptococcal infection. During this response, the antibodies attack the basal ganglia in error, thereby triggering brain dysfunction and resulting in the development of neuropsychiatric symptoms.[5]

The proposed autoimmune induction mechanism appears to be explained by molecular mimicry, which involves a foreign antigen sharing a sequence or structural similarity with self-antigens. Other evidence that supports the immune-mediated linkage includes the presence of circulating antineuronal antibodies, the increased prevalence of a B-cell surface marker that is associated with rheumatic fever, and the rapid clinical response to antibiotics and immunomodulatory therapy.[6]

The autoimmune-mediated linkage of PANDAS to GABHS infections was investigated by Singer et al[7] in 12 children diagnosed with PANDAS. It was determined that no correlation existed between clinical exacerbations and autoimmune markers. Exacerbations were temporally linked to GABHS infections in 50% (6 of 12) of the sample, whereas no linkage was discovered in the other 50% (6 of 12) of the sample.

Clinical Course

The clinical course of PANDAS is characterized by a sawtooth pattern with periods of abrupt explosions of symptoms followed by slow gradual symptom resolution over weeks to months. Symptom presentation typically begins at the time of or within 1 to 2 weeks of GABHS infection. Once symptoms begin to occur, maximum symptom impairment typically occurs in 24 to 48 hours and may last from weeks to months. Symptoms may resolve for weeks before a new symptom flare-up may occur. These flare-ups are often preceded by a new or recurrent GABHS infection.

Because presentation of tics or obsessive-compulsive symptoms is often similar to OCD, Tourette syndrome, and other tic disorders, differentiating PANDAS from these other disorders can be difficult for clinicians. The timing between the sudden exacerbation of tics or OCD symptoms and the GABHS infection is the distinguishing feature that separates PANDAS from the other disorders, but finding the correlation between the two events is difficult. Following the initial infection, the exacerbation of tics or OCD symptoms, as described above, may not occur for many months, but following recurrent infections, symptoms may develop within several weeks.

Two retrospective cohort database studies by Mell et al[8] and Leslie et al[9] evaluated the association between GABHS infections and the onset of tics and OCD

exacerbations in those diagnosed with OCD, TS, and tic disorders. Patients were more likely to have a GABHS infection 3 months prior to an exacerbation, and multiple GABHS infections within the previous 12 months.[8,9]

Kurlan et al[10] completed a prospective study finding no temporal association between the onset of OCD and tic disorder symptoms and GABHS infection. Of the 64 individuals included in the study, only 5 individuals (7%) had a GABHS infection within 4 weeks of OCD and tic disorder symptoms.

Factors to consider when determining causality include the high rates of GABHS infections in children, GABHS carriers, and the frequency of OCD and tic disorders in prepubertal children.

Treatment

The development of practical treatment guidelines has been debated. Treatment should not be delayed waiting for GABHS infection confirmation, but treatment for the infection, OCD, and tic disorder symptoms should be initiated.

Several nonpharmacologic treatment options exist for the treatment of tic disorders and OCD. Treatment for tic disorders includes comprehensive behavioral intervention for tics, habit reversal training, and exposure and response prevention (ERP). All three treatment modalities are patient-centered. Comprehensive behavioral intervention for tics trains the patient to be more aware of his or her tics, perform a competing behavior when the urge to tic occurs, and adjust his or her daily activities to reduce tics. Habit reversal training uses a previously learned alternative behavior to reduce the occurrence of tics, and ERP interrupts the necessity to produce a tic after a premonitory urge. Both habit reversal training and ERP have been proven to decrease tic occurrence by 30%.[3]

Cognitive behavioral therapy and ERP are frequently used to minimize OCD symptoms. The preferred method of psychotherapy for the treatment of mild to moderate symptoms is ERP. ERP formats include individual, group, and family therapy. In family ERP, the family develops accommodations for the individual's OCD symptoms that help the family work on their own distress associated with the patient's OCD symptoms. Cognitive therapy is an alternative to ERP. Cognitive therapy focuses on alternating dysfunctional beliefs about intrusive thoughts.

Antibiotics should be initiated in children with evidence of acute streptococcal infections or pharyngitis. Penicillins, including ampicillin and amoxicillin, cephalosporins, macrolides, and clindamycin, are suitable treatment options. Because of high rates of resistance and their inability to eliminate the organism, sulfonamides and tetracyclines should be avoided. Although penicillin is the preferred treatment for GABHS infections, amoxicillin is frequently more favorable because of the more palatable taste of the suspension. For children with beta-lactam allergies, cephalosporins are appropriate alternatives, but they are not recommended as first-line options. The recommended treatment course is 10 days to allow for eradication of the organism, but symptoms resolution should begin in 3 to 4 days.[11]

The effect of antibiotics for the management of OCD and tic symptoms has never been the subject of a randomized, placebo-controlled trial. Anecdotal evidence of antibiotics decreasing PANDAS symptoms is available; however, the exact mechanism by which symptoms respond to antibiotics is unclear. It has been proposed that some neuropsychiatric symptoms may be transient and self-limiting.

The prophylactic use of antibiotics to prevent future streptococcal infections is debatable. An uncontrolled, longitudinal observational study conducted by Bottas and Richter[12] demonstrated prompt resolution of OCD symptoms following eradication of GABHS infections with antibiotics. A placebo-controlled, double-blind trial failed to demonstrate significant improvement in symptoms tics or OCD symptoms of children treated with penicillin V prophylaxis.[13] A study comparing daily penicillin and weekly azithromycin prophylaxis demonstrated a decrease in OCD and tic symptoms; however, no difference was observed between the two groups.[14]

First- and second-generation antipsychotics may be used to minimize the impact of the tics on the individual's activities of daily living and quality of life. Haloperidol and pimozide are approved by the Food and Drug Administration for the management of tic disorders. Haloperidol is indicated for the control of tics and vocal utterances of Tourette syndrome in children ages 3 years and older and adults, whereas pimozide is indicated for the suppression of severe motor and vocal tics in patients ages 12 years and older with Tourette syndrome who have failed to respond satisfactorily to standard treatment. Pimozide requires electrocardiogram monitoring prior to medication initiation and periodically during treatment. Because of the increased risk of movement disorders, second-generation antipsychotics and alpha-adrenergic agonists are sometimes preferred for the management of tic disorders over first-generation antipsychotics.

For the treatment of OCD symptoms, selective serotonin reuptake inhibitors are preferred.[4] Fluoxetine, fluvoxamine, and sertraline are approved by the Food and Drug Administration for OCD in children and adolescents. No

one selective serotonin reuptake inhibitor has been proven to be more effective than the others for the management of OCD symptoms. Although clomipramine was the first medication to demonstrate efficacy for OCD symptoms, selective serotonin reuptake inhibitors have demonstrated superiority in pediatric meta-analyses.[3] In addition, electrocardiogram and blood level monitoring are suggested for clomipramine, and adverse effects include orthostatic hypotension, seizures, and urinary retention.

Immunomodulatory therapy, including glucocorticoids, plasmapheresis and intravenous immunoglobulin, is not recommended as routine treatment for PANDAS.[15] These therapies focus on the concept that the treatment disrupts the autoimmune process, thereby decreasing symptom severity and/or frequency of exacerbations. These therapies may be effective for the treatment of severe, disabling, strep-triggered OCD and tics. Tics appear to respond and improve more with plasma exchange compared with intravenous immunoglobulin. The disadvantages are adverse effects (eg, nausea, vomiting, headache, and dizziness) and the risk of infection. Further research needs to be completed prior to the recommendation of these therapies for the treatment of PANDAS.

Controversies

The existence of PANDAS is controversial. The supporting evidence is that GABHS infections can precipitate tics and OCD symptoms in a subset of patients. Those with signs and symptoms of GABHS infection should be evaluated for such an infection, and treatment should address the GABHS infection, OCD symptoms, and/or tic disorder symptoms. The areas of controversy include whether PANDAS is distinctly different from OCD and tics disorders, if GABHS is the only precipitating infection, if PANDAS should be considered an autoimmune disorder, and whether evaluation for GABHS infection should occur in all children with OCD and tic disorders. Also, some parents feel it is more acceptable to treat their child with antibiotics rather than seek specialized attention from a psychiatrist.

Conclusion

Determining whether PANDAS is a unique neuropsychiatric disorder remains undecided. Although the temporal relationship between GABHS infections and the sudden exacerbation of symptoms occurs, prospective and retrospective studies to determine such linkage are conflicting. The treatment of PANDAS is symptomatic: antibiotics for the infection, antipsychotics and alpha-adrenergic agonists for tics, and SSRIs for OCD symptoms. Nonpharmacologic treatment should be used as appropriate for mild to moderate OCD and tic disorder symptoms. Prophylactic antibiotics and immunomodulatory treatments are not recommended at this time because current efficacy data are conflicting and not robust. Further research should be completed on these treatment modalities before they can be routinely recommended. Other areas for improvement include the development of PANDAS treatment guidelines with additional research into factors that may influence the development of PANDAS, such as environmental factors. In conclusion, there is conflicting evidence regarding the linkage of GABHS infections to the development of PANDAS. It is likely that GABHS is one of many factors that may lead to OCD or tic disorder symptoms.

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