JPPT | Case Report

Azithromycin Prophylaxis in an Adolescent With PANDAS

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Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) is a type of pediatric obsessive-compulsive disorder with an acute symptom onset and periodic recurrence that is triggered by streptococcal infection. Due in part to the multifaceted assessment involved in the diagnosis of PANDAS and lack of consensus on the best treatment, management of these cases is complex. A background and case of PANDAS exacerbation in an adolescent patient, who presented with visuomotor impairment and was treated with azithromycin (Zithromax, Pfizer, New York, NY) prophylaxis to prevent further clinical deterioration, is described here.

ABBREVIATIONS ANA, antinuclear antibody; GABHS, group A beta-hemolytic streptococcal; OCD, obsessive-compulsive disorder; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

KEYWORDS antibiotic; autoimmune neuropsychiatric disorders; azithromycin; PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection); pediatric; prophylaxis; streptococcal infection

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Introduction

Streptococcus pyogenes bacteria are referred to as group A beta-hemolytic streptococcus, where group A refers to the antigen on the cell surface, and beta-hemolytic refers to the presence of the enzyme streptolysin that lyses nearby red blood cells.[1] *Streptococcus pyogenes* has M protein on its cell wall, which is highly antigenic and results in a host immune response. This produces antibodies against the M proteins, which have the ability to cross-react with proteins on the host cells, such as cells in the heart, joints, and brain. This phenomenon, in which the host's antibodies accidentally target proteins on its own cells because they look like foreign cells, is called molecular mimicry. Once bound to cells such as those in the brain, the antibodies activate nearby immune cells, which causes a cytokine-mediated inflammatory response and tissue destruction. This aforementioned autoimmune phenomenon is the proposed mechanism for the pathogenesis of PANDAS.

The discovery of PANDAS occurred in the 1990s when researchers at the National Institute of Mental Health recognized that some children with obsessive-compulsive disorder (OCD) had a characteristic symptom presentation.[2] In a description of these investigators' first cases, children with PANDAS demonstrated a sudden onset of symptoms that was triggered by infection with group A beta-hemolytic streptococcal (GABHS) infections. As compared with the non-GABHS patients, they exhibited an "overnight" evolution of obsessive-compulsive symptoms, choreiform movements, emotional lability, separation anxiety, cognitive deficits, and hyperactivity that followed a relapsing-remitting pattern. The study established a temporal relationship between streptococcal infections and exacerbation of symptoms in the first episode. Recurrent symptom exacerbations were preceded by GABHS as well as viral infections and other illnesses. This supports the accepted models of immune response, in which primary responses are specific and secondary responses are generalized. The criteria used today to diagnose PANDAS are shown in the Table.

A comprehensive diagnostic evaluation is important when a patient is suspected of having PANDAS, which includes family history, medical history, physical examination, psychiatric evaluation, general laboratory studies, and infectious disease evaluation.[4] Neuropsychiatric disorders and autoimmune diseases are common among patients diagnosed with PANDAS, which indicates an inherited vulnerability.

Patients meeting the criteria for PANDAS benefit from cognitive-behavioral therapy and medications routinely used for the treatment of OCD, such as selective serotonin reuptake inhibitors. Medications for other symptoms, such as PANDAS-related anxiety and concentration difficulties are also effective.[5] However, these therapies may be inadequate to treat all patients with PANDAS. Some clinicians support use of antibiotics in the absence of laboratory confirmation of streptococcal infection to treat influx of PANDAS symptoms. One clinical trial observed improvement of symptom exacerbations among children with PANDAS

Table. Guidelines for Diagnosis of PANDAS[2]

1. Presence of clinically significant obsessions, compulsions, and/or tics
2. Unusually abrupt onset of symptoms or a relapsing-remitting course of symptom severity
3. Pediatric onset (age 3 yr to puberty)
4. Association with other neuropsychiatric symptoms. The most common accompanying symptoms are: • Severe separation anxiety • Generalized anxiety, which may progress to episodes of panic • Motoric hyperactivity, abnormal movements, and a sense of restlessness • Sensory abnormalities, including hypersensitivity to light or sounds, distortions of visual perceptions, and occasionally, visual or auditory hallucinations • Concentration difficulties, and loss of academic abilities, particularly in math and visual-spatial areas • Increased urinary frequency and a new onset of bed-wetting • Irritability (sometimes with aggression) and emotional lability • Developmental regression, including temper tantrums, "baby talk," and handwriting deterioration
5. Association with group A streptococcal infection

after 12-month antibiotic prophylaxis in groups treated with azithromycin or penicillin,[6] but this study lacked a non-antibiotic placebo group. There is a large body of research exploring treatment options for PANDAS that is continually expanding; yet there is no consensus and comprehensive treatment recommendation. Thus, practitioners often approach treatment from the perspective of personalized medicine on a case-by-case basis.

Case Report

A 16-year-old male patient (63.8 kg) was transferred to the emergency department from a rural hospital for ptosis and blurred vision of the left eye. There was a history of a diagnosis of PANDAS at the age of 4 with anxiety, OCD with tic disorder, attention-deficit/hyperactivity disorder-inattentive type, and bradycardia. Home medications included guanfacine 4 mg daily and citalopram 10 mg daily.

Prior to the hospitalization, the patient experienced marked twitching of the left eye and consequently developed pain in that location. This was followed by photophobia, decreased motor control of the left eye, inability to open the eye, blurred vision, and tunnel vision. Upon examination by the patient's family practitioner, it was noted that there was visible drooping and inability to raise the eyebrow. The patient was brought to the local emergency department. Workup included complete blood count and basic metabolic panel that were within normal limits and a head computed tomography that showed sinus inflammation.

Upon evaluation at our facility, it was noted that the patient was alert and oriented, had poor eye contact, but communicated well. An initial eye examination revealed equal pupils that were round and reactive to light, photophobia, normal conjunctiva, blurriness in the left eye, a left upper eyelid droop that was slightly asymmetrical, and weakness to the left brow lift. The patient reported a sinus headache, nasal discharge, and difficulty navigating while walking. Approximately 2 weeks prior to these complications, the patient experienced exacerbated anxiety, nightmares, poor sleep, and poor concentration that were accompanied by a decline in school performance. The patient also demonstrated a hand tic and tapping that led to some dysgraphia. It was reported that 1 year earlier, the patient developed an arrhythmia that caused recurrent bouts of bradycardia. Echocardiogram was negative, and was thus evaluated by a cardiologist who ordered a 30-day cardiac event monitor. It was determined that the arrhythmia was related to the patient's anxiety. There was a family history of autoimmune disorders (i.e., rheumatoid arthritis and Hashimoto's disease) as well as glaucoma. Differential diagnoses included Lyme disease, autoimmune disorder, Bell's palsy, sinusitis, Horner's syndrome, or central nervous system anomaly.

On admission, the patient was started on prednisone for possible Bell's palsy. Pediatric neurology stated the patient's condition was less likely to be Horner's syndrome due to lack of miosis or anhidrosis, and it was recommended to begin with a brain MRI, Lyme titers, antinuclear antibody (ANA), and erythrocyte sedimentation rate. Upon further review, neurology ruled out Bell's palsy and discontinued prednisone. The MRI was normal except for severe opacification of the right maxillary sinus, which radiology noted could be sinusitis or a polyp. Neurology concluded that this did not explain the patient's visual disturbances. However, upon review of the patient's history, the recently increased anxiety, sleep disturbances, concentration difficulty, decline in school performance, and visuomotor impairment support the hypothesis that the patient's condition was related to an immune response and exacerbation of PANDAS.

After the establishment of PANDAS being the cause of the signs and symptoms experienced, the patient was treated with azithromycin based on its coverage against streptococcal species. Since there was no evidence of active or recent infection, neurology opted

not to use a full treatment course of antibiotics. The patient was then started on oral azithromycin 250 mg 3 times weekly. In the physical examinations roughly 24 hours after treatment initiation, the patient's eyelids became symmetrical, movement in the left forehead and eyebrow improved, and vision became less blurry. The Lyme titer and erythrocyte sedimentation rate yielded negative results, whereas the ANA obtained was positive. After 3 days of observation, during which time the patient received 2 doses of azithromycin, he was discharged home on azithromycin 250 mg 3 times weekly. There were no subsequent hospitalizations or complaints of symptom exacerbation at the 1-month follow-up appointment.

Discussion

This case is representative of the complicating factors involved in both the differential diagnosis and treatment of individuals with PANDAS. In previous works, the difficulty in determining causality between an autoimmunity-provoking event and PANDAS symptom exacerbation has been referenced. In this case, determining the etiology behind the patient's sudden-onset ptosis was further complicated by the decreased incidence of GABHS infections after puberty due to the development of antibodies against the conserved portion of the M-protein.[2]

When considering treating GABHS, penicillins are generally thought to be the first-line class of agents to use due to the narrow spectrum of activity. However, prophylaxis would require daily administration, which could potentially reduce patient compliance in the outpatient setting. Azithromycin also offers GABHS coverage. Due to its long half-life, azithromycin can be given 3 times weekly. This schedule is much more likely to be adhered to, which ultimately increases the patient's chances of reducing future exacerbations or disease progression due to repeat infections. The patient had no complaints of any adverse effects while on 3 times weekly azithromycin during follow-up, showing its efficacy and tolerability in this setting. The azithromycin was planned to be continued indefinitely, and there is a severe lack of direction in the literature in regards to duration of prophylaxis needed for this condition.

There were several limitations in this case. Foremost, there was no confirmation of a GABHS infection with an antistrep antibody titer, in which elevated levels would have indicated a recent infection. Yet, it is known that PANDAS recurrence may be caused by other infections, and the positive ANA indicates the presence of antibodies and there may be an autoimmune disorder. In addition, this case may not be representative of all PANDAS patients, but consideration of a PANDAS history is important to guide treatment options and potential prevention of future recurrence. Finally, it must be noted that the local resistance pattern must be taken into account, as streptococcal resistance to macrolide antibiotics such as azithromycin is becoming increasingly more prevalent.

This case report illustrates the difficulty in diagnosing such a rare condition and sheds light onto possible prophylactic treatment options in order to prevent further exacerbations and worsening symptoms. As opposed to daily administration of penicillin, three times weekly azithromycin was shown to be a reasonable treatment option in preventing GABHS and similar infections in the setting of PANDAS.

ARTICLE INFORMATION

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REFERENCES

1. Pichichero ME. Group A beta-hemolytic streptococcal infections. *Pediatr Rev*. 1998;19(9):291–302.
2. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155(2):264–271.
3. Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol*. 2015;25(1):3–13.
4. Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. *Neurosci Biobehav Rev*. 2018;86:51–65.
5. Snider LA, Lougee L, Slattery M et al. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry*. 2005;57(7):788–792.