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Case Report

Childhood-Onset Obsessive-Compulsive Disorder and Tic Disorders: Case Report and Literature Review

Lisa A. Snider, M.D. and Susan E. Swedo, M.D.

ABSTRACT

A subgroup of childhood-onset obsessive-compulsive disorder (OCD) and tic disorders has been found to have a postinfectious autoimmune-mediated etiology. Clinical observations and systematic investigations have shown that a subgroup of children with OCD and/or tic disorders have the onset and subsequent exacerbations of their symptoms following infections with group A beta-hemolytic streptococci (GABHS). This subgroup has been designated by the acronym PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Five clinical characteristics define the PANDAS subgroup: presence of OCD and/or tic disorder, prepubertal symptom onset, sudden onset or abrupt exacerbations, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and the temporal association between symptom exacerbations and GABHS infections. The proposed poststreptococcal inflammatory etiology provides a unique opportunity for treatment and prevention, including immunomodulatory therapies such as plasma exchange and intravenous immunoglobulin. A placebo-controlled trial revealed that both intravenous immunoglobulin and plasma exchange were effective in reducing neuropsychiatric symptom severity (40 and 55% reductions, respectively) for a group of severely ill children in the PANDAS subgroup. Further research is required to determine why the treatments are helpful and to ascertain whether or not antibiotic prophylaxis can help prevent poststreptococcal symptom exacerbations.

CASE STUDY

A previously healthy 5½-year-old boy suddenly developed obsessive-compulsive behaviors while on vacation with his family. He was unable to get dressed one morning in the hotel, as all of his clothes were "dirty" or not "right." He became very upset and asked his parents continuously to look at his hands to be sure "they were clean." His reluctance to put on dirty clothes forced his parents to buy a new shirt and pair of shorts that he was willing to

Pediatrics and Developmental Neuropsychiatry Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

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wear. During that day he continued to ask questions about the cleanliness of his clothes. He also requested reassurance for fears that he had hurt someone or damaged something. "I know I touched that table. Am I going to be in trouble for it?" "I bumped into that man. Is he going to die?" These obsessive-compulsive symptoms continued throughout the remaining 4 days of the vacation. During this time his parents also noticed multiple motor and vocal tics with nearly continuous eye blinking, eye rolls, nose twitching, and mouth stretching. He also made a frequent sniffing noise. None of these movements or noises had been observed previously.

Once they returned home it became apparent that he had drastically changed from last week's easy-going child who had no school difficulties. On his first day back at school he asked to be excused to wash his hands every 5 to 10 minutes. His teacher explained to him why he could not do this, but he would come back up again in 10 minutes. Although he had been a model student for the previous 6 months, the teacher now was unable to get him to sit and focus on any activity without constant supervision and redirection. His parents also reported that he began having episodes of nighttime bed-wetting again after a year of being completely toilet trained and had frequent tempertantrums over almost nothing. He was able to get through the day at school and at home but only with constant reassurance and supervision from his parents and teachers.

His pediatrician evaluated him and found no evidence of a new psychosocial stressor or abuse. He recommended that they wait and see where this behavior went, as he was able to get to school. Two weeks prior to the onset of his symptoms he had been diagnosed with a group A beta-hemolytic streptococci (GABHS) throat infection and had received a 10-day course of amoxicillin. After 3 weeks he was brought to his pediatrician for an evaluation for ear pain and continued abnormal behavior. He was diagnosed with bilateral ear infections and again treated with a 10-day course of amoxicillin. He had no symptoms of sore throat, and no GABHS testing was done at that time. Within 48 hours of starting this second course of antibiotics, his obsessive-compulsive, tic, and hyperactivity/inattention symptoms began to decrease in intensity and frequency. Within 1 week he had no obsessive-compulsive symptoms and only occasional eye blinking and mild hyperactivity/inattention. Over the next 16 months the patient was without further documented GABHS infection and only occasional eye blinking tics with a gradual return to his previous baseline of no hyperactivity or inattention problems.

GABHS INFECTIONS AND OBSESSIVE-COMPULSIVE TIC DISORDERS

Through complementary research studies conducted at the National Institute of Mental Health on obsessive-compulsive disorder (OCD) and Sydenham's chorea (SC), researchers discovered a shared etiopathogenesis between the two disorders (Swedo et al. 1989a, 1993, 1994). SC is the well-recognized neuropsychiatric manifestation of rheumatic fever in which patients develop symptoms of chorea after a preceding GABHS infection (Stollerman 2001). Although the exact pathogenesis has not yet been established, GABHS is known to be the inciting agent in the development of rheumatic fever and SC (Taranta and Stollerman 1956). The production of antibodies to streptococcal antigens associated with the M-protein of GABHS has been shown to cross-react with epitopes on neuronal tissue. This has been proposed as a possible etiology for the central nervous system sequlae of SC (Bronze and Dale 1993; Husby et al. 1976). It has also been postulated that the pathogenesis of chorea results from immune complex disease produced by nondestructive antistreptococcal antibodies that localize to the basal ganglia and striatal areas of the brain (Husby et al. 1976; Moore 1996; Swedo et al. 1994). The same regions of the brain have been hypothesized to be affected in OCD. Structural and functional neuroimaging studies have demonstrated abnormalities of the basal ganglia structures and their related corticostriato-thalamocortical circuitry in the pathobiology of OCD (Demirkol et al. 1999; Hahm et al. 2001; Max et al. 1995; Mordecai et al. 2000; Peterson et al. 1996) and SC (Giedd et al. 1995).

There is significant symptom overlap in patients with SC and childhood-onset OCD (Allen

et al. 1995; Chapman et al. 1958; Swedo et al. 1989a). For nearly three quarters of SC patients, the neuropsychiatric symptoms include obsessions and compulsions identical to those seen in childhood-onset OCD: contamination concerns, worries about harm coming to self or others; violent images; and checking, washing, and arranging rituals (Swedo 1994; Swedo et al. 1989a, 1993). These obsessive-compulsive symptoms are reported to begin 2–4 weeks before the onset of the adventitious movements, leading to speculation that OCD might occur as a sequela of streptococcal infections, even in the absence of frank chorea (Swedo et al. 1994). This postulate was confirmed by prospective observations of a large cohort of children and adolescents with OCD (Swedo et al. 1989b). A subgroup of pediatric patients with OCD was observed to have an unusual clinical course characterized by abrupt symptom onset and a relapsing-remitting pattern of severity; often, the symptom relapses followed streptococcal throat infections or bouts of scarlet fever (Allen et al. 1995).

There have also been studies documenting the onset of tic disorders after infection with GABHS. For example, exposure to streptococcal antigens correlated with the onset of tics in an Italian pediatric population (Cardona and Orefici 2001). An association between a community outbreak of GABHS infections and a 10-fold rise in the number of children presenting with a new onset of tics has also been documented (Kiessling et al. 1993a).

CLINICAL CHARACTERISTICS OF THE PANDAS SUBGROUP

The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) was applied to the subgroup of children who experienced obsessive-compulsive and/or tic symptoms after a GABHS infection to indicate their common clinical features and presumed pathophysiology of symptoms (Swedo et al. 1998). The PANDAS subgroup is identified by five clinical criteria.

1. Presence of OCD and/or tic disorder meeting *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV; American Psychiatric Association 1994), criteria
2. Prepubertal symptom onset
3. Episodic course characterized by acute, severe onset and dramatic symptom exacerbations
4. Neurological abnormalities (e.g., choreiform movements) present during symptom exacerbations
5. Temporal relation between GABHS infections and symptom exacerbations

The major distinguishing feature of the PANDAS subgroup is the temporal association between neuropsychiatric symptom exacerbations and GABHS infections. A methodological difficulty in establishing this association stems from the fact that GABHS infections occur so frequently during childhood that randomly collected antistreptococcal titers are frequently elevated (Kaplan 1996). Throat cultures may also be spuriously positive, particularly during the grade-school years, when up to 10% of students are "strep carriers" (i.e., positive throat culture but no serologic evidence of infection) (Wannamaker 1972). A prospective longitudinal evaluation is often the only means available to make the determination of whether or not the child belongs in the PANDAS subgroup. The relation between OCD/tics symptom exacerbations and GABHS infections is frequently difficult to demonstrate retrospectively, because medical records often fail to provide documentation of the presence of GABHS infections. In the original cohort, over 40% of the OCD/tics symptom exacerbations occurred after an episode of pharyngitis for which no throat culture had been obtained (Swedo et al. 1998). If physicians diagnose pharyngitis as viral without obtaining a throat culture (the only means of identifying GABHS infections), it not only obscures the GABHS–OCD/tics relation, but also raises concerns about the consequence of untreated or improperly treated GABHS infections in vulnerable individuals.

The PANDAS subgroup is characterized by an unusually young age at onset of symptoms (6.3 ± 2.7 years for tics and 7.4 ± 2.7 years for OCD), male predominance (2.6:1), and abrupt symptom onset (Swedo et al. 1998). In the original cohort of 50 children, there was an equal

representation of both OCD and tic disorders, with 48% of the group (24 children) having a primary diagnosis of OCD and 52% of the group (26 children) having a primary diagnosis of tic disorder. However, 80% of the children had both tics and obsessive-compulsive symptoms. The obsessive-compulsive symptoms of the PANDAS subgroup were similar to those previously reported for childhood-onset OCD: contamination fears; harm to self or others; somatic concerns; and washing, checking, repeating, and counting rituals. Tic distribution was also similar to that previously reported, with eye-blinks and facial tics predominating.

Neuropsychiatric comorbidities are common among children in the PANDAS subgroup (Swedo et al. 1998). Twenty (40%) of the first 50 children evaluated met DSM-IV criteria for attention deficit hyperactivity disorder and/or oppositional defiant disorder, 18 (36%) for major depressive disorder, 14 (28%) for overanxious disorder, and 10 (20%) for separation anxiety disorder. Six children (12%) had enuresis—often this was episodic and correlated closely with periods of OCD/tic symptom worsening. Attention deficit hyperactivity disorder and separation anxiety disorder also appeared to relapse and remit in concert with the OCD/tic symptoms. Choreiform movements were present in 25 of 26 children examined during an exacerbation (Swedo et al. 1998). Exacerbations of OCD/tics were also accompanied by emotional lability and irritability, tactile/sensory defensiveness, motoric hyperactivity, messy handwriting, and symptoms of separation anxiety (Perlmutter et al. 1998; Swedo et al. 1998). This constellation of symptoms was so unique and consistent that the question arose as to whether or not it defined a specific neuropsychiatric syndrome. Such a pattern might also point to specific abnormalities of regional brain function (Casey et al. 2001), which in turn could increase our understanding of the pathophysiology of OCD and tic disorders.

IMMUNOMODULATORY TREATMENTS FOR THE PANDAS SUBGROUP

The pathophysiology proposed for SC and PANDAS suggests that treatments, which interrupt the autoimmune process, might reduce symptom severity. Preliminary results for a controlled trial of plasma exchange (PEX) and intravenous immunoglobulin (IVIG) in patients with SC demonstrated efficacy of both treatments (Garvey et al. 1996). A double-blind randomized study compared PEX with IVIG and sham IVIG (placebo) for the treatment of tics and obsessive-compulsive symptoms in children with PANDAS (Perlmutter et al. 1999). PEX and IVIG were chosen because of their record of safety and effectiveness in a variety of childhood and adult immune-mediated diseases and because anecdotal reports demonstrated symptom improvement in patients with infection-triggered exacerbations of OCD (Barron et al. 1992; Guillain-Barre Syndrome Study Group 1985). Steroid therapy was not a viable treatment option for children in the PANDAS subgroup because tics and OCD have been reported to worsen during steroid administration (Jonasson and Wilkinson 1993). Thus, children were randomly assigned to receive PEX (5–6 single volume exchanges on an alternate day schedule), IVIG (1 g/kg on each of 2 consecutive days), or sham IVIG (double-blind administration in a manner identical to IVIG).

Twenty-nine children completed the trial, which found that both PEX and IVIG produced dramatic improvements in obsessive-compulsive symptoms, anxiety, depression, emotional lability, and global functioning. Clinical Global Impressions (CGI) change scores revealed that patients in both the PEX and IVIG groups were much improved (CGI change = 1.9 ± 1.1 and 2.4 ± 1.1; mean improvement of 48% and 41%, respectively). In the PEX group, symptom improvement was often observed near the end of the first week of treatment, whereas in the IVIG group, improvement was not usually seen until 3 weeks after treatment. The PEX group also appeared to have greater symptom relief than did the IVIG group, with particularly striking individual improvements seen for obsessive-compulsive symptomatology. In contrast, placebo administration was associated with little or no change in overall symptom severity (CGI change = 4.1 ± 0.6; mean change of -2%).

Adverse effects of PEX were frequent but mild among the 19 children receiving at least

one course of therapy. The side effects of PEX were limited to the duration of the procedure (1–1.5 hours) and included dizziness, nausea, and perioral tingling. In most cases, the discomfort occurred only during the first or second exchange, and the remaining procedures were tolerated well. The side effects of IVIG (nausea, vomiting, and headache) seemed more problematic, as they often persisted for 12–24 hours, whereas those related to PEX were brief and limited to the procedure period. Of note, most children undergoing PEX required a central line for venous access. Central line insertion carries the risk of significant morbidity, including vascular perforation and infection, although these are reported to occur rarely. Because of these inherent risks, PEX is recommended only for severely ill patients. The nationwide shortage of IVIG presents a public health risk to immunodeficient individuals, so its use in the PANDAS subgroup is not recommended.

The treatment gains of PEX and IVIG were sustained over the long term. Over 80% of patients who received IVIG or PEX remained "much" or "very much" improved at 1-year follow-up, with their symptoms now in the subclinical range of severity. These results are particularly striking when considered in light of previous reports of the intractable nature of pediatric OCD and tic disorders. Long-term outcome studies in OCD typically have found that fewer than one third of the patients show clinically meaningful symptom improvements (Leonard et al. 1993).

The results of this investigation suggest that PEX and IVIG may be beneficial to a subgroup of patients with tics and obsessive-compulsive symptoms, but these findings require replication. Further, the National Institutes of Health study did not provide support for the routine use of immunomodulatory agents in OCD and tic disorders. In fact, a trial of PEX for five children and adolescents with chronic, treatment-refractory OCD (who did not meet criteria for the PANDAS subgroup) found no benefit (Nicolson et al. 2000). This lack of response suggests that the benefits of immunomodulatory therapy will be limited to those children whose symptoms have an autoimmune etiology.

At present, the nature of the poststreptococcal autoimmunity in the PANDAS subgroup is unknown. Clinical observations suggest that there may be a combination of local, regional, and systemic abnormalities. The striking effectiveness of immunomodulatory therapies, such as PEX and IVIG, suggests that there is systemic involvement, at least in severely affected individuals. Magnetic resonance imaging scans reveal enlargements of the basal ganglia, which points to regional inflammatory changes (Giedd et al. 1996).

Local autoimmune reactions are suggested by the presence of serum antibodies that recognize both streptococcal antigens as well as the basal ganglia in patients with tic disorders and OCD. Serum antineuronal antibodies were isolated from patients who cross-reacted streptococcal antigens and neurons from the human caudate and neuroblastoma cell line (Kiessling et al. 1993b). In subsequent studies, antineuronal antibodies with cross-reactivity to the streptococcal antigens and human caudate and putamen were found in children with Tourette syndrome but were also present in 40% of the control group (Singer et al. 1998). In more recent studies, children with Tourette syndrome were found to have significantly higher levels of antineuronal and antinuclear antibodies compared with age-matched controls (Morshed et al. 2001). There is also limited research on these antineuronal antibodies in animal models of Tourette syndrome. Stereotypies and episodic utterances, felt to be analogous to the involuntary movements seen in Tourette syndrome, have been induced in rats by intrastriatal microinfusion of serum gamma globulins from patients with Tourette syndrome (Hallett et al. 2000).

ANTIBIOTIC PROPHYLAXIS FOR THE PANDAS SUBGROUP

The streptococcal pathogenesis of rheumatic fever is supported by studies that demonstrated the effectiveness of penicillin prophylaxis in preventing recurrences of this illness (Massell et al. 1988). A placebo-controlled trial of penicillin prophylaxis among children in the PANDAS subgroup was conducted to determine if the prevention of GABHS infections would result in neuropsychiatric symptom improvement via the prevention of poststreptococcal exacer-

bations (Garvey et al. 1999). This study found that penicillin was not superior to placebo as prophylaxis against GABHS. Streptococcal infections occurred frequently in both the active (14 infections among 37 subjects) and placebo (21 infections among 39 subjects) phases. However, the effectiveness of the penicillin prophylaxis appeared to have been compromised by poor compliance, particularly during the first year of the investigation when liquid preparations were used and the bad taste made it difficult for parents to give the medicine as directed. Without a reduction in the number of GABHS infections in the penicillin group, it was not surprising that there were no significant differences in the number or severity of neuropsychiatric symptoms between the penicillin and placebo groups.

CLINICAL GUIDELINES FOR GABHS PREVENTION IN THE PANDAS SUBGROUP

The assessment for GABHS infection in a young child with abrupt-onset OCD and/or tic disorder should be done, and all positive cultures should be treated promptly with a 10-day course of penicillin or other appropriate antibiotic. This can be done by a simple throat culture for GABHS that is read at 24 and 48 hours of growth, with or without a rapid GABHS antigen test being done at the time of the visit. It is important to perform a 48-hour culture on all negative rapid GABHS antigen tests, as a negative test does not exclude the presence of GABHS (Dajani et al. 1995). If the culture is negative and the onset of the OCD and/or tic symptoms occurred at least 4 to 6 weeks prior to the visit, then a blood test for antistreptococcal antibody titers (antistreptolysin O and antideoxyribonuclease B) could be done to attempt to document a preceding GABHS infection. If the GABHS culture is negative and the titers are found to be elevated, there is no indication for a 10-day course of antibiotic treatment for elevated antistreptococcal titers alone. The prospective assessment for GABHS infections in a child with an episodic course of symptoms should also be assessed in the same manner with the recurrence of the OCD and/or tic symptoms. This is also true for a child with OCD and/or tic symptoms who has had a sudden loss of medication response.

It is still unclear whether antibiotic prophylaxis benefits outweigh the potential risks in a child with a documented GABHS association with the onset or recurrence of his or her OCD and/or tic symptoms. The decision to begin prophylaxis with penicillin should be based on a clinical indication in each individual child. The prompt diagnosis and adequate treatment of a GABHS infection in this subgroup of patients is clearly indicated. Treatment with immunomodulatory therapies (e.g., PEX and IVIG) for children with severe symptoms who fit the PANDAS description carries significant risks and should be used only in research protocols at this point.

CONCLUSION

The PANDAS subgroup is characterized by abrupt neuropsychiatric symptom onset or exacerbations following infections with GABHS. A prospective longitudinal evaluation of symptom course and GABHS infection in a child who appears to fit the criteria at presentation is the best way of confirming membership in the PANDAS subgroup. Novel treatment and prophylaxis regimens have brought us closer to our goal of providing complete symptomatic relief to acutely ill children in this subgroup, but further research is required before such regimens can be implemented in clinical practice. Until that time, children in the PANDAS subgroup should be managed with standard therapies (e.g., serotonin reuptake blocking medications and cognitive-behavior therapy) and followed prospectively for GABHS infections. Once an association between GABHS infection and neuropsychiatric exacerbation is confirmed, aggressive screening and early treatment for GABHS infections should then become indicated adjuncts to the standard therapies.

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Address reprint requests to:
Lisa A. Snider, M.D.
10 Center Drive–MSC 1255
Bethesda, MD 20892-1255

E-mail: sniderl@intra.nimh.nih.gov