Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

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ABSTRACT

A group of childhood-onset neuropsychiatric disorders has been found to have a postinfectious autoimmune-mediated etiology, related to infections with group A beta-hemolytic streptococci. This group has been designated by the name: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections(PANDAS). Some clinical characteristics define the PANDAS group : presence of OCD and/or tic disorder, prepubertal symptom onset (controversial as adult cases were reported), sudden onset or abrupt exacerbations, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and the temporal association between symptom exacerbations and streptococcal infections. The proposed post streptococcal inflammatory etiology provides a unique opportunity for treatment and prevention, including immunomodulatory therapies such as plasma exchange and intravenous immunoglobulin. Documented case study was incited. **(Int. J. Ch. Neuropsychiatry, 2005, 2(2): 195-202)**

INTRODUCTION

Following an outbreak of streptococcal infections on Rhode Island in 1991, Dr. Louise Kiessling observed that streptococcal infections seemed to precipitate the onset of tic disorders[1,2]. The subsequent link made between alpha beta hemolytic streptococcal infections and neurological sequelae, evidence for which had already appeared sporadically within the literature[3,4] was a valuable display of reciprocal transaction in the medical literature. Rather than engaging in fruitless and tired debates over whether a particular disorder's etiology lies in "nature" or "nurture", neurology or psychology, both environmental trigger and neurological diathesis could readily be seen to interact and influence one another in the development of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

Now that PANDAS has been established and verified as a diagnosis, however, discussions now turn to the question of where PANDAS fits in the context of other syndromes and disorders with similar collections of symptoms. Is PANDAS similar enough to other manifestations of rheumatic fever (such as Sydenham's Chorea; SC) to be subsumed under this? Are all instances of disorders such as Tourette Syndrome (TS) and Obsessive-Compulsive Disorder (OCD) subsumed under the label PANDAS – is PANDAS simply our first clear etiological delineation of these conditions? Or are all three (SC, PANDAS, TS) unique diagnoses unto themselves? While definitive answers to these issues are yet to be found, the elucidation of how at least a subset of the population experiencing tics, obsessions, and compulsions have come to develop these symptoms brings to attention whole new perspectives on prevention and treatment.

CASE STUDY

A previously healthy 8.5-years-old boy suddenly developed severe depressive manifestations, which was followed by obsessive-compulsive behaviors while on mid-semester vacation. He was unable to sit on chairs, or to get dressed one morning, as all of chairs, and his clothes were "dirty" or not "right", from his own point of view. 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 wash and rewash his clothes separately. 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, damaged something, or given obscene names to god. "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? Because of that". These obsessive-compulsive symptoms continued throughout the following days. During that time his parents also noticed multiple motor and vocal tics with nearly continuous eye blinking, nose twitching, and throat cleaning. He also frequently cried, with no apparent cause. None of these abnormal behaviors had been observed previously.

It became apparent that he had 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, and cries and went into temper tantrum when his teacher banned him. Then 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 very good student for the previous semester, the teacher now was unable to get him to sit and focus on any activity without constant supervision and redirection. He, also, gave abnormal sounds, which are sometimes obscene. He was able to get through the day at school and at home but only with constant reassurance 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.

After 3 weeks he suffered an attack of fever with loss of appetite and increase of his abnormal behavior. His parents seek another medical opinion, and consulted child neurologist. The child neurologist found in history that prior to the onset of the child symptoms he had been diagnosed with a throat infection and had received Cephalsporine.

Child neurologist admitted the patient to hospital, asked for specialized ENT consultation, and asked for group A beta-hemolytic streptococci (GABHS) testing, in addition to routine laboratory work. Child was clinically diagnosed with sore throat and bilateral ear infections and treated with a 10-day course of amoxicillin, after getting positive GABHS testing. ECG was normal, and CRP was negative.

Within three days of starting amoxicillin course of antibiotics, his obsessive-compulsive, tic, and hyperactivity/inattention symptoms began to decrease in intensity and frequency. Within two week he had no obsessive- compulsive symptoms and only occasional eye blinking and mild hyperactivity/inattention. Over the next 6 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.

Streptococcal Infections and Neuropsychiatric Disorders.

Researchers discovered a shared etiopathogenesis between obsessive-compulsive disorder (OCD) and Sydenham's chorea (SC)[5,6,7]. Sydenham's chorea is the well-recognized neuropsychiatric manifestation of rheumatic fever in which patients develop symptoms of chorea after a preceding GABHS infection[8]. Although the exact pathogenesis has not yet been established, GABHS is known to be the inciting agent in the development of rheumatic fever and Sydenham's chorea[9]. 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 Sydenham's chorea[10,11]

It has also been postulated that the pathogenesis of chorea results from immune complex disease produced by nondestructive anti-streptococcal antibodies that localize to the basal ganglia and striatal areas of the brain[11,12,13]. The same regions of the brain have been hypothesized to be affected in OCD[14]. Structural and functional neuroimaging studies have demonstrated abnormalities of the basal ganglia structures and their related corticostriato-thalamocortical circuitry in the etiopathogenesis of OCD[15,16,17,18,19] and Sydenham's chorea[20]. There is significant symptom overlap in patients with Sydenham's chorea and childhood-onset OCD[21,22,5]. For nearly three quarters of Sydenham's chorea 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, …..etc[13,5,6]. These obsessive-compulsive symptoms are reported to begin 2–4 weeks before the onset of the involuntary movements, leading to speculations that OCD might occur as a sequela of streptococcal infections, even in the absence of frank chorea[13]. This postulate was confirmed by prospective observations of a large cohort of children and adolescents with OCD[23]. A group 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[21]. 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[24]. 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[25].

PANDAS: Criteria for Diagnosis

The name PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) was applied to the group of children who experienced obsessive-compulsive and/or tic symptoms after a GABHS infection to indicate their common clinical features and presumed pathophysiology of symptomatology[26]. The PANDAS group is identified by the following 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)[27], criteria
2. Prepubertal symptom onset (to comply with name)
3. Episodic course characterized by acute onset and dramatic symptom exacerbations
4. Neurological abnormalities (e.g., choreiform movements) may present during symptom exacerbations
5. Temporal relation between GABHS infections and symptom exacerbations.
6. Invariable response to antibiotics, and immune modulating regimens.

The major distinguishing feature of the PANDAS group 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[28]. Throat cultures may also be spuriously positive, particularly during the school years, when up to 10% of students are "streptococal carriers" (i.e., positive throat culture but no serologic evidence of infection)[29]. A prospective longitudinal evaluation is often the only means available to make the determination of whether or not the child belongs in the PANDAS group. 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.

The PANDAS group 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[26]. In report 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 group 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 group[26]. 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 that 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[26]. Exacerbations of OCD/tics were also accompanied by emotional lability, motor hyperactivity, messy handwriting, and symptoms of separation anxiety[30,26]. 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[31], which in turn could throw light on the pathophysiology of OCD and tic disorders.

Immunotherapy for the PANDAS

The pathophysiology proposed for Sydenham's chorea and PANDAS suggests that treatments, which interrupt the autoimmune process, might reduce symptom severity. Preliminary results for a controlled trial of plasma exchange and intravenous immunoglobulin (IVIG) in patients with Sydenham's chorea demonstrated efficacy of both treatments[32]. A double-blind randomized study compared plasma exchange with IVIG and sham IVIG (placebo) for the treatment of tics and obsessive-compulsive symptoms in children with PANDAS[33]. plasma exchange and IVIG were chosen because of their record of safety and effectiveness in a variety of childhood and adult immune-mediated diseases and because some rare reports demonstrated symptom improvement in patients with infection triggered exacerbations of OCD[34,35]. Steroid therapy was not a viable treatment option for children in the PANDAS group because tics and OCD have been reported to worsen during steroid administration[36]. Thus, children were randomly assigned to receive plasma exchange (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 plasma exchange 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 plasma exchange and IVIG groups were much improved (CGI change = 1.9 6 1.1 and 2.4 6 1.1; mean improvement of 48% and 41%, respectively). In the plasma exchange 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 plasma exchange 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 6 0.6; mean change of 22%). Adverse effects of plasma exchange were frequent but mild among the 19 children receiving at least one course of therapy. The side effects of plasma exchange were limited to the duration of the procedure (1–1.5 hours) and included dizziness, nausea, and peri-oral 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 plasma exchange were brief and limited to the procedure period. The treatment gains of plasma exchange and IVIG were sustained over the long term. Over 80% of patients who received IVIG or plasma exchange remained "much" or "very much" improved at 1-year follow-up, with their symptoms now in the subclinical range of severity. The results of this investigation suggest that plasma exchange and IVIG may be beneficial to a group of patients with tics, attention deficits with hyperkinesis and obsessive-compulsive symptoms, but these findings require replication. At present, the molecular nature of the post-streptococcal autoimmunity in the PANDAS group 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 plasma exchange 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[37]. 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[38]. 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[39]. 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[40]. 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[41].

Is Antibiotic Prophylaxis for PANDAS feasible?

The streptococcal pathogenesis of rheumatic fever is supported by studies that demonstrated the effectiveness of penicillin prophylaxis in preventing recurrences of this illness[42]. A placebo-controlled trial of penicillin prophylaxis among children in the PANDAS group was conducted to determine if the prevention of GABHS infections would result in neuropsychiatric symptom improvement via the prevention of post-streptococcal exacerbations[43]. 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. So, study was considered to be non-efficacious, and there is a bad need for replication. It is recommended to treat promptly with a 10-day course of penicillin or other appropriate antibiotic, all young children with, abrupt-onset OCD and/or tic disorder, and positive cultures for beta hemolytic streptococci. 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 anti-streptococcal 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 anti-streptococcal 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 and tailored individually. Treatment with immunomodulatory therapies (e.g., Plasma Exchange and IVIG) for children with severe symptoms who fit the PANDAS description carries significant risks and should be used only in severely ill children and under research protocols restrictions.

Conclusion

The PANDAS group 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 the diagnosis of PANDAS. Novel treatment and prophylaxis regimens have brought us closer to our goal of providing complete symptomatic relief to acutely ill children in this group, 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 inhibitors and cognitive-behavior psychotherapy) 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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