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PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—an uncommon, but important indication for tonsillectomy

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Summary Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, also know as ''PANDAS,'' is well described in the neurologic and psychiatric literature. PANDAS is associated with obsessive compulsive disorders (OCD) and tic disorders. The streptococcal infections may trigger an autoimmune reaction that exacerbates these conditions. Recurrent streptococcal tonsillitis is one of the recurrent infections associated with PANDAS. This paper reviews the case reports of two brothers, one with OCD and the other with a tic disorder, both of whom improved significantly after undergoing adenotonsillectomy for treatment of their recurrent tonsillitis. A review of the pathophysiology and current understanding of PANDAS is presented.

1. Introduction

PANDAS, or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, is an uncommon disorder that is infrequently encountered by otolaryngologists. However, it is a disease entity for which otolaryngologists may play an important role in formulating an effective treatment plan. More commonly seen by neurologists or psychiatrists, the diagnostic criteria for PANDAS includes: [1]

1) Presence of obsessive compulsive disorder (OCD) and/or tic disorder.
2) Pediatric onset (age 3 years to puberty).
3) Episodic course of symptom severity.
4) Association with group A beta-hemolytic streptococcal infections (GABHS).
5) Association with neurological abnormalities (motor hyperactivity or adventitious movements, such as choreiform movements).

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We describe two siblings with recurrent tonsillitis, one with Tourette syndrome (TS), the other with OCD, whose psychiatric symptoms were exacerbated by their recurrent tonsillitis. Both fulfilled the criteria for a diagnosis of PANDAS.

2. Case 1

The first patient is 9-year old male who presented to our office for evaluation of his recurrent tonsillitis. He had a history of three documented cases of strep tonsillitis and four additional cases of tonsillitis in the past year. He had previously been diagnosed with TS based upon the presence of motor and vocal tics for 1 year, which had been severe enough to cause functional impairment and physical discomfort. He was being treated with daily clonidine. The patient's mother reported that her son's tic symptoms worsened with each episode of tonsillitis. Anti-streptococcal antibodies were obtained because of a recent history of sore throat and history of worsening tic symptoms at the time of streptococcal infections. These showed mild elevation: the anti-streptolysis O titer was 195 Units (normal < 160), and the anti-streptococcal deoxyribonuclease-B level was 170 Units (normal < 170). The child's father had a history of tics, stuttering, and eye blinking in childhood but had never been diagnosed with TS. Both the mother and brother of the patient had a history of anxiety disorder.

Due to his history of recurrent tonsillitis, a T&A was performed.

Two months after this surgery, the patient was almost totally free of tics, and the clonidine dose could be decreased.

3. Case 2

The second patient, brother of our first case report, is a 10-year old male, who also presented with a history of recurrent tonsillitis, with five documented occurrences of tonsillitis in the past year. He had a history of OCD and anxiety disorder, and had been taking sertraline for the past 5 months. On exam, tonsillitis was present, and a throat culture was negative for GABHS. T&A was performed due to his history of recurrent tonsillitis.

Three weeks post-operatively, the patient, who was previously afraid to leave his home because of his OCD, was outside playing. Sertraline was discontinued after 1 year and he has been discharged by his psychiatrist.

4. Discussion

We describe two siblings with recurrent tonsillitis whose symptoms associated with TS and OCD were exacerbated by tonsil infections and who fulfilled the criteria for the diagnosis of PANDAS. In the diagnostic criteria for PANDAS, a patient must have a pre-existing neurological condition, typically OCD or TS. OCD is well recognized in patients with troubling obsessions and compulsions. Table 1 reviews some of the most common symptoms associated with OCD. OCD is well recognized in-patients with troubling obsessions and compulsions. Obsessions are recurring notions, ideas, or impulses. Compulsions are repeated behaviors carried out to alleviate worry and/or fear [2]. The obsessions typically center on a preoccupation and/or ritualistic behavior of some kind [3]. Tic disorder, or Gilles de la TS, is characterized by intermittent periods of vocal and motor tics. According to the American Psychiatric Association 1994 Diagnostic Criteria for TS, tics are typically present daily and do not recess for periods longer than 3 months. Onset is before age 18 [4]. There is a high prevalence of overlap between OCD and TS [2,4]. In addition, co-morbid psychiatric diagnoses have been identified in cases of PANDAS. In 50 pediatric cases, 40% had ADHD, 42% had affective disorders, and 32% had anxiety disorders [5]. This is of interest to case 2, where the patient had both OCD and anxiety disorder.

In PANDAS, it is believed that the GABHS infection triggers the development of anti-neuronal antibodies that then cross-react with the basal ganglia, an area of the brain responsible for movement and behavior [1]. This pathophysiology of PANDAS is similar to that of Sydenham's chorea, a variant of rheumatic fever. When studies of Sydenham's chorea demonstrated a subgroup of children whose symptoms of OCD were present days or even weeks before the onset of frank chorea, the diagnostic criteria of PANDAS was proposed [5]. Furthermore, since the obsessive–compulsive symptoms appeared before or without the chorea, the notion of ''compensatory psycho-

Table 1 Most common symptoms in children with OCD (Swedo et al. [3])

Compulsions	%
Excessive or ritualized bathing habits	85
Repeating rituals	51
Checking	46
Concern with dirt, germs, or environmental toxins	40

pathology'' was ruled out, and PANDAS was established as a distinct neuropsychiatric disorder [5].

In PANDAS, streptococcal infections trigger the exacerbation of OCD symptoms and/or tics associated with TS. There can be significant lag time between the GABHS infection and the appearance of neuropsychiatric symptoms — in PANDAS, this is usually several days to a few weeks [5].

The GABHS infection is confirmed by a positive throat culture or elevated anti-GABHS antibody (ASO) titers. There should be at least two episodes where there is a clear relationship between the GABHS infection and symptom exacerbation [5]. However, positive ASO titers obtained at the time of increased tic or OCD symptoms do not necessarily confirm a diagnosis of PANDAS since the ASO titers may remain elevated for several months after an infection. More importantly, in making the diagnosis of PANDAS, you need to establish a relationship of both worsening symptoms associated with increased antibody titers and then decreased symptoms associated with decreased antibody titers.

In addition, sero-negativity does not necessarily rule out the diagnosis. Although it is believed that the initial auto-immunity-inciting event is caused by the GABHS infection, stressors such as illness, fever, or fatigue can increase the severity of OCD and TS. Viruses and other illnesses may also trigger more generalized immune responses and symptom exacerbation may follow illnesses besides a GABHS infection [5]. In the fifty cases of PANDAS reported by Swedo et al., symptom onset confirmed by GABHS infections occurred in 42%, with GABHS exposure in 2%, and with symptoms of pharyngitis where no throat cultures or ASO titers were obtained in 28% [5].

Host factors may also be important. PANDAS seems to be more common in males. Age of the patient may also be important with younger children being more susceptible. Rheumatic fever, also caused by GABHS infections, is very uncommon after puberty and there may be some post-adolescent protection to cross-reactive auto-immunity. Genetic and familial factors may also play a role in the pathogenesis of PANDAS. It has been found in rheumatic fever that certain families have a higher incidence of a monoclonal antibody, D8/17. Similarly, patients with PANDAS have been shown to have similar elevations of D8/17 [5].

Specific treatment recommendations for PANDAS have not been established. A randomized, double-blinded study of 37 subjects failed to demonstrate a treatment benefit with the use of prophylactic penicillin in children with PANDAS [6]. At this time, since it is believed that it is not the actual bacteria, but rather the cross reaction of the streptococcal-triggered antibodies with the basal ganglia which instigates the symptom exacerbation, prophylactic antibiotic therapy is not recommended [1]. However, Murphy and Pichichero published a 3 year, prospective study of 12 children diagnosed with PANDAS and reported that in this group each exacerbation of the OCD symptoms associated with GABHS infection responded to antibiotic therapy [7]. In an uncontrolled trial of 29 children, therapeutic plasma exchange and intravenous immunoglobulin were both shown to be superior to placebo for treatment of children with OCD or tic disorders whose neuropsychiatric symptoms were exacerbated by streptococcal infections [8]. However, the exact mechanism of this treatment is not yet known, study populations have been small, and studies of this therapy are still ongoing.

Similar to our cases, in 2001, Orvidas reported on two siblings for whom tonsillectomy was effective treatment. In these cases, both children were free of GABHS infections and symptom exacerbation of OCD and tics 11 months postoperatively [9].

At this time, because there are no large, prospective studies available, we feel that tonsillectomy should be considered in children who meet current tonsillectomy indication standards and a possible history of PANDAS. Parents need to understand the limitations of the surgery and expectations of results must be realistic in view of the lack of larger studies. Investigators at Cincinnati Children's Hospital Medical Center are currently participating in a multi-center trial to further investigate PANDAS and treatment possibilities.

5. Conclusion

Otolaryngologists should be aware of the possibility of PANDAS in children who present with recurrent tonsillitis and comorbid neurologic diagnoses. The history should include questions about a possible relationship between tonsillitis and streptococcal infection and exacerbations of the child's neurological symptoms. Streptococcal antibody titers should be correlated with the child's symptoms if possible. Consultation with the patient's neurologist or psychiatrist may be helpful. Although further prospective studies are needed, tonsillectomy may represent an effective treatment for PANDAS.

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