The Role of Tonsillectomy in the Treatment of Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)

Daniel Demesh, MD; Jordan M. Virbalas, MD; John P. Bent, MD

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) describes neuropsychiatric symptom exacerbations that relate temporally to streptococcal infections. Recent case reports suggest tonsillectomy may effectively reduce these symptoms; however, no consensus treatment guidelines exist. This study examines whether tonsillectomy improves neuropsychiatric symptoms in children with PANDAS who have incomplete response to antibiotic therapy.

Methods

This study was conducted as a retrospective medical chart review of 30 patients suspected as having PANDAS seen from 2006 to 2013 at our tertiary care children's hospital in Bronx, New York. Institutional review board approval was given by The Children's Hospital at Montefiore. To supplement medical chart data, a 9-item questionnaire assessing medical history, timeline of neuropsychiatric symptoms, and symptom response to treatment was administered to parents of all potential participants. Oral consent was obtained, and no stipend was given to participants. Inclusion criteria were based on fulfillment of the 5 diagnostic standards as described by Swedo et al as follows: (1) presence of OCD and/or tic disorder, (2) pediatric onset (age 3 years to puberty), (3) episodic course of symptom severity,
(4) association with GABHS, and (5) association with neurological abnormalities (motor hyperactivity or adventitious movements, eg, choreiform movements).

The 10 patients who met diagnostic criteria for PANDAS were contacted by phone after the procedure to further evaluate the historical timeline of their neuropsychiatric symptoms. Parents of the 9 patients who underwent tonsillectomy were also asked (at a mean follow-up of 4.6 years after surgery) to recall their child’s symptoms at 3, 6, and 36 months after surgery. All of our data regarding timeline of symptoms were gathered retrospectively. A nonvalidated symptom severity scale was developed for our outcomes measurement. Parents were asked to consider the frequency and severity of their child’s symptoms at specific periods in the disease course and compare those symptoms with those at the point at which the symptoms were most severe. They were asked to report on a scale of 0 to 10 (with 0 representing no symptoms and 10 representing the most profound symptoms), the severity and frequency of symptoms prior to any initial treatments, after antibiotic treatment, and at 3-, 6-, 12-, and 36-month intervals after tonsillectomy. From these data, comparisons were made between symptom severity at the time of diagnosis, after treatment with antibiotics alone (10 patients), and after tonsillectomy (9 patients). We compared scores prior to intervention and after antibiotic treatment, and compared scores after tonsillectomy with scores after antibiotics alone. Symptom severity scores were not normally distributed, so they are reported as median (interquartile range [IQR]). Comparisons of symptom severity scores measured at the baseline, after antibiotic administration, and intervals after tonsillectomy of 3 months, 6 months, 1 year, and 3 years were compared using the Wilcoxon signed rank sum test. A 2-tailed α of .05 was used to denote statistical significance. Statistical analysis was performed with SPSS statistical software for Windows (version 20).

Results

Our cohort consisted of 10 patients (8 boys and 2 girls). The average age of onset of the first neuropsychiatric symptoms was 6.5 years. Nine of 10 patients demonstrated tics, and 4 of 10 had psychiatric symptoms, such as anxiety or OCD traits. All of the patients had been treated with antibiotics in the past or were currently receiving antibiotic prophylaxis for recurrent streptococcus infections. In most cases, patients had been exposed to multiple antibiotics over a period of several months. However, the precise duration of each patient’s antibiotic course was unclear because it was frequently implemented outside of our institution. Nine of the 10 children underwent extracapsular tonsillectomy with adenoidectomy. One child, who had experienced partial resolution of symptoms during the first year of treatment with antibiotics, continued to receive antibiotic therapy alone. The total duration of follow-up for this child was 5 years.

The Table displays the compilation of the symptom severity scores across each patient’s treatment course. None of these children experienced spontaneous improvement prior to treatment with antibiotics. During antibiotic treatment, symptom severity scores decreased from a baseline of 10 to a median (IQR) score of 8 (6.5-10.0) (P = .03). Fifty percent of children showed no response to antibiotics, and no child exhibited a complete resolution of symptoms with antibiotics alone. All 9 children who underwent tonsillectomy, including those patients who did not have any response to antibiotic therapy alone, reported decreased symptom severity scores after tonsillectomy. Six of 9 children showed improvement in their symptoms 3 months after they had a tonsillectomy, 3 of whom reported a complete resolution of symptoms. The Figure shows that symptom severity scores improved at all measured time points after tonsillectomy when compared with antibiotics.

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Abbreviations: NA, not applicable; ND, no data.

*Symptom severity scores (on a scale of 0 to 10, with 0 representing no symptoms and 10 representing the most profound symptoms) for all 10 patients at each stage in the treatment timeline, and results of comparison between scores after tonsillectomy and after antibiotics alone.

**Patient 1 did not receive tonsillectomy.

* Comparison for after antibiotics with baseline symptom score.
alone: 3 months posttonsillectomy, the symptom severity scores dropped to a median (IQR) of 3 (0.0-6.5) ($P=0.01$); 6 months postoperatively, 3 (0.0-5.0) ($P=0.02$); 12 months postoperatively, 3 (0.0-5.0) ($P=0.02$); and 36 months postoperatively, 0.5 (0.0-2.3) ($P=0.02$). At maximal follow-up (mean duration of follow-up, 2.2 years) all patients experienced a dramatic decrease in symptom severity. Four of the 9 children, including 2 patients who had no response to antibiotics, reported complete resolution of their neuropsychiatric symptoms. The single child who did not undergo tonsillectomy reported a symptom score as low as 2, but reported multiple exacerbations of neuropsychiatric symptoms requiring continued antibiotic prophylaxis. Similar episodes of worsening symptoms were not reported in any children after tonsillectomy.

**Discussion**

PANDAS has been a controversial disease entity since the original 1998 publication by Swedo et al.² at the US National Institute of Mental Health describing a subset of children with GABHS-associated exacerbations of OCD and tic symptoms.⁴ The controversy behind the diagnosis stems from the broad array of attributable symptoms, the prevalence of streptococcal infections in the pediatric population, and the lack of an identifiable biomarker. Many children diagnosed as having PANDAS have neuropsychiatric comorbidity, including movement disorders, anxiety, emotional lability, and attention-deficit/hyperactivity disorder.⁴ Furthermore, the underlying cause of the disease continues to be a matter of debate, confounding the development of a standard treatment algorithm.⁵ Currently, the most widely accepted hypothesis states that an autoimmune poststreptococcal process in susceptible children leads to development of antineuronal antibodies that cross-react with the basal ganglia, resulting in manifestation of behavioral and motor disturbances.⁶ Because the proposed autoimmune mechanism resembles that of SC, it has led to experimental trials with prophylactic antibiotics and immunomodulatory agents such as intravenous immunoglobulin (IVIG) and plasma exchange (PE).³ Both IVIG and PE were successfully used by Perlmutter et al.⁷ to decrease symptom frequency in patients who met PANDAS diagnostic criteria. However, because immunomodulatory therapies carry considerable morbidity and the study has not been replicated, use of this treatment modality has not been widely accepted. Currently, treatment guidelines do not exist, although some have recommended antibiotic treatment for GABHS infections with standard nonpharmacologic and pharmacologic treatment of persistent OCD or tic disorder symptoms with selective serotonin reuptake inhibitors and cognitive-based therapy.⁸ Studies to evaluate the effectiveness of antibiotics for treatment of acute symptoms and for prophylaxis against future exacerbations have shown equivocal results.⁹⁻¹¹

Recent case reports provide anecdotal evidence that children with PANDAS who undergo tonsillectomy experience fewer subsequent streptococcal infections and neuropsychiatric symptoms.³ From 2001 to 2010, 5 case reports or series.⁴⁻⁵,¹²⁻¹⁴ described a total of 7 children with PANDAS who experienced improvement of symptoms following tonsillectomy. One series⁴ described frequent recurring streptococcal infections despite antibiotic treatment in 2 siblings, who both experienced eradication of OCD and tics within 11 months of tonsillectomy. These reports suggest that adenotonsillectomy may be a valuable treatment option for children with PANDAS.

This study investigates the impact of tonsillectomy on neuropsychiatric symptoms in patients with PANDAS who experienced incomplete response to appropriate antibiotics. These data demonstrate that these children obtained clinically significant relief after tonsillectomy, and 33% experienced complete resolution of symptoms immediately following the procedure. All 9 children who underwent tonsillectomy, even those whose symptoms failed to improve after receiving antibiotics, reported reduced neuropsychiatric symptoms at all measured time points after tonsillectomy. This suggests that tonsillectomy offers a useful treatment alternative for children with PANDAS who incompletely respond to antibiotics.

A recently published prospective study¹⁵ looked at 112 patients with PANDAS who had previous tonsil and or adenoid surgery. The authors showed that PANDAS symptom severity and antibody titer levels did not differ between the surgical and nonsurgical groups. However, 22 of the 32 patients had undergone surgery prior to the development of neuropsychiatric symptoms, 10 of the patients received only an adenoidectomy, and 4 patients received only a tonsillectomy. While these findings seem to show that previous tonsil and/or adenoid surgery does not prevent a child from getting PANDAS, they do not address the question about whether extracapsular tonsillectomy with adenoidectomy diminishes PANDAS symptoms in comparison to antibiotics alone.

Our study is limited by its retrospective design and sample size of 10. The potential for recall bias exists because we have extracted historical accounts of symptom severity from par-
ents. Because parents consented for surgery and were therefore invested in a positive outcome, they were more likely to form favorable perceptions. The absence of a control group makes it difficult to prove that posttonsillectomy improvement was not due to the natural course of the disease. Furthermore, the symptom severity scores that we used have not been validated and rely on potentially biased parental recollection of past symptoms. Nevertheless, this study shows statistically significant improved symptom scores at all time points after tonsillectomy in comparison to antibotics alone. A prospective study could provide more persuasive evidence of the efficacy of tonsillectomy for patients with PANDAS, but such a study would be challenging because of both disease variability and the desire of most families to have surgical treatment.

Conclusions

Although current evidence is inconclusive, the data reported herein support previously described smaller case series and further strengthens the notion that tonsillectomy may benefit patients with PANDAS whose symptoms are not controlled with antibiotic therapy.

REFERENCES