THE FAMILIAL AGGREGATION OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME

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Objective: To determine the role of genetic mechanisms in the development of pediatric obstructive sleep apnea syndrome (OSAS).

Design: Genetic-epidemiologic survey of families of index children with laboratory-confirmed OSAS.

Setting: Tertiary care academic medical center.

Participants: Six-hundred nap polysomnograms performed in our institution's pediatric sleep laboratory over a 6-year period (1994-2000) were reviewed, and the 497 children who tested positive for OSAS were selected. A caretaker of 200 of these index patients was contacted, and 115 were enrolled in the study.

Intervention and Main Outcome Measure: Questionnaire-type telephone interviews were conducted with the current caretakers of the index patients to assess the distribution of sleep-disordered breathing in the first-degree relatives.

Results: Data were collected for 445 first-degree relatives (256 adults and 189 children) of the 115 index patients. Habitual snoring was found in 194 (43.6%) of the family members, while symptoms highly suggestive of OSAS (nighttime "gasping for air" or "cessation of breathing") were found in 91 (20.4%). Sixty-eight (26.6%) of the adult first-degree relatives and 23 (12.2%) of the pediatric first-degree relatives had symptoms highly suggestive of OSAS. Of the 115 index children, 50 (43.5%) had at least 1 relative with symptoms highly suggestive of OSAS; 6 (1.3%) of the first-degree relatives had sleep study results positive for OSAS, 4 (0.9%) were using nasal continuous positive airway pressure, and 21 (4.7%) had prior surgery for the treatment of OSAS.

Conclusion: Considering the established prevalence of OSAS in the general population (2%-4%), the results of this study support a familial basis for this disorder.


OBSTRUCTIVE SLEEP apnea syndrome (OSAS) is a disorder characterized by episodic upper airway obstruction during sleep that is associated with reduction of oxyhemoglobin saturation or hypercarbia. It has been shown that the lifetime risk of developing OSAS in children is about 2%, and the prevalence of OSAS in the general population is about 3% to 4%. Sleep apnea causes excessive daytime sleepiness, snoring, and nonrestorative sleep. In its severe form, OSAS may result in significant physiological and psychological abnormalities such as cor pulmonale, developmental delay, failure to thrive, or even death.

Previous studies have suggested that the main risk factors for OSAS are obesity, male sex, middle age, and the presence of a narrow airway. In adults, it has also been associated with several anatomical abnormalities such as macrosomia, smaller airway volume, and a low-set hyoid bone. In younger individuals, the mechanism of the disease is different. It is associated mainly with immaturity of the respiratory center in infants and adenotonsilar hypertrophy in children.

The first report of familial obstructive sleep apnea was published by Strohl et al in 1978. Since then, a few studies supported the role of genetic mechanisms in the etiology of OSAS. Despite these reports, no previous attempts have been made to evaluate the role of familial factors in the pathogenesis of OSAS in children, in whom the proposed pathophysiological mechanism of OSAS, namely, adenotonsilar hypertrophy, is different from the adults.

RESULTS

There were 77 male (67.0%) and 38 female (33.0%) index subjects (Table 1): of these 115, 97 were African American
**PARTICIPANTS AND METHODS**

We reviewed 600 nap polysomnograms performed at our institution’s pediatric sleep laboratory over a 6-year period (1994-2000) and 497 children had sleep study results positive for OSAS. The criteria for a positive study result were a respiratory disturbance index score of 5 or greater or the presence of moderate or severe desaturations during sleep (arterial oxygen saturation [SaO₂] <92%). We were able to contact a caretaker of 200 index patients, 115 of whom were enrolled in the study. The study was approved by the institutional review board at SUNY Health Science at Brooklyn, Brooklyn, NY.

Standardized questionnaire-type telephone interviews were conducted with the current caretakers of the index patients to assess the distribution of sleep-disordered breathing in the first-degree relatives (parents and siblings). The questionnaire consisted of general and epidemiological data, medical history, and specific questions for OSAS symptoms including snoring, mouth breathing, daily somnolence, tiredness, gasping and choking, nightly awakenings, apneic episodes, restless sleep, and enuresis. Data regarding history of OSAS in the first-degree relatives (ie, having a positive sleep study result or previous surgery for OSAS) were also included in the questionnaire. Comparison of the incidence of OSAS in the relatives of the index probands with the general incidence of OSAS was performed using a confidence interval for binomial proportion.

Data were collected for 445 first-degree relatives of the 115 index cases (256 adults and 189 children) (Table 2). Habitual or disruptive snoring was present in 194 (43.6%) family members, of whom 115 (59.3%) were adults and 79 (40.7%) were children or adolescents (Figure 1). Interestingly, snoring alone without symptoms of apnea or gasping was found only in 103 (23.1%) of first-degree relatives.

We considered the presence of symptoms of nighttime “gasing for air” and “cessation of breathing” as highly suggestive of OSAS. Of the 445 first-degree relatives, 91 (20.4%) were found to have at least 1 or both of the above symptoms: 68 were adults and 23 were children (Figure 2). Thus, 68 (26.6%) of all 256 adult first-degree relatives and 23 (12.2%) of all 189 pediatric first-degree relatives were found to have symptoms highly suggestive of OSAS.

The presence of a cluster of certain symptoms in the first-degree relatives with no history of gasping or cessation of breathing was considered as “suspicious for OSAS.” For adult first-degree relatives, there were 3 groups of symptom clusters: (1) snoring and daytime somnolence; (2) snoring and enuresis; and (3) snoring, restless sleep, and nightly awakenings. We found 15 adult first-degree relatives to belong to group 1, 3 to group 2 and 13 to group 3 (Figure 3). Thus, 31 (12.1%) of the adult first-degree relatives had symptoms suspicious for OSAS. For pediatric first-degree relatives, there also were 3 groups of symptom clusters considered suspicious for OSAS, which, in addition to the adult symptoms, required the presence of “mouth breathing” in each of the cluster groups. Six children belonged to group 1 (snoring, daily somnolence, and mouth breathing), 3 to group 2 (snoring, enuresis, and mouth breathing), and 4 to group 3 (snoring, restless sleep, nightly awakenings, and mouth breathing) (Figure 4). Therefore, 13 (6.9%) of the pe-
First-degree relatives (adults and children/adolescents) with symptoms either highly suggestive of or suspicious for obstructive sleep apnea syndrome (OSAS). The present study shows that 20.4% (95% confidence interval, 16.8%-24.5%) of first-degree relatives of 115 index cases with pediatric OSAS had symptoms either highly suggestive of or suspicious for OSAS highly suggestive of OSAS. Of the siblings of the index cases, 55 (12.3%) had symptoms highly suggestive of OSAS (gasping and/or apnea), 4 (0.9%) were using nasal continuous positive airway pressure, and 21 (4.7%) had prior surgery for the treatment of OSAS. A total of 14 first-degree relatives reported having a sleep study in the past: 6 had sleep study results positive for OSAS, 5 were negative, and 3 of the first-degree relatives were unsure about the results.

**COMMENT**

The present study shows that 20.4% (95% confidence interval, 16.8%-24.5%) of first-degree relatives of 115 index cases with pediatric OSAS had symptoms highly suggestive of OSAS highly suggestive of OSAS. Of the siblings of the index cases, 55 (12.3%) had symptoms highly suggestive of OSAS (gasping and/or apnea), 4 (0.9%) were using nasal continuous positive airway pressure, and 21 (4.7%) had prior surgery for the treatment of OSAS. A total of 14 first-degree relatives reported having a sleep study in the past: 6 had sleep study results positive for OSAS, 5 were negative, and 3 of the first-degree relatives were unsure about the results.

Our findings corroborate the results of a similar questionnaire-based study by Redline et al. in which 21%
of the first-degree relatives of the index cases with OSAS were found to have OSAS. Douglas et al., in a combined questionnaire-polysomnogram study, also showed a similar (25%) incidence of this syndrome in the first-degree relatives of patients with apnea. Other studies quote even higher incidences.

The exact mechanism of OSAS inheritance is yet unknown. It has been speculated that the genetic transmission of such OSAS risk factors as craniofacial structure, body habitus, and ventilatory control mechanisms may play a role. In the pediatric population, in whom adenotonsillar hypertrophy is considered to be the main causative factor for OSAS, the role of inheritance is unclear. It is possible that the genetic factors play a role in the etiology of adenotonsillar hypertrophy per se or make it more significant by encoding for smaller airway volumes.

The data presented in the present study are based on the responses to the standardized questionnaire. The degree to which questionnaires allow for accurate identification of sleep apnea is controversial. Several previous studies that used both questionnaires and polysomnograms to diagnose sleep apnea showed that the positive predictive value of questionnaires is considerably high, ranging from 60% to 90%, thus supporting the questionnaire's validity in sleep apnea research. Reporting bias, in which relatives of the index probands tend to overreport the symptoms, must also be considered when using questionnaires as a research tool. The study by Redline et al. compared the frequency of symptom reporting by the relatives of the patients with sleep apnea and the control group. They found no significant overreporting of the symptoms by the relatives of the index cases. Thus, although a reporting bias cannot be completely excluded, it is unlikely to be the sole factor causing this large difference in the prevalence of sleep apnea symptoms among the first-degree relatives of the patient with OSAS.

**CONCLUSIONS**

The significant increase in the OSAS incidence among the first-degree relatives of the children and adolescents with OSAS supports the role of genetic factors in the etiology of this syndrome. Our study, along with the other published studies, may have significant implications both in diagnosing and caring for patients with sleep apnea.

Families of children with OSAS need to be counseled about the increased incidence of this syndrome in other siblings. A physician should be highly suspicious for sleep apnea in a child who has 1 or more siblings diagnosed as having OSAS. This heightened awareness will potentially provide for timely diagnosis of OSAS, thus decreasing the incidence of potential long-term complications of this syndrome.

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**REFERENCES**