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Tonsillectomies and Adenoidectomies Do Not Prevent the Onset of Pediatric Autoimmune Neuropsychiatric Disorder Associated with Group A *Streptococcus*

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Abstract

Background—In children presenting with obsessive compulsive disorder (OCD) and/or tics, especially those with a temporal association with streptococcal pharyngitis (e.g., PANDAS; Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), there is speculation about whether tonsillectomy/adenoidectomy might improve the child's neuropsychiatric course. Our objective was to examine whether removal of tonsils and/or adenoids impacted streptococcal antibody titers, the timing of onset of OCD and/or tics, and the clinical severity of these symptoms.

Methods—Study participants (n=112; average age=9.2 ± 2.4; 44 female) were recruited as part of a prospective investigation of neuropsychiatric phenomena with temporal association to streptococcal pharyngitis and examined by family history, diagnostic interview, physical examination, medical record review, psychological testing, and streptococcal antibodies and divided into surgical or non-surgery groups. The surgical group consisted of children having previously had a tonsillectomy and/or adenoidectomy (n=32). The remaining children were categorized as non-surgery (N=76). Measures of OCD and tic severity, streptococcal antibody titers, and PANDAS classification were compared between both groups.

Results—There were no significant differences as determined by streptococcal antibody titers, PANDAS classification, and OCD or tic severity between the surgical and non-surgery groups. Most participants had surgery before onset of neuropsychiatric symptoms and surgery did not affect symptomology.

Conclusions—Streptococcal antibodies and neuropsychiatric symptom severity did not differ on the basis of surgical status. From these data we cannot support that tonsillectomy and adenoidectomy are likely to impact positively the course of OCD/tics or streptococcal antibody concentrations.

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Keywords

Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcus (PANDAS); tonsillectomy; adenoidectomy; group A streptococcus (GAS); tics

Introduction

Pharyngitis is a common pediatric medical complaint with 15–30% of infections attributed to group A streptococcus (GAS) [1]. Although a relatively mild illness, untreated GAS pharyngitis can lead to more serious conditions including acute glomerulonephritis, rheumatic fever (RF), and Sydenham chorea (a neurological presentation of RF). Similarly, Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcus (PANDAS), a proposed subtype of OCD/tics has been temporally associated with GAS pharyngitis [2]. To prevent the progression from GAS infection to these chronic morbidities, prompt antibiotic intervention remains the primary course of treatment to eradicate the GAS infection [3]. In PANDAS patients antibiotic treatment of GAS infection has been shown to improve neuropsychiatric symptoms of obsessive-compulsive disorder (OCD) and tics [4, 5].

Tonsillectomy and/or adenoidectomy have also been considered a treatment alternative for the aforementioned infection mediated conditions (e.g., GAS, RF) since the early 1900's [6] and are becoming a more common recommendation as a viable treatment option for PANDAS [7–9] without empirical support. Severe recurrent infections (7 or more episodes in the preceding year, 5 or more in the preceding 2 years or 3 or more in the preceding 3 years), a common feature in PANDAS patients, is often a common indication for surgery [10]. Despite this connection, there is still disagreement as to its efficacy of this treatment option in alleviating these symptoms, and little evidence to support its efficacy in PANDAS [8, 11, 12]. In pathologies resulting from hypertrophy, however, the necessity of surgery in obstructive conditions is accepted as a viable and necessary therapeutic option as morbidity may be reduced and even eliminated through surgery [10, 13].

Surgical treatment modality has been prompted by case reports citing reductions in the symptoms of OCD and tics following surgery [11] as well as reported decreases in the recurrence of GAS pharyngitis [11, 14]. Whereas guidelines exist for tonsillectomy and/or adenoidectomy for the treatment of recurrent GAS pharyngitis [10] no clinical standard exists for utilizing this treatment for symptoms of OCD and/or tics without the presence of indications per the established guidelines.

The objective of the present research was to examine whether removal of tonsils and/or adenoids influenced the clinical presentation (e.g., streptococcal antibody levels, the timing of symptom onset, symptom severity) of OCD and tics in PANDAS patients. We hypothesized that removal of tonsils and/or adenoids does not reduce titer elevations or decrease the intensity of neuropsychiatric symptoms (e.g., OCD or tics) associated with PANDAS.

Method

Participants

Participants were recruited as part of a prospective investigation of neuropsychiatric phenomena with temporal association to streptococcal pharyngitis where the majority of the children were prospectively assessed for over one year. Parents provided written consent, and subjects gave oral assent, and when age appropriate (≥7 years), written assent.

Procedures were approved by the appropriate human subjects review board. A total of 112 participants, ages 4 to 17 years (mean=9.18 ± 2.38 years) were enrolled. Participants were recruited based on the following criteria outlined in Murphy et al. [15]. First, all participants met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [16] criteria for OCD, a tic disorder, or both. Diagnosis was confirmed by clinical interview with the first author and semi-structured diagnostic interview conducted by a trained clinician. Second, participants were specifically questioned regarding any infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms and were then classified as PANDAS (n=43) or non PANDAS (n=69) based on these characteristics. Participants with a psychotic disorder, significant medical illness, or non-tic neurologic disorder at baseline were excluded from the study. Participants on stable doses of psychotropic medication for their condition were not excluded. About half the subjects had multiple GAS infections before the age of 7 years (43% of non-PANDAS participants, 53% of PANDAS). The surgical group comprised children who had a tonsillectomy and/or adenoidectomy procedure (N=36: 4 tonsillectomies, 10 adenoidectomies, and 22 both procedures) and was matched for age and sex in a 1:2 ratio, with non-surgery participants (n=76) (SDC Table 1).

Measures

All assessments were conducted or reviewed by the first author or, for the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS [17]) and Yale Global Tic Severity Scale (YGTSS [18]), by a trained clinician with experience in pediatric OCD and tic disorders.

Laboratory Assays

Three streptococcal antibody assays, antistreptolysin O (ASO), antideoxyribonuclease B (Anti-DNAse B), and anti-A carbohydrate (anti-ACHO), were collected and analyzed according to previously published procedures [15]. Thresholds used to designate groups into elevated or non-elevated categories were: ≥ 200 for ASO, ≥ 240 for the anti-DNASeB, and ≥ 2.76 for the anti-ACHO antibody levels. These thresholds are not age adjusted and may result in some false-negative results for children in the preschool range and false positives for those in middle childhood [19].

Statistical Analysis

Chi-square was used to examine differences in surgical status as a function of antibody elevation status and PANDAS status. Independent t-tests were used to evaluate differences in symptom severity as a function of surgical status. Due to the exploratory nature of this research, alpha of .01 was used to define statistical significance unless otherwise noted; no other statistical correction procedures were implemented.

Results

Do those with a surgical history have lower Streptococcal antibody titers

When titers were examined, there was no significant difference in streptococcal titer elevations among participants who had previously had a surgical procedure 69.4% (n=25) and those without surgery 65.8% (n=50) suggesting that surgery had no effect on lowering streptococcal titers (χ^2=0.97, p=0.37). Similarly, when participants were subdivided on the basis of clinical diagnosis or PANDAS status, there were no significant differences in streptococcal titers observed between participants who had surgery and those who did not have a surgical procedure (see Table 1). Additionally, there was no significant effect of age on titer elevations levels among PANDAS and non PANDAS participants (see Table 2).

Does surgery affect severity of OCD/tics symptoms

CY-BOCS and YGTSS scores were compared among the surgical and non surgical group to determine whether surgery improved the severity of OCD and tic symptoms, respectively. No group differences in CY-BOCS scores (t=0.37; p=0.71) or YGTSS scores (t=0.04; p=0.97) were found on the basis of surgical status (see Table 1). There was no significant difference in the occurrence of OCD and/or tic disorder diagnoses among surgery and non surgery groups (χ^2=1.52, p=0.43 and χ^2=1.17, p=0.38, respectively).

Does surgery influence the age at which OCD/tics symptoms first present

Participants in the surgical group were examined based on time of surgery relative to initial onset of OCD and/or tic symptoms, to assess on the relationship between surgery and delaying (or preventing) the onset of neuropsychiatric symptoms (i.e., tics or OCD). Participants were defined as pre-surgery onset, designating an onset of symptoms before any surgical procedure (tonsillectomy and/or adenoidectomy), or post-surgery onset designating an onset of symptoms after their first surgical procedure. More than half of the surgical group had an initial onset of OCD and/or tic symptoms after their first surgical procedure with the average time of onset 2.4 years after surgery for OCD and 2.9 years for tics (Table 3). The percentage of participants with elevated streptococcal titers did not differ on the basis of time of surgery, with 80.0% having titer elevations in the pre-surgery group and 81.8% with elevated titers in the post-surgery group (χ^2=0.16, p=1.00) (Table 3).

Do participants with PANDAS benefit from surgery

Finally, we examined clinical differences on the basis of surgical status in participants deemed to meet putative criteria for PANDAS. Forty-three participants, 30 of whom were male, met criteria for PANDAS. A total of 20 PANDAS participants had a previous surgical procedure (Table 4). There were no significant differences observed in titer elevations, or OCD and/or tic onset or severity as assessed by CYBOCS and YGTSS scores and age of onset. While there were no significant changes attributable to surgery within our PANDAS population, there was an increased likelihood of having surgery among PANDAS patients with 46.5% of the PANDAS population having surgery compared to 23.2% of the non PANDAS population (p=0.01).

Discussion

In this study, we focused on the effect of tonsillectomy and/or adenoidectomy on the symptoms of OCD and tics associated with PANDAS by examining streptococcal antibody titer levels and OCD/tic symptomology. In 2006, the rate of tonsillectomy, adenoidectomy and the combined surgery among children within the general population was 0.80, 6.87 and 1.76 per 1000 children respectively, a combined rate of 9.43 per 1000 children [20]. In our study, we observed a surgery rate of approximately 32 per 100 children, significantly higher than the overall population rate of 0.943 per 100 and infection related rate of 0.22 per 100 children [20]. Whether this finding of higher rates is due to the direct association of frequent GAS infections in those with PANDAS or whether the removal of this pharyngeal lymphoid tissue indirectly predisposes these patients to increased immunologic risks needs further investigation as there have been mixed reviews on the long term immunologic outcomes of tonsillectomies in children [21, 22]. Additionally a large number of our patients had an onset of OCD/tic symptoms after surgery further necessitating the need for more research in this area.

History of frequent GAS infections is prevalent within the PANDAS patient population [15] and may explain this increased surgical rate but in many cases, the surgeries were performed due to adenoidal and tonsillar hypertrophy. We examined streptococcal titers to determine if

surgery was associated with reduced levels of circulating antibodies, and if this was a potential mechanism for its proposed efficacy. There was no significant difference observed between the surgical and control group. The lack of variation of titer values in association with time since surgery further suggests that neither the age when the surgery was performed nor the time elapsed since the procedure, has a significant impact on biological markers of GAS infection or severity of symptoms. The percentage of patients with elevated streptococcal antibodies was highest in the adenoidectomies group compared with the other surgical and non-surgery groups, but this finding had no impact on clinical severity scores. Streptococcal antibodies and neuropsychiatric symptom severity did not differ on the basis of surgical status. These data suggest that tonsillectomy/adenoidectomy do not impact the course of OCD/tics or streptococcal antibody level. In addition, two children had tonsillectomies while in the study but showed no symptom improvement after the procedure was performed. In fact, many of our subjects developed tics and OCD after tonsillectomy further suggesting that this surgery does little to prevent the onset of these neuropsychiatric symptoms.

More research needs to be conducted to determine if this is more related to the chronicity and recurrence of GAS, or if related to a deficiency of the immune system that causes susceptibility of recurrent infections that may contribute to the PANDAS presentation. In a study by Bombaci and colleagues for example, which compared the sera reactivity to GAS antigens among various groups including those with a diagnosis of tics, with a diagnosed GAS pharyngitis and controls, increased reactivity to streptococcal antigens in tic patients was reported suggesting an enhanced reaction to GAS infection [23]. Interestingly, the sera of tic patients not only showed greater immunoreactivity to GAS antigens but also preferentially recognized specific antigens when compared to other patient groups [23]. These observations may speak to an inherent immunological difference within the tic, and possibly the PANDAS patient population, that manifest an aberrant response to immunological challenge. It is possible that the psychiatric symptoms may be secondary to neuroimmune reactions that are non-specific to the type of infectious trigger but secondary to an inherent, broader immune risk such as an overactive innate immune system and/or a critical period of mild immunodeficiency due to delayed immunological maturation.

Tonsillectomies in early childhood may have negative effects on localized immunological responses [24]. However, symptomatic GAS infections have been shown to decrease within the first two post operative years in patients who required the procedure due to repeated GAS pharyngeal infections [25, 26]. Reports also state that tonsillectomized children are three times less likely to have subsequent GAS infections [25]. However, measurable short-term parameters of immunologic function modification have been observed post surgery. Both humoral (immunoglobulins A, G, M) and cellular (CD3, CD4, CD8) parameters significantly decrease postoperatively, but tend to normalize six months later [27, 28]. The long-term impact of this transient, mild immunosuppression caused by surgical removal of the tonsils and/or adenoids in the development of autoimmune sequelae has yet to be determined. A pattern of decreased and predictable normalization of immunoglobulins has been identified [27] along with increase in cellular immunity, indicating a reactive pattern in cellular and humoral immunity [27]. What we have yet to determine is whether these fluctuations have a direct effect on the development of neuropsychiatric illness.

Our study had several limitations including a lack of prospective follow-up of the larger sample of children receiving tonsillectomies for any indication and specifically for neuropsychiatric conditions and the lack of prospective measurement and analysis of antibody titer levels. All of our subjects had existing OCD and/or tics at study entry. If a subset of youth did have OCD/tic remission after the surgical procedure, our study would not have detected those. Of those having the surgical procedure during the prospective

study, none remitted. Several factors can influence titers and subsequent analysis. As titers were assessed at study entry, most of the antibody levels obtained for this analysis were not in temporal proximity to OCD/tic onset as the subjects had a variable duration of illness at baseline. Furthermore, antibody levels may remain elevated for months [29] so that a single time point showing a titer elevation provides very little information about the timing of the streptococcal infection. A rise in serial titers has been shown to be a more reliable determinant of a recent infectious trigger [19, 29]. Age adjustment of titers was also a limitation in this study, as it has been shown that normal titer values vary depending on patient age [19]. Subjects were predominantly ages 7–12.9 years with 72% of the surgical population and 81.6% of the non-surgical population belonging to this age group. Similarly 81.4% of our PANDAS and 76.8% of our non-PANDAS group fell within this age range.

Based on our data however, we conclude that removal of tonsils and/or adenoids is not associated with lower titers or with a decrease in the intensity of neuropsychiatric symptoms (e.g., OCD or tics). This is especially important when considering tonsillectomies as a therapeutic option in the treatment of PANDAS in light of the potential complications. Although tonsillectomies remain the most performed surgery for patients under the age of 15 years, and is often performed on an ambulatory basis, it still poses inherent risk including post operative hemorrhage, trauma to the larynx and surround structures and cardiac arrest [10]. Research must still be done in order to clarify whether the association between the clinical need for surgical intervention has a causal, circumstantial, or parallel relationship to PANDAS presentation development in the context of an infection-associated immune reaction. Additionally, reports of symptom improvement must be carefully examined to determine the extent to which surgery may be implicated in perceived improvement. Reports by Ovidas and colleagues for example have reported significant reductions in the number of GAS infections, and the latency between infections following tonsillectomies [14]. Since post infection exacerbation is a key feature of PANDAS, several studies have also reported improvements in neuropsychiatric symptoms (e.g. OCD and tics) following surgery. While these case studies have reported symptom eradication up to a year post surgery, it is important to note that several of these cases also report the concurrent use of antibiotic and or psychotropic treatment. In one notable case report for example, the patient initially presented with Tourette syndrome, a history of recurrent infection, and symptom exacerbation following infection. While symptoms were reported as almost completely eradicated following surgery, the patient was concurrently on psychotropic intervention [30]. In another study, which focused on two brothers ages 9 and 10, alleviation of symptoms (tics and anxiety respectively) were again reported although in both instances, they remained on psychotropic medications, albeit at a decreased dosage, following the procedure [31]. While we are not discounting the validity of these accounts, it is important to address the potential confounds of these cases such as concurrent pharmacological intervention, as well as reports of OCD and tic symptoms emergence following tonsillectomy procedures [32]. In light of our findings, and the ongoing debate as to the long-term immunological effects of tonsillectomy, these studies reiterate the need for more research in this area.

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Table 1

Characteristics and clinical diagnosis among surgery and non surgery participants

Diagnosis	Surgery	Non surgery	*p*
OCD	35 (97.2%)	69 (90.8%)	
Elevated titers	24 (68.6%)	45 (65.2%)	*0.37*
Age of Onset (yrs)	5.9 ± 2.1	6.5 ± 2.7	*0.32*
Duration of symptoms (yrs)	2.5 ± 2.1	3.3 ± 2.5	*0.09*
CY-BOCS total	17.9 ± 9.9	18.7 ± 10.5	*0.71*
Tic Disorder	33 (91.7%)	64 (84.2%)	
Elevated titers	24 (72.7%)	43 (67.2%)	*0.47*
Age of Onset (yrs)	5.9 ± 2.3	6.6 ± 2.6	*0.22*
Duration of symptoms (yrs)	2.6 ± 2.3	3.0 ± 2.2	*0.40*
YGTSS total	33.4 ± 23.5	33.6 ± 21.6	*0.97*

Titer levels were not available for two participants (one in the surgery group and one in the non-surgery group).

Table 2

Streptococcal titer characteristics of PANDAS population based on surgical status.

	*PANDAS (n=43)		Non-PANDAS (n= 69)	
	Surgery n=20 (46.5%)	**Non surgery n=23 (53.5%)**	**Surgery n=16 (23.2%)**	**Non surgery n=53 (76.8%)**
Male	14 (70%)	16 (70%)	9 (56%)	30 (57%)
Female	6 (30%)	7 (30%)	7 (44%)	23 (43%)
Age < 6.9	4 (20%)	3 (13%)	5 (31%)	7 (13%)
Age 7–12.9	15 (75%)	20 (87%)	11 (69%)	42 (79%)
Age > 13	1 (5%)	0	0	4 (8%)
Elevated titers	17 (85%)	20 (87.0%)	10 (63%)	31 (59%)
Male	12 (86%)	16 (100%)	8 (89%)	21 (68%)
Female	5 (83%)	4 (57%)	2 (25%)	10 (32%)
ASO Mean	2.40	2.38	2.32	2.23
Age < 6.9	2.11	2.27	2.27	2.18
Age 7–12.9	2.42	2.40	2.33	2.26
Age > 13	2.90	.	.	2.0
Anti-DNASe Mean	2.20	2.27	2.11	2.09
Age < 6.9	1.81	1.53	1.93	1.94
Age 7–12.9	2.25	2.39	2.16	2.13
Age > 13	2.68*	.	.	1.89
ACHO Mean	2.64	2.44	2.50	2.51
Age < 6.9	2.31	2.46	2.37	2.42
Age 7–12.9	2.64	2.44	2.53	2.51
Age > 13	3.21*	.	.	2.65

Analysis were based on intra-group (PANDAS surgery vs. non-surgery) and inter-group (surgery PANDAS vs. non-PANDAS, non-surgery PANDAS vs. non-PANDAS). Participants were stratified by age for titer analysis. Titers expressed in log scale.

Table 3

OCD/tic/PANDAS symptomology based on time of surgery.

Neuropsychiatric Symptom		Pre-surgery onset	Post-surgery onset
Total	**N**	**10**	**22**
	Elevated titers, N (%)	**8 (80.0)**	**18 (81.8)**
PANDAS	N	6	13
	Elevated titers, N (%)	6 (100.0)	11 (84.6)
OCD	N (%)	6	25
	Elevated titers, N (%)	4 (66.7)	21 (84.0)
	Mean age at onset (yrs)	4.6 ± 1.5	6.4 ± 2.2
	Mean CYBOCS score	19.90	16.50
	Mean age at surgery (yrs)	7.4 ± 3.7	4.1 ± 1.7
	Mean onset to surgery duration (yrs)	−2.8 ± 3.2	2.4 ± 1.9
Tics	N (%)	8	22
	Elevated titers, N (%)	7 (87.5)	17 (77.3)
	Mean age at onset (yrs)	3.6 ± 2.0	6.7 ± 1.9
	Mean YGTSS score	39.00	27.35
	Mean age at surgery (yrs)	6.6 ± 3.7	3.9 ± 1.7
	Mean onset to surgery duration (yrs)	−3.0 ± 3.7	2.9 ± 2.1

Of the 36 participants in the surgery group, age at surgery was not available for 4 youth; titers were not available for one youth. Mean onset to surgery duration was taken as the difference between the time of initial neuropsychiatric symptom onset/diagnosis (i.e., OCD or tics) to the time of first surgical procedure.

Table 4

Diagnostic characteristics of PANDAS population based on surgical status.

	*PANDAS (n=43)		Non-PANDAS (n= 69)	
	Surgery n=20 (46.5%)	**Non-surgery n=23 (53.5%)**	**Surgery n=16 (23.2%)**	**Non-surgery n=53 (76.8%)**
Male	14 (70%)	16 (70%)	9 (56%)	30 (57%)
Female	6 (30%)	7 (30%)	7 (44%)	23 (43%)
OCD and tics	19 (95.0%)	17 (73.9%)	13 (81.3%)	40 (75.5%)
Male	13 (92.9%)	9 (56.3%)	6 (66.7%)	25 (83.3%)
Female	6 (100%)	7 (100%)	7 (100%)	15 (65.2%)
OCD only	1 (5.0%)	4 (17.7%)	2 (12.5%)	8 (15.1%)
Tics only	0 (0%)	2 (8.7%)	1 (6.3%)	5 (9.4%)
OCD onset (yrs)	6.0 ± 1.8	6.0 ± 2.9	5.8 ± 2.6	6.4 ± 2.9
CY-BOCS Total	20.3 ± 8.8	17.3 ± 10.4	14.8 ± 10.6	18.2 ± 11.1
Tic onset (yrs)	6.2 ± 1.8	6.6 ± 2.1	5.5 ± 2.8	6.6 ± 2.9
YGTSS Total	32.7 ± 23.6	26.6 ± 23.4	32.0 ± 25.0	34.2 ± 21.7

A significant portion of PANDAS participants had surgery when compared to their non-PANDAS counterparts (p=0.01). Analysis were based on intra-group (PANDAS surgery vs. non-surgery) and inter-group (surgery PANDAS vs. non-PANDAS, non-surgery PANDAS vs. non-PANDAS). Differences based on sex were not significant.