ORIGINAL ARTICLE

A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea

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ABSTRACT

BACKGROUND

Adenotonsillectomy is commonly performed in children with the obstructive sleep apnea syndrome, yet its usefulness in reducing symptoms and improving cognition, behavior, quality of life, and polysomnographic findings has not been rigorously evaluated. We hypothesized that, in children with the obstructive sleep apnea syndrome without prolonged oxyhemoglobin desaturation, early adenotonsillectomy, as compared with watchful waiting with supportive care, would result in improved outcomes.

METHODS

We randomly assigned 464 children, 5 to 9 years of age, with the obstructive sleep apnea syndrome to early adenotonsillectomy or a strategy of watchful waiting. Polysomnographic, cognitive, behavioral, and health outcomes were assessed at baseline and at 7 months.

RESULTS

The average baseline value for the primary outcome, the attention and executive-function score on the Developmental Neuropsychological Assessment (with scores ranging from 50 to 150 and higher scores indicating better functioning), was close to the population mean of 100, and the change from baseline to follow-up did not differ significantly according to study group (mean [±SD] improvement, 7.1±13.9 in the early-adenotonsillectomy group and 5.1±13.4 in the watchful-waiting group; P=0.16). In contrast, there were significantly greater improvements in behavioral, quality-of-life, and polysomnographic findings and significantly greater reduction in symptoms in the early-adenotonsillectomy group than in the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%).

CONCLUSIONS

As compared with a strategy of watchful waiting, surgical treatment for the obstructive sleep apnea syndrome in school-age children did not significantly improve attention or executive function as measured by neuropsychological testing but did reduce symptoms and improve secondary outcomes of behavior, quality of life, and polysomnographic findings, thus providing evidence of beneficial effects of early adenotonsillectomy. (Funded by the National Institutes of Health; CHAT ClinicalTrials.gov number, NCT00560859.)

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This article was published on May 21, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1215881
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The childhood obstructive sleep apnea syndrome is associated with numerous adverse health outcomes, including cognitive and behavioral deficits.[1] The most commonly identified risk factor for the childhood obstructive sleep apnea syndrome is adenotonsillar hypertrophy. Thus, the primary treatment is adenotonsillectomy, which accounts for more than 500,000 procedures annually in the United States alone.[2] Nevertheless, there has been no controlled study evaluating the benefits and risks of adenotonsillectomy, as compared with watchful waiting, for the management of the obstructive sleep apnea syndrome.

The Childhood Adenotonsillectomy Trial (CHAT) was designed to evaluate the efficacy of early adenotonsillectomy versus watchful waiting with supportive care, with respect to cognitive, behavioral, quality-of-life, and sleep factors at 7 months of follow-up, in children with the obstructive sleep apnea syndrome. Our primary outcome was a neurobehavioral measure of attention and executive function, a domain that has been shown to be sensitive to intermittent hypoxemia related to the obstructive sleep apnea syndrome.[3] Given the prevalence of this syndrome among black children and obese children,[4,5] we also evaluated whether the relative efficacy of the treatment differed according to race, weight, or baseline severity of the syndrome.

METHODS

STUDY DESIGN AND PATIENTS

We conducted this multicenter, single-blind, randomized, controlled trial at seven academic sleep centers. Methodologic details have been published previously[6] and are provided in the full protocol and in the Supplementary Appendix (available with the full text of this article at NEJM.org).

Eligible children were 5 to 9 years of age, had the obstructive sleep apnea syndrome without prolonged oxyhemoglobin desaturation, and were considered to be suitable candidates for adenotonsillectomy. The obstructive sleep apnea syndrome 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.[7-10] Children with an AHI score of more than 30 events per hour, an OAI score of more than 20 events per hour, or 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 (ADHD).

Children were randomly assigned to early adenotonsillectomy (surgery within 4 weeks after randomization) or a strategy of watchful waiting. At the baseline visit, children with coexisting conditions that could exacerbate the obstructive sleep apnea syndrome (e.g., allergies and poorly controlled asthma) were referred for treatment as needed.

STUDY OVERSIGHT

The study was approved by the institutional review board at each participating site. Written informed consent was obtained from caregivers, and assent from children who were 7 years of age or older. An independent data and safety monitoring board reviewed interim data on safety and study quality. An external medical monitor adjudicated treatment failures, defined as changes in clinical status requiring a change in the assigned therapy.[6] All the authors vouch for the completeness and accuracy of the data and the fidelity of the study to the protocol (available at NEJM.org). There was no commercial support for this study.

ASSESSMENTS

Children underwent standardized polysomnographic testing with scoring at a centralized sleep reading center, cognitive and behavioral testing, and other clinical and laboratory evaluations at baseline and 7 months after randomization.[6] At both examinations, caregivers were asked to complete survey instruments, and teachers were mailed behavioral assessments (see the Supplementary Appendix).

OUTCOMES

The primary study outcome was the change in the attention and executive-function score on the Developmental Neuropsychological Assessment (NEPSY; scores range from 50 to 150, with 100 representing the population mean and higher scores indicating better functioning).[11] This test

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has well-established psychometric properties[11] and comprises three tasks (tower building, visual attention, and auditory attention) performed under the supervision of a psychometrist.

Other outcomes included caregiver and teacher ratings of behavior (Conners' Rating Scale Revised: Long Version Global Index, comprising Restless–Impulsive and Emotional Lability factor sets [caregiver-rated T scores range from 38 to 90, and teacher-rated T scores range from 40 to 90, with higher scores indicating worse functioning]),[12] and the Behavior Rating Inventory of Executive Function [BRIEF] Global Executive Composite T score, comprising summary measures of behavioral regulation and metacognition [caregiver-rated scores range from 28 to 101, and teacher-rated scores range from 37 to 131, with higher scores indicating worse functioning])[13]; symptoms of the obstructive sleep apnea syndrome, as assessed by means of the Pediatric Sleep Questionnaire sleep-related breathing disorder scale (PSQ-SRBD), in which scores range from 0 to 1, with higher scores indicating greater severity[14]; sleepiness, as assessed with the use of the Epworth Sleepiness Scale modified for children, in which scores range from 0 to 24, with higher scores indicating greater daytime sleepiness[15]; global quality of life (caregiver-rated total score from the Pediatric Quality of Life Inventory [PedsQL], in which scores range from 0 to 100, with higher scores indicating better quality of life)[16]; disease-specific quality of life (total score on the 18-item Obstructive Sleep Apnea-18 assessment tool, in which scores range from 18 to 126, with higher scores indicating worse quality of life)[17]; generalized intellectual functioning (General Conceptual Ability score from the Differential Ability Scales-II [DAS], in which scores range from 30 to 170, with higher scores indicating better functioning)[18]; and polysomnographic indexes.

STATISTICAL ANALYSIS

We calculated that with a sample of 400 children, randomly assigned in a 1:1 ratio to early adenotonsillectomy or a strategy of watchful waiting, the study would have 90% power to detect an effect size of 0.32 or more (on the basis of an estimate from one previous study[19]) for the primary outcome. We planned to enroll 460 children to compensate for withdrawal from the study. Children who crossed over to the other treatment were included in their assigned study groups for the primary analysis, consistent with the intention-to-treat principle.

Primary and secondary outcomes were evaluated with the use of an analysis of covariance with adjustment for the stratification factors of age, race, weight status, and study site. Additional prespecified analyses included adjustments for other factors and restrictions to certain subgroups (see the Supplementary Appendix). Models evaluating possible effect modification of treatment according to race, obesity status, AHI score, and age were tested by including terms for interactions between the two groups and by the effect of each of these factors on each of the study outcomes. A sensitivity analysis was performed with the use of multiple imputation to assess the effect of missing values on the primary outcome.[20]

RESULTS

STUDY OVERVIEW

Figure 1 shows the enrollment and randomization of the participants. From January 2008 through September 2011, a total of 464 children underwent randomization. Follow-up visits were conducted for 400 children (86%), with 397 children having measurements of attention and executive function on the NEPSY that could be evaluated. A comparison of children who completed the study and those who did not showed a significant difference only with respect to race; black children were less likely to complete the study ($P=0.04$), but this trend was evident in both study groups.

Baseline characteristics are shown according to study group (Tables 1 and 2, and Table S1 in the Supplementary Appendix). Baseline demographic and clinical characteristics were generally well balanced between the study groups, and cognitive and behavioral scores were close to population means. Nearly half the participants were overweight or obese. A similar number of children in each group used nasal glucocorticoids (19 children in the early-adenotonsillectomy group and 8 in the watchful-waiting group) or montelukast (7 in the early-adenotonsillectomy group and 8 in the watchful-waiting group) for allergic rhinitis or asthma; the data were the same at baseline and at 7 months of follow-up.

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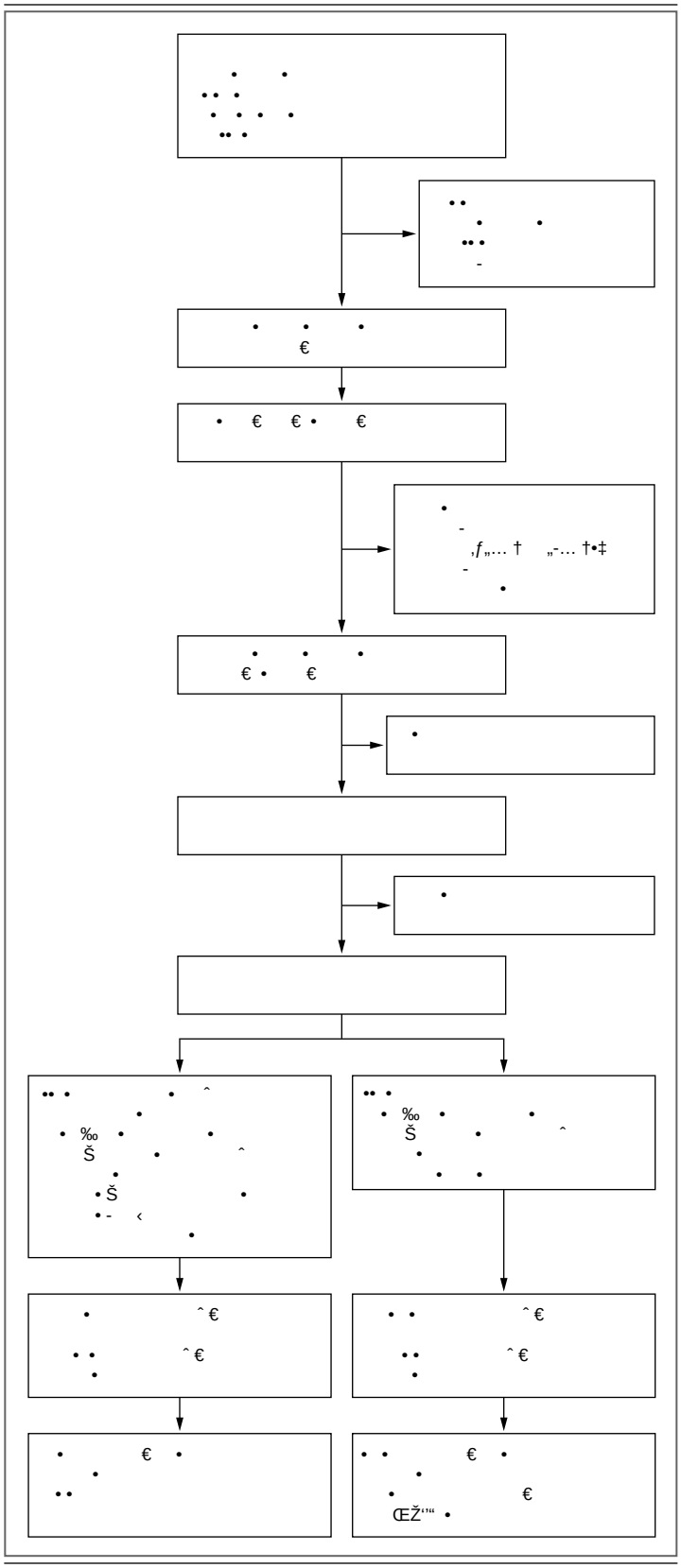

Figure 1. Study Enrollment and Randomization.
A total of 464 children underwent randomization, with 226 children assigned to early adenotonsillectomy and 227 to a strategy of watchful waiting with supportive care. A total of 194 children in the early-adenotonsillectomy group and 203 in the watchful-waiting group were included in the analysis of the primary outcome, the attention and executive-function score on the Developmental Neuropsychological Assessment (NEPSY).

STUDY OUTCOMES

The baseline attention and executive function score on the NEPSY was close to the population mean of 100 in both groups. Average scores increased in both groups; the difference between the groups favored early adenotonsillectomy but was not significant (P = 0.16). A sensitivity analysis to assess the possible effect of missing data yielded results that were essentially identical to those presented in Table 2.

There was a significantly greater improvement on the caregiver-reported Conners' Rating Scale among children randomly assigned to early adenotonsillectomy than among those assigned to watchful waiting. Teacher-reported data for this measure, which were available for 212 children, also showed significantly greater improvement in the early-adenotonsillectomy group. The caregiver-reported BRIEF score was lower (indicating an improvement) in the early-adenotonsillectomy group, with a small increase in score in the watchful-waiting group; the teacher-reported version, which was available for 207 children, showed changes that paralleled the caregiver data but were not significantly different between the groups.

Symptoms of the obstructive sleep apnea syndrome were measured with the use of the PSQ-SRBD and the Epworth Sleepiness Scale, and generic and disease-specific measures of quality of life were assessed by means of the PedsQL and OSA-18, respectively. All these instruments showed a significantly greater reduction in symptoms in the early-adenotonsillectomy group than in the watchful-waiting group. The DAS score did not change significantly in either study group (data not shown).

The AHI score improved in both groups but significantly more so in the early-adenotonsillectomy group. Similar results were observed for the oxygen desaturation index (the number of times per hour of sleep that the blood oxygen level drops by 3% or more from baseline) and

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the level of hypercapnia. The early-adenotonsillectomy group had significantly larger decreases in the arousal index and in the percentage of sleep time in stage N1 (light sleep), consistent with improved sleep continuity. However, no changes were observed in stage N3 or in rapid-eye-movement sleep. Normalization of the obstructive sleep apnea syndrome, as defined by a reduction in both the AHI score to fewer than two events per hour and the OAI score to fewer than one event per hour,[7-10] was more common in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%, P<0.001).

EFFECT OF BASELINE CHARACTERISTICS

For all the outcomes, relative improvements with early adenotonsillectomy, as compared with watchful waiting, were similar in subgroups defined according to age or obesity status. However, relative improvements with early adenotonsillectomy were significantly smaller among black children than among children of other races on the Conners' Rating Scale, the BRIEF, and the PSQ-SRBD scale (see the Supplementary Appendix). Among children with more severe obstructive sleep apnea syndrome at baseline (i.e., AHI score above the median), those randomly assigned to early adenotonsillectomy had a greater improvement in AHI score than did those assigned to watchful waiting (Fig. S1 in the Supplementary Appendix). There was no interaction between the severity of the obstructive sleep apnea syndrome and treatment with respect to the attention and executive-function score on the NEPSY or the behavioral or symptom outcomes.

Table 1. Baseline Characteristics of Patients Who Completed the Study.*

Characteristic	Watchful Waiting (N=203)	Early Adenotonsillectomy (N=194)
Age — yr	6.5±1.4	6.5±1.4
Male sex — no. (%)	106 (52)	89 (46)
Race — no. (%)†		
Black	108 (53)	103 (53)
White	76 (37)	67 (35)
Other	19 (9)	24 (12)
Hispanic ethnicity — no. (%)†	17 (8)	15 (8)
Height — cm	124.7±10.5	125.1±11.2
Height z score	0.6±1.0	0.7±1.0
Weight — kg	30.1±11.7	31.2±13.1
Weight z score	1.0±1.2	1.0±1.3
Weight class — no. (%)‡		
Overweight or obese	94 (46)	93 (48)
Obese	67 (33)	68 (35)
Failure to thrive	3 (1)	4 (2)
Maternal educational level less than high school — no. (%)	64 (32)	62 (32)
Annual household income <$30,000 — no. (%)	82 (40)	73 (38)

* Plus–minus values are means ±SD. There were no significant differences between the study groups. The characteristics of the sample included in the primary outcome analysis were similar to those of the baseline population, except that black children were less likely to complete the study (P=0.04), but this trend was evident in both study groups (Table S1 in the Supplementary Appendix).

† Race reported by caregivers.

‡ Overweight or obese was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) in the 85th percentile or higher, obese as a BMI in the 95th percentile or higher, and failure to thrive as a BMI in less than the 5th percentile.

SUBGROUP ANALYSES

Substantial subgroup differences with regard to the normalization of polysomnographic findings were observed within each study group. Regardless of the assigned treatment, normalization of polysomnographic findings was seen less frequently in black children than in children of other races, in obese children than in nonobese children, and in children with a baseline AHI score above the median than in those with a baseline AHI score at or below the median (Fig. 2).

OTHER EXPLORATORY ANALYSES

No consistent relationships were observed between changes in AHI score and changes in other study outcomes, nor were substantive differences seen in models adjusted for additional covariates or restricted to children with low cognitive scores at baseline. The exclusion from the analyses of 24 children who did not receive the assigned intervention (8 children in the early-adenotonsillectomy group who declined surgery and 16 in the watchful-waiting group who underwent early surgery) did not yield any appreciable changes in the study results (see the Supplementary Appendix).

ADVERSE EVENTS

There were 15 serious adverse events after randomization, 6 of which occurred in children randomly assigned to early adenotonsillectomy and 9 in those assigned to watchful waiting (Table 3, and

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Table 2. Outcome Measures.*

Outcome	Normative Mean	Watchful Waiting		Early Adenotonsillectomy		Effect Size†	P Value
		Baseline	Change from Baseline to 7 Mo	Baseline	Change from Baseline to 7 Mo		
Primary outcome							
NEPSY attention and executive-function score‡	100±15	101.1±14.6	5.1±13.4	101.5±15.9	7.1±13.9	0.15	0.16
Secondary outcomes							
Conners' Rating Scale score§	50±10						
Caregiver rating		52.6±11.7	−0.2±9.4	52.5±11.6	−2.9±9.9	0.28	0.01
Teacher rating		55.1±12.8	−1.5±10.7	56.4±14.4	−4.9±12.9	0.29	0.04
BRIEF score¶	50±10						
Caregiver rating		50.1±11.5	0.4±8.8	50.1±11.2	−3.3±8.5	0.28	<0.001
Teacher rating		56.4±11.7	−1.0±11.2	57.2±14.1	−3.1±12.6	0.18	0.22
PSQ-SRBD score‖	0.2±0.1	0.5±0.2	−0.0±0.2	0.5±0.2	−0.3±0.2	1.50	<0.001
PedsQL score**	78±16	76.5±15.7	0.9±13.3	77.3±15.3	5.9±13.6	0.37	<0.001
Apnea–hypopnea index — no. of events/hr††	NA						
Median		4.5	−1.6	4.8	−3.5	0.57	<0.001‡‡
Interquartile range		2.5 to 8.9	−3.7 to 0.5	2.7 to 8.8	−7.1 to −1.8		

* Plus–minus values are means ±SD, and nonnormally distributed data are medians with interquartile ranges. All P values were adjusted for the stratification factors of age (5 to 7 years of age vs. 8 to 9 years of age), race (black vs. other), weight status (overweight or obese vs. nonoverweight), and study site. NA denotes not applicable.

† Effect sizes were calculated with the use of Cohen's d, relating the magnitude of group difference to the standard deviation, and may be interpreted as follows: small, more than 0.20 to 0.49; medium, 0.50 to 0.79; and large, 0.80 or more.

‡ Scores on the attention and executive-function domain of the Developmental Neuropsychological Assessment (NEPSY) range from 50 to 150, with higher scores indicating better functioning. Data are shown for 203 patients in the watchful-waiting group and 194 in the early-adenotonsillectomy group.

§ Scores on the Conners' Parent Rating Scale Revised: Long Version Global Index, comprising the Restless–Impulsive and Emotional Lability factor sets, range from 38 to 90, with higher scores indicating worse functioning. Data are shown for 199 patients in the watchful-waiting group and 193 in the early-adenotonsillectomy group. Scores on the Conners' Teacher Rating Scale Revised (with scores ranging from 40 to 90 and higher scores indicating worse functioning) are shown for 109 patients in the watchful-waiting group and 103 in the early-adenotonsillectomy group.

¶ On the Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite section, comprising summary measures of behavioral regulation and metacognition, higher scores indicate worse functioning. Data on the caregiver ratings, with a range of 28 to 101, are shown for 197 patients in the watchful-waiting group and 195 in the early-adenotonsillectomy group. Data on the teacher ratings, with a range from 37 to 131, are shown for 103 patients in the watchful-waiting group and 104 in the early-adenotonsillectomy group.

‖ Scores on the Pediatric Sleep Questionnaire sleep-related breathing disorder scale (PSQ-SRBD) range from 0 to 1, with higher scores indicating greater severity. Data are shown for 202 patients in the watchful-waiting group and 194 in the early-adenotonsillectomy group.

** Scores on the Pediatric Quality of Life Inventory (PedsQL) range from 0 to 100, with higher scores indicating better quality of life. Data are shown for 204 patients in the watchful-waiting group and 195 in the early-adenotonsillectomy group.

†† A score of 2 or more on the apnea–hypopnea index indicated the obstructive sleep apnea syndrome. Higher scores indicate more severe obstructive sleep apnea.

‡‡ Testing was performed on naturally log-transformed variables.

Results and Table S3 in the Supplementary Appendix). A total of 8 events were associated with perioperative complications, 3 of which occurred in children who were randomly assigned to watchful waiting but who had crossed over to surgery. Nine treatment failures were identified, all in the watchful-waiting group.

DISCUSSION

This large, randomized, controlled trial of therapy for the pediatric obstructive sleep apnea syndrome included rigorous assessments of cognitive and behavioral measurements, sleep apnea symptoms, and sleep. After a 7-month interven-

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tion period, school-age children with the obstructive sleep apnea syndrome without prolonged oxyhemoglobin desaturation who underwent surgery did not have significantly greater improvement in attention and executive function, as measured by means of neuropsychological testing, than did children in the watchful-waiting group. However, surgery resulted in greater reductions in symptoms and greater improvements in behavior, quality of life, and polysomnographic findings, with effect sizes in the moderate-to-large range. Polysomnographic findings were normalized in the majority of children (79%) in the early-adenotonsillectomy group, although polysomnographic abnormalities also resolved in 46% of the children randomly assigned to watchful waiting. Among obese children, those randomly assigned to early adenotonsillectomy had greater