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ASSOCIATION OF ADENOTONSILLECTOMY WITH WHEEZING EPISODES IN CHILDHOOD: A SECONDARY ANALYSIS OF THE CHILDHOOD ADENOTONSILLECTOMY TRIAL

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Abstract

Background: Observational studies suggest that asthma/wheezing improve after adenotonsillectomy (AT). However, there is a paucity of RCT specifically studying the effects of AT in asthma/wheezing. Therefore, we conducted a post-hoc analysis of the Childhood Adenotonsillectomy Trial, the largest RCT of AT in children with obstructive sleep apnea (OSA) to test the hypothesis that AT would result in fewer wheezing episodes. **Methods**: In the CHAT study, 464 children with OSA, aged 5 to 9 years, were randomized to early AT (n=226) or watchful waiting with supportive care (WWSC) (n= 227). For this post-hoc analysis children were categorized as having "any wheezing" vs. "no wheezing" at baseline and at 7 months of follow-up. A multivariate analysis was conducted to evaluate the association between "any wheezing" at follow-up and treatment group after controlling for several potential confounders. **Results**: Children in the "any wheezing" group were predominantly black, had more allergic rhinitis, eczema, second-hand smoke exposure, more siblings and siblings with asthma, lower maternal education and family income than those in the "no wheezing group". At baseline, wheezing characteristics were similar between AT and WWSC arms. At follow-up (at 7 months of the intervention) those in the AT arm had significatively less wheezing than those in the WWSC (22.4% vs. 43.8%, p=0.00001). However, the multivariate analysis of "any wheezing" vs. "no wheezing" at follow-up showed that the treatment arm was not associated with wheezing. **Conclusion:** This study demonstrated that AT has not effect on wheezing at 7 months of follow-up.

INTRODUCTION

Adenotonsillectomy (AT) is one of the most common surgical procedures performed in children. The most frequent indications for AT are obstructive sleep apnea (OSA), refractory or recurrent sinusitis or middle ear infections, and recurrent infection of the tonsils and/or adenoids. Since birth to adolescence, several mucosal immune systems develop in the upper and lower respiratory tract. The nasopharyngeal-associated lymphoid tissues comprise the nasopharyngeal adenoidal tissue nasopharyngeal, tubal, palatine, and lingual tonsils. Hypertrophy or frequent episodes of inflammation can occur within adenotonsillar tissues due to continuous exposure to antigens, such as micro-organisms and allergens [1,2].

Asthma is a common chronic disease in children and its association with sleep-disordered breathing (SDB) has been observed by our group and others [3-5]. Furthermore, SDB may affect asthma control [6]. Although, causality has not been proven [4].

Published evidence regarding the effect of AT on asthma in children is controversial. Some observational studies have demonstrated that AT has a positive effect on childhood asthma by reducing the effect of

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stressors on the lower airway, leading to decreased inflammation and improved asthma control [7-9]. In most of these studies, adenotonsillar hypertrophy, and symptoms of sleep-disordered breathing, were the commonest indications for AT. In contrast, one cohort study showed that early-life adenoidectomy due to recurrent otitis media or otitis media with effusion, may contribute to the subsequent development of asthma in children [10], and a recent South Korean cohort study showed that the adjusted asthma hazard ratio was 2.25 in the AT vs. non-AT groups [11]. However, the only randomized clinical trial (RCT) that has analyzed the role of adenoidectomy in the development of atopy and respiratory function changes characteristic of asthma in young children, showed that adenoidectomy did not promote the occurrence of asthma or allergy [12]. Since tonsils have an important function in the differentiation of B lymphocytes to antibody-producing plasma cells and were not removed in that RCT; results should be interpreted with caution.

Therefore, our objective was to conduct a post-hoc analysis of CHAT [13], the largest RCT of AT in children with OSA to test the hypothesis that AT would result in fewer wheezing episodes in children randomized to AT vs watchful waiting.

METHODS

The Childhood Adenotonsillectomy Trial (CHAT) was a single-blind, randomized, controlled trial at seven academic sleep centers (ClinicalTrials.gov number, NCT00560859). Methodologic details have been published previously [13]. Briefly, eligible children aged 5 to 9 years, with OSA syndrome (OSAS) without prolonged oxyhemoglobin desaturation considered suitable candidates for AT were enrolled. OSAS was defined as an obstructive apnea–hypopnea index (AHI) score of 2 or more events per hour or an obstructive apnea index (OAI) score of 1 or more events per hour. Children with an AHI score of more than 30 events per hour, an OAI score of more than 20 events per hour, arterial oxyhemoglobin saturation of less than 90% for 2% or more of the total sleep time were not eligible, owing to the severity of the polysomnographic findings. Exclusion criteria included recurrent tonsillitis, a z score based on the body-mass index (the weight in kilograms divided by the square of the height in meters) of 3 or more, and medication for attention deficit–hyperactivity disorder. Children were randomly assigned to two arms of treatment: early AT within 4 weeks after randomization or a strategy of watchful waiting with supportive care (WWSC).

The primary outcome of this post-hoc analysis was wheezing at 7-months of follow-up after AT. Wheezing was divided in two groups: "no wheezing" and "any wheezing". The latter included rarely (less than once a week), sometimes (1 to 2 times per week), frequently (3 to 4 times per week) and always or almost always (5 to 7 times per week). "Any wheezing" was further divided according to the severity of wheezing in three groups: frequent wheezing (sometimes, frequent, and always), rarely wheezing, and no wheezing.

Statistical analysis:

Bivariate analyses comparing baseline demographic and clinical characteristics of children in the "no wheezing" vs. "any wheezing" groups were performed using Fisher's exact test or t tests as appropriate. Also, bivariate analysis for wheezing characteristics at baseline and at follow-up between the two treatment arms were conducted. Multivariable analyses were then performed using logistic regression to evaluate the association between wheezing characteristics at follow-up and arm of treatment (AT vs. WWSC), conservatively adjusting for variables with a p value < 0.10 in the bivariate analysis: gender, race, rhinitis, eczema, second hand-smoke exposure, premature, number of siblings, sibling with asthma, maternal level of education and family income. In addition, a priori selected potential confounder factors, such as age, BMI z-score, AHI, and parental asthma were also included. These were retained in the final model if their coefficients were significant, altered the significance of the wheezing characteristics, or contributed significantly to the best model fit. A $p < .05$ was considered statistically significant. The R version 4.1.3 ® software was used (www.r-project.org).

RESULTS

In the CHAT study, 464 children, aged 5 to 9 years, with the OSA syndrome were randomized to AT (n=226) or WWSC (n= 227). Information for wheezing characteristics at baseline was available for 216 children in

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the AT and 216 in the WWSC. Baseline characteristics per study group (any wheezing vs no wheezing) are shown on Table 1. Children in the "any wheezing" group were predominantly black and had more allergic rhinitis, eczema, second-hand smoke exposure, more siblings and sibling with asthma than the children in the no wheezing group. In contrast the any wheezing group had lower maternal education and family income than the no wheezing group. Nearly half the participants in both groups were overweight or obese, and the AHI was similar between groups.

At baseline, wheezing characteristics were similar between AT and WWSC (Table 2a). However, at the 7-month follow-up the AT arm had significantly less wheezing (Table 2b). Upon dichotomization of the wheezing variable between any vs. no wheezing, no difference by treatment arms was present at baseline. However, children in the AT arm had significatively less "any wheezing" than those in the WWSC arm (22.4% vs. 43.8%, p=0.00001) at follow-up, (Figure 1). Results were similar when the three different severities of wheezing groups were analyzed according to the treatment arms (data not shown).

Importantly, the multivariate analysis of "any wheezing" vs. "no wheezing" at follow-up as a dependent variable, showed that treatment arm was not associated with 'any wheezing". Only paternal asthma. maternal education and BMI z-score were significantly associated with "any wheezing" (Table 3). Using the three groups of wheezing severities as dependent variable, the results were similar (data not shown).

DISCUSION

This secondary analysis of the CHAT data aimed at investigating the effect of AT on recurrent wheezing in children with OSAS at the 7-month follow up visit. Results showed that recurrent wheezing was no different in children randomized to AT compared to those randomized to WWSC after controlling for the following confounders: age, gender, race, parents and siblings with asthma, exposure tobacco, siblings, AHI, BMI z-score, maternal education, and family income.

The results of the present study, which is the first RCT of AT, were similar to an adenoidectomy RCT previously conducted by Mattila et al. in Finland [12]. They analyzed 166 children (aged 12–48 months) with recurrent or persistent otitis media who were followed for 3 years after randomization to undergo insertion of tympanostomy tubes with or without adenoidectomy and showed that adenoidectomy did not influence baseline lung function, exercise-induced bronchoconstriction, exhaled nitric oxide concentration, the development of positive skin prick tests, or physician-diagnosed asthma [12].

Those results were in contrast with several observational studies performed in US. Saito et al. [7] found in 25 asthmatic children that 88% of them improved their symptoms and reduced or eliminated the need for asthma medications after AT. Busino et al. [8] compared 93 children with asthma and 372 without asthma who underwent AT mainly for OSA/adenotonsillar hypertrophy and showed that the Asthma Control Test (ACT) scores significantly improved 12 months following AT. Levin et al. [9] conducted a retrospective cohort analysis of 66 children with asthma and 64 controls and showed 6 months after AT that improvement in the ACT in 85% of the asthmatic children. In a prospective cohort, 52 out of 92 children with poorly controlled asthma had OSA and after 1-year follow-up of 35 children who underwent AT due to OSA decreased annual frequency of asthma exacerbation, rescue inhalers use, and asthma symptoms compared to no changes in the group without OSA [14]. Also, a large longitudinal cohort comparing asthma outcomes one year preceding vs. one year following AT, showed that AT was associated with significant reductions in asthma exacerbation, status and emergency visits, hospitalization rate and asthma prescription, but no information was available for race and obesity status [15]. Finally, a systematic review suggested an overall reduction in asthma severity following AT e.g., decline in the use of respiratory medications, reduction in the frequency of asthma exacerbations, decrease in asthma symptoms and in medication use and emergency department visits for severe distress [16]. However, since several biases could affect observational studies, we considered important to further analyze RCT data. Both RCTs done in Finland [12] and CHAT showed no effect of adenoidectomy or AT on asthma or wheezing, respectively.

This study has some limitations. First, the diagnosis of asthma was assessed by questionnaires, and the available baseline and follow up outcome were wheezing episodes. However, results did not change by wheezing

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severity. Second, no pulmonary function tests, respiratory medications use, decrease in asthma symptoms and emergency department visits for severe distress were assessed and atopic markers were not performed. Finally, follow up was limited to 7 months and since asthma is a chronic condition, a larger follow up time may be required. Nonetheless, CHAT is the largest AT RCT to date, most patients (more than 90%) completed the study, and the effect of AT on wheezing was controlled for several potential confounders.

Conclusions. This post-hoc analysis of the largest AT RCT demonstrated that AT has not effect on wheezing at 7 months of follow-up.

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