PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH GROUP A STREPTOCOCCAL INFECTION: THE ROLE OF SURGICAL TREATMENT

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Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) is a well-defined syndrome in which tics (motor and/or vocal) and/or obsessive compulsive disorders (OCD) consistently exacerbate in temporal correlation to a Group A beta-haemolytic streptococcal infection. In children with PANDAS, there is speculation about whether tonsillectomy or adenotonsillectomy might improve the neuropsychiatric course. Our objective was to examine whether such surgery impacted remission or, in patients without remission, modified clinical course of the disease, streptococcal antibody titers, neuronal antibodies or clinical severity of Obsessive-Compulsive Disorder (OCD) and/or tics. Study participants (*n* = 120) with positive PANDAS criteria were recruited, examined, and divided into surgical or non-surgery groups. The surgical group consisted of children with tonsillectomy or adenotonsillectomy (n=56). The remaining children were categorized as non-surgery (n=64). Clinical follow-up was made every 2 months for more than 2 years. Surgery did not affect symptomatology progression, streptococcal and neuronal antibodies, or the clinical severity of neuropsychiatric symptoms in these children. In conclusion, in our series clinical progression, antibody production, and neuropsychiatric symptom severity did not differ on the basis of surgical status. We cannot uphold surgical management as likely to impact positive remission rates, course of OCD/tics, or antibody concentrations in children with PANDAS.

Streptococcal infection in children is usually benign and self-limited. Sydenham chorea is one of the best-defined and best-recognized post-streptococcal pathology. The term "Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus" infections (PANDAS) was coined by Swedo et al. in 1998 to describe a subset of childhood Obsessive-Compulsive Disorder (OCD)

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and tic disorders triggered by group A β-hemolytic streptococcal (GABHS) infection (1-20).

PANDAS have become a popular concept among patients, clinicians and researchers. However, their clinical definition and prevalence are still debated. During the last 15 years, several limitations of the working diagnostic criteria for PANDAS have been highlighted (10-20). Moreover, different attempts to ascertain their frequency within the general population of youths with tics and OCD were not successful. Reliable diagnostic biomarkers are still not available and their pathogenesis remains undefined. This led to a recent nosographic reappraisal of PANDAS, implying that further work is needed to define the clinical boundaries of post-streptococcal disorders within the rubric of acute pediatric neuropsychiatric symptoms (14). For this reason the term PANDAS, were less used and some Authors try to change it into Pediatric Autoimmune Neuropsychiatric Disorder (PANS) or Childhood Acute Neuropsychiatric Syndromes (CANS) (14). The purpose of our work is to evaluate the impact of surgery (tonsillectomy or adenotonsillectomy) in children with PANDAS.

PANDAS constitutes a subset of children with tics and/or OCD that sometimes overlap Tourette syndrome. Like adult OCD, PANDAS is associated with basal ganglia dysfunction (4, 20).

Prompt antibiotic intervention remains the primary course of treatment to eradicate the GABHS infection and to prevent the progression from GABHS infection to these chronic morbidities (17-20). In PANDAS patients, antibiotic treatment of GABHS infection has been shown to improve neuropsychiatric symptoms OCD and tics (14, 17, 20-23).

Tonsillectomy or adenotonsillectomy have also been considered a treatment alternative for the aforementioned infection-mediated conditions, becoming a more common recommendation as a viable treatment option for PANDAS without empirical support (12, 18). 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 (1, 5). Despite this connection, there is still disagreement as to the efficacy of this treatment option in alleviating these symptoms, and little evidence to support its efficacy in PANDAS (4, 5, 7, 19).

The objective of the present research was to examine whether removal of tonsils or of adenoids and tonsils influenced the clinical course or the clinical features in PANDAS patients. We hypothesized that removal of tonsils or of adenoids and tonsils does not affect remission rates and in patients with persisting disease does not affect the time progression (interval between onset and first relapse). Likewise, we hypothesized that surgical treatment does not reduce titer values or decrease the intensity of neuropsychiatric symptoms (e.g., OCD or tics) associated with PANDAS.

MATERIALS AND METHODS

All the participants included in our study had met the criteria of PANDAS (see below); all the children were prospectively assessed for over 2 years. Parents provided written consent; subjects gave oral approval and, when age appropriate (8 or more years), written consent. Procedures were approved by the appropriate human subjects review board. Participants were recruited based on the following criteria outlined in Pavone et al. (20) and Murphy et al. (15). First, all participants met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (2) criteria for OCD, a tic disorder, or both. Diagnosis was confirmed by clinical interviews with one of the first six authors and semi-structured diagnostic interviews 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 (all this neuropsychiatric phenomena were in temporal association to streptococcal pharyngeal tonsillitis), and were then classified as PANDAS (n = 120) based on these characteristics. The PANDAS diagnosis is a clinical diagnosis without any specific test for the diagnosis at the present time (20). Below are reported the five clinical findings for making a diagnosis of PANDAS. 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 and or psychiatric medications for their condition were also excluded (to make the sample more homogeneous). A small percentage of patients, less than 5%, at the same time underwent non-drug psychological therapy such as behavioural therapies. Some patients were

treated with antibiotic therapy, anti-inflammatory and intravenous immunoglobulin (IVIG) in the acute phase in combination with behavioural therapies in 5% of the children. We utilized only IVIG in 8 patients with acute or chronic disease with a striking symptomatology with a temporary improvement of symptoms at the dosage of 2g/kg/die for 1 day in 6 patients and for 2 days in 2 patients. Frequently, but not in the PANDAS children, unlike patients with ODC and Tourette syndrome (TS), patients may require narcoleptics or psychotic therapy. Plasmapheresis has never been carried out in our series. The patients were subjected to antibiotic therapy when inflammatory markers were high or when required by the clinical conditions and we used third-generation cephalosporins for 5-7 days orally bis a/day or azithromycin for 3-5 days/daily.

Study participants (n = 120; average age = 11.05±1.2 yrs; 57 female, 63 male) with positive PANDAS diagnostic criteria (20, 24) [All five diagnostic criteria must be met: i) presence of obsessive-compulsive disorder (OCD) or a tic disorder; ii) prepuberal symptom onset; iii) acute symptom onset and episodic (relapsing-remitting) course; iv) temporal association between Group A streptococcal infection and symptom onset/exacerbations; v) associated with neurological abnormalities, particularly motor hyperactivity and choreiform movements] were enrolled and examined by family history, diagnostic interview, physical examination, medical record review, psychological testing, and streptococcal and neuronal antibodies and divided into surgical or non-surgery groups (21). The surgical group consisted of children referred for tonsillectomy and adenotonsillectomy (n=56: 25 tonsillectomies and 31 adenotonsillectomies). The referral criteria were essentially a clinical history of recurrent inflammation, according to the aforementioned guidelines.

Surgical treatment was decided after a briefing consultation from an othorinolaringologist, a pediatric neurologist and/or a child neuropsychiatrist, with the presence of a chronic inflammatory process or other respiratory involvement, such as Obstructive Sleep Apnea Syndrome (OSAS), and the children were not assigned for surgery prior to the beginning of the follow-up. The remaining children were categorized as non-surgery (n=64). Clinical assessment was made every 2 months for each person and were followed up for 2 years. The study is part of a research project in progress for "The study group of immunological and immune-mediated disorders of the SINP (Italian Society of Paediatric Neurology).

Neuropsychiatric evaluation

All assessments were made by a pediatrician with a subspeciality in pediatric neurology and/or child psychiatry, and many of the main Authors had specific knowledge of this disease; for the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and Yale Global Tic Severity Scale (YGTSS), assessment was made by a trained clinician with experience in pediatric OCD and tic disorders (2, 13, 22).

Laboratory assays

Antistreptolysin O (ASO), antideoxyribonuclease B (anti- DNAse B), and antineuronal antibodies were collected and analyzed according to previously published procedures (15, 21). Thresholds used to designate groups into elevated or non-elevated categories were: 266 for ASO and 232 for the anti-DNASe B. The antineuronal antibody were positive when staining at 1:10 serum dilution (defined as detectable staining) conversely, negatives were absent (21).

Statistical analysis

Statistical comparisons were carried out using SPSS 18.0; *chi*-square analysis and independent *t*-test were computed to identify group differences regarding the clinical course of the syndrome and the presence of antibodies and to compare neuropsychiatric severity based on CY-BOCS and YGTSS between the surgical group and the non-surgery group. Risk ratio (RR) was computed to assess the effects of surgery on remission rates of the disease.

RESULTS

No differences were observed between the two groups regarding remission rates. Surgical management did not prove to increase significantly the percentage of patients with resolution of the syndrome (RR = 1.39; 95% Confidence intervals (CI) = 0.75 - 2.55; p = 0.29) (Table I - Rates of remitted patients in the 2 groups).

When comparing the patients with persisting disease, there were no significant differences regarding the progression of the syndrome between the 2 groups, and indeed no differences were observed in the time interval from the onset to the first relapse (p = 0.09), suggesting that surgery has no efficacy in delaying or changing the course of pathology (Table II).

Furthermore, during the first disease relapse no differences were found after we focalized our attention in relapsing form of PANDAS; antibody levels were assessed and we found no significant differences in ASO, anti-DNAse B and antineural antibody presence between the two groups, suggesting that surgery had no effect on streptococcal

Table I. *Rates of remitted patients in the two groups.*

	Number of remitted patients (%)	Number of relapsing patients (%)	Total numbers (%)
Surgerygroup	17 (30.357%)	39 (69.642%)	56 (100%)
Non-surgerygroup	14 (21.875%)	50 (78.125%)	64 (100%)

p = 0.29; Risk ratio (RR) = 1.39; 95% Confidence intervals (CI) = 0.75 - 2.55

Table II. *Time between onset and the first relapse.*

	Patients with persisting disease in surgery group (n=39)	Patients with persisting disease in non-surgery group (n=50)
Mean number of days between onset and first relapse (SD)	45.1 (17.8)	39.3 (14.2)

p = 0.09; n: number of patients; SD: standard deviation

Table III. *Antistreptolysin O (ASO) differences at first relapse.*

	ASO < 266	ASO > 266	Total numbers (%)
Patients with persisting disease in surgery group	14 (36%)	25 (64%)	39 (100%)
Patients with persisting disease in non-surgery group	23 (46%)	27 (54%)	50 (100%)

p=0.45; ASO: antistreptolysin O

Table IV. *Antideoxyribonuclease B (Anti-DNAse B) differences at first relapse.*

	Anti- DNAseB < 232	Anti- DNAseB > 232	Total numbers (%)
Patients with persisting disease in surgery group	14 (36%)	25 (64%)	39 (100%)
Patients with persisting disease in non-surgery group	22 (44%)	28 (56%)	50 (100%)

p=0.57; Anti-DNAse B: antideoxyribonuclease B

Table V. *Antineural antibodies differences at first relapse.*

	Antineural antibodies: negative	Antineural antibodies: positive	Total numbers (%)
Patients with persisting disease in surgery group	21 (64%)	18 (46%)	39 (100%)
Patients with persisting disease in non-surgery group	29 (58%)	21 (42%)	50 (100%)

p=0.85

Table VI. *Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and Yale Global Tic Severity Scale (YGTSS) differences at first relapse.*

	Patients with persisting disease in surgery group (n=39)	Patients with persisting disease in non-surgery group (n=50)	
CY-BOCS: M (SD)	17.5 (6.1)	18.1 (5.9)	p= 0.63
YGTSS: M (SD)	19.9 (6.4)	20.7 (6.2)	p= 0.57

N: number of patients; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; YGTSS: Yale Global Tic Severity Scale; M: mean; SD: standard deviation

titers (ASO: p=0.45; anti-DNAse B: p=0.57 and antineural antibodies: p=0.85) (Tables III, IV, V).

Likewise, surgery did not seem to affect the severity of neuropsychiatric symptoms in our children. At first relapse we compared OCD and/or tic clinical severity as assessed by CYBOCS and YGTSS scores; no differences were seen between the groups (CYBOCS: p = 0.63; YGTSS: p = 0.57) (Table VI).

DISCUSSION

Children with obsessive compulsive disorder or tic disorders that are associated with streptococcal infections (Group A beta-hemolytic) in the oro-pharyngeal region are given the diagnosis of Pediatric Autoimmune Neuropsychiatric Disorders associated with streptococcal infections (PANDAS). Tonsillectomy has been reported to resolve the neuropsychiatric symptoms in these children (1, 15). Alexander et al. in 2011 (1), reported on a 9-year-old boy with multiple recurrent streptococcal infections of the oro-pharyngeal cavity associated with neuropsychiatric symptoms including agitation, hyperactivity and tics. These symptoms followed his recurrent infections. Tonsillectomy was performed and in one-year follow-up the patient did not have any recurrent streptococcal infections and his neuropsychiatric symptoms had resolved completely.

From the perspective of an otorhinolaryngologist, several reports of tonsillectomies have been curative of both recurrent GABHS infections and PANDAS symptoms (1, 8). Batuecas et al. (4) describe a child with PANDAS, namely facial grimaces and tics, associated with recurrent GABHS, who, after undergoing tonsillectomy, had resolution of his neuropsychiatric symptoms. Huebi and Shott (9), reported clinical improvement in two brothers, one with OCD and the other with tics related to PANDAS, with recurrent tonsillitis, who

had complete resolution after tonsillectomy. Two siblings with PANDAS-associated symptoms and recurrent GABHS infections of the oropharynx also had resolution of their neuropsychiatric symptoms with tonsillectomy (18).

Fusco et al. (8), describe the case of an 11-year-old boy who developed PANDAS with severe choreic movements. The criteria for PANDAS diagnosis were met, with serum antibrain antibodies also present. The patient was initially treated with tetrabenazine 12.5 mg twice daily with remission of the neurological symptoms. Subsequently, the patient underwent tonsillectomy with a resolution of the symptomatology, and antistreptolysin O titers were found to be within the normal range. These cases, of course, are ambigous because perhaps, the right diagnosis would be Sydenham Chorea. Some authors (1, 6), assert that in the lack of complete resolution with conservative management, tonsillectomy should be considered as an indication for children with recurrent oropharyngeal GABHS infections with PANDAS, and that tonsillectomy should be included as an indication for PANDAS with recurrent GABHS infections by the American Academy of Otolaryngology-Head and Neck Surgery. However, this has not found widespread agreement because of the lack of strong evidence (5).

Some children developed tics and OCD after tonsillectomy, further suggesting that this surgery does little to prevent the onset of these neuropsychiatric symptoms (15).

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 (5, 19, 26).

In 2013, Murphy et al. (16) explored 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 symptomatology. 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 1,000 children respectively, a combined rate of 9.43 per 1,000 children (16). These authors 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 (16). Whether this finding of higher rates is due to the direct association of frequent GABHS 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 (25, 27). Additionally, a large number of these patients had an onset of OCD/tic symptoms after surgery, highlighting the need for further research in this area. History of frequent GABHS 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. Murphy et al. (15, 16), examined streptococcal titers to determine whether surgery was associated with reduced levels of circulating antibodies, and whether this was a potential mechanism for its proposed efficacy. In our series, no significant difference was observed between the surgical and the control groups. The lack of variation of titer values in association with time from 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 GABHS infection or severity of symptoms. In all our children, there was no statistically significant difference in any of the analyses we made, suggesting that tonsillectomy does not impact the course of the disease.

Of course, our study had several limitations, the first being the small number of the children implicated. Furthermore, several factors can influence titers and subsequent analysis, and antibody levels may remain elevated for months (11), 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 (10, 11). 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 (11). Subjects ages 8-14 years were predominant; about 90% of the surgical population and 88.6% of the non-surgical population belonged to this age group.

Based on our data, however, we conclude that removal of tonsils or adenoids and tonsils is not associated with lower titers or with a decrease in the intensity of neuropsychiatric symptoms (e.g., OCD or tics); moreover, it does not affect either the interval time between onset and relapse or the rates of remission, this last point being the most important. This is especially important when considering adenotonsillectomy as a therapeutic option in the treatment of PANDAS in light of the potential complications (3). Still, these surgical options remained the most-performed surgery for patients under the age of 15 years, when tonsils are cryptic or with sign of chronic inflammation, or in the presence of other condition associated with PANDAS (for example, OSAS) (4, 5, 19). In the light of our findings, research must still carried out in order to clarify whether the surgical intervention could have a relationship to PANDAS presentation and development. Literature review reveals quite opposed findings on the role of surgical treatment in PANDAS syndrome management. Our study provides evidence regarding the lack of efficacy of tonsillectomy or adenotonsillectomy in affecting the clinical course and the clinical severity of PANDAS syndrome. Furthermore, the immune response of the patients, which is now considered the pathogenesis basis of the syndrome, does not seem to be affected by surgical management. According to these findings, surgery should not be considered as a treatment option unless more significant pathological elements, such as chronic inflammation or concurrent obstructive sleep apneas, are present.

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