

# Early Occurrence of Obstructive Sleep Apnea in Infants and Children With Cystic Fibrosis

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**Objectives:** To assess the occurrence of sleep-disordered breathing, hypoxemia, and sleep architecture in a cohort of infants and children with cystic fibrosis (CF) and normal or mildly impaired lung function in stable clinical condition.

**Design:** Case-control study.

**Setting:** Cystic Fibrosis Unit of a university hospital and pediatric sleep laboratory.

**Participants:** A total of 40 children (aged 6 months to 11 years) with CF in stable condition and 18 healthy age-matched control subjects.

**Intervention:** Nocturnal sleep and cardiorespiratory monitoring was performed using a full polysomnographic recording in a sleep laboratory.

**Main Outcomes Measures:** Sleep architecture and respiratory variables.

**Results:** Although awake oxyhemoglobin saturation (SaO<sub>2</sub>) values were similar in the 2 groups (98%), the CF

group had significantly lower values of nocturnal mean SaO<sub>2</sub>. The apnea-hypopnea index was significantly higher in the CF group compared with the controls (mean [SE], 7.3 [1.3] vs 0.5 [0.4], respectively,  $P < .001$ ), particularly in preschool-aged children and in children with upper airway abnormalities. In addition, 28 (70%) of the 40 children with CF had mild to moderate obstructive sleep apnea (defined as an apnea-hypopnea index  $> 2$ ). Children with CF compared with controls also had reduced sleep efficiency (CF group vs controls mean [SE], 80% [41%] vs 88% [13.1%],  $P < .001$ ), rapid eye movement sleep duration (11% [0.9%] vs 13% [1%],  $P < .05$ ), and increased number of arousals per hour (11.0 [10] vs 8.2 [0.7],  $P < .001$ ).

**Conclusions:** This study showed an early occurrence of obstructive sleep apnea in children with CF in stable condition, associated with a mild level of sleep disruption. Early routine nocturnal respiratory monitoring is advised in children with CF.

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**C**YSTIC FIBROSIS (CF) IS THE most common genetic disorder in white individuals, caused by a number of mutations of the CF transmembrane conductance regulator, which functions as a chloride channel at the apical cell surface.<sup>1</sup> This multiorgan-involving disease affects mainly the lung and is associated with chronic lower airway inflammation/infection causing a progressive airway obstruction and decline in pulmonary function, progressively leading to respiratory failure and death.<sup>1</sup> Along with lower airway involvement, patients with CF commonly exhibit upper airway (UA) inflammation and obstruction. About two-thirds of the patients will present, through the course of life, with chronic rhinosinusitis, in some cases severe, and

nasal polyps.<sup>2</sup> Chronic or acute inflammation is a common cause of UA collapse during sleep determining obstructive apneic events, associated with different degrees of intermittent hypoxia and sleep disruption.<sup>3,4</sup> In adults with CF, the occurrence of nocturnal apneic events, with mild hypoxia and reduced sleep efficiency, has been documented during acute or stable conditions.<sup>5</sup> Little is known in infancy and childhood when the disease is generally milder, airway inflammation is less severe, and lung function is scarcely affected. Although one study<sup>4</sup> suggests that acute UA inflammation may determine nocturnal apneas in infants, earlier studies of nocturnal breathing in children with CF were performed using nocturnal oxymetry, rather than full polysomnography. The objective of the present study was

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to assess the occurrence of sleep-disordered breathing, nocturnal hypoxemia, and sleep architecture in a cohort of infants and children with CF and mild lung impairment in stable condition.

## METHODS

### PARTICIPANTS

We studied a total of 40 children (21 children aged from 6 months to 5 years and 19 children aged from 6 to 11 years) with CF in a stable condition followed up in the Cystic Fibrosis Unit, Department of Pediatrics, University of Catania, Catania, Spain, and 18 healthy age-matched controls. Controls were all volunteers recruited via an advertisement in the Cystic Fibrosis Unit. All the clinical data, including the time of the diagnosis, sweat test result, and genotypes were available for all the patients. Informed consent was obtained for all the patients (signed by the parents), and the protocol was approved by the Azienda Policlinico Ethics Committee.

### STUDY PROTOCOL

Day anthropometric data were collected and all the patients underwent clinical evaluation to exclude a state of exacerbation. Resting oxyhemoglobin saturation ( $\text{SaO}_2$ ) was recorded for 5 minutes (using the CompuMedics S-Series oxymeter) with the patient sitting upright. All the cooperating patients aged 6 years or older underwent standard spirometry (Cosmed SrL), performed according to the American Thoracic Standard criteria.<sup>6</sup> Values of forced expiratory volume in 1 second ( $\text{FEV}_1$ ) and forced vital capacity (FVC) were expressed as percentage predicted of normal values adjusted for age, sex, height, and weight. A stable clinical condition was defined as the absence of increased cough and/or sputum production, increased dyspnea, and significant changes in  $\text{FEV}_1$  from the baseline. Patients who required intravenous or oral antibiotic therapy during the last month, patients requiring chronic oxygen administration, or those having an  $\text{FEV}_1$  less than 60% were excluded from the study. None of the patients was treated with oral corticosteroids. Sleep studies were performed during the night of the study day. All the patients were also evaluated by an otolaryngologist to assess UA abnormalities.

### POLYSOMNOGRAPHY

Patients underwent overnight standard polysomnography performed in the sleep laboratory using a computerized system (CompuMedic S-Series Sleep System). Sleep stages were identified by electroencephalography, electrooculography, and bipolar submental electromyography; all the recordings were obtained from surface electrodes. Thoracic and abdominal excursions were detected by inductance plethysmography bands. Airflow was detected by nasal prongs attached to flow sensor, and  $\text{SaO}_2$  percentage was determined using finger pulse oximetry. An electrocardiogram was monitored from precordial leads. Sleep staging was performed according to standard criteria.<sup>7</sup> Total sleep time (TST) was defined as all sleep incurred from sleep onset until morning awakening. Sleep efficiency was defined as TST divided by total recording time, expressed as a percentage. Sleep stages were reported as a percentage of TST. Arousals were defined as abrupt changes in electroencephalographic frequency for 3 seconds or longer, and the arousal index was calculated as the number of arousals per hour. The mean value of  $\text{SaO}_2$  during sleep time was calculated by averaging values for every 30-second period of sleep, and the lowest abso-

lute values of  $\text{SaO}_2$  reached during rapid eye-movement (REM) and non-REM (NREM) sleep were also recorded. Respiratory events were defined according to standard criteria.<sup>8,9</sup> Obstructive apnea was defined as the absence of airflow for 2 or more respiratory cycles, associated with paradoxical movement of the chest and abdomen. Hypopnea was defined as a decrease of 50% or more in oronasal flow and a concurrent arousal and/or a decrease of 3% or more in  $\text{SaO}_2$  from the baseline. Central apnea was defined as the absence of both airflow and respiratory effort (not immediately preceded by an arousal or awakening) that lasted for 10 seconds or longer and/or events of any duration associated with a decrease of 3% or more in  $\text{SaO}_2$  from the baseline. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The diagnosis of obstructive sleep apnea (OSA) was made when the AHI was greater than 2.<sup>10-12</sup>

### DATA ANALYSIS

Data are presented as mean (SE). Comparison among groups were made using a Mann-Whitney test. Significant differences among percentages of patients were calculated using the Fisher exact test.  $P < .05$  was considered statistically significant. No adjustment for multiple comparisons was used. Linear regression was used to assess correlations between parameters. Statistical analysis was performed using a commercially available software statistical package (GraphPad Prism).

## RESULTS

### DIAGNOSTIC GROUPS

All the patients had mild lung disease with  $\text{FEV}_1$  ranging from 72% to 98% (in children  $\geq 6$  years). Mean values of  $\text{FEV}_1$  and FVC were significantly lower ( $P < .01$ ) in patients with CF than in healthy controls, whereas no difference was noted between groups for daytime levels of  $\text{SaO}_2$  (**Table 1**). Ten of 40 children were already chronically infected with *Pseudomonas aeruginosa*. The otolaryngological evaluation revealed the following: 10 (26%) of 40 children with CF exhibited adenotonsillar hypertrophy (mean age, 3.8 years), 14 children (36%) had chronic rhinosinusitis (mean age, 8.6 years), and only 2 children (5%) had both conditions. None of the controls was seen with UA abnormalities.

### SLEEP ARCHITECTURE

Compared with healthy controls, children with CF in stable clinical condition had a slightly lower TST (CF group vs controls, 421 [113] minutes vs 442 [73.3] minutes,  $P < .05$ ) and reduced sleep efficiency (80.4% [40.9%] vs 87.8% [13.1%],  $P < .001$ ). Distribution of NREM sleep stages was similar for the 2 groups; however, children with CF had a lower percentage of REM sleep (CF group vs controls, 11.7% [5.6%] vs 13.1% [8.0%],  $P < .05$ ). Children with CF also exhibited an increased number of arousals per hour (CF group vs controls, 11.0 [10.6] vs 8.2 [0.7],  $P < .001$ ) (**Table 2**).

**Table 1. Demographic and Respiratory Functional Data**

Variable	Mean (SE)	
	Children With CF (n = 40)	Controls (n = 18)
Age, y, No.		
0-1	9	6
2-5	12	5
6-11	19	7
Male, %	58	62
Height, centile <sup>a</sup>	31.5 (26.1)	52.0 (25.0)
Weight, centile <sup>a</sup>	25.0 (21.2) <sup>b</sup>	58.0 (36.3)
BMI <sup>c</sup>	17.8 (3.4) <sup>b</sup>	18.9 (2.3)
FEV <sub>1</sub> , % predicted <sup>d</sup>	78.6 (4.7) <sup>e</sup>	88.2 (3.9)
FVC, % predicted	81.7 (3.9) <sup>e</sup>	90.4 (5.9)
Awake SaO <sub>2</sub> , %	98.2 (1.2)	98.9 (0.6)
Mean sleep SaO <sub>2</sub> , %	94.7 (1.8) <sup>e</sup>	97.0 (2.1)
AHI	7.3 (1.3) <sup>e</sup>	0.5 (0.4)

Abbreviations: AHI, apnea/hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; SaO<sub>2</sub>, oxyhemoglobin saturation.

<sup>a</sup>Height and weight in centiles for children 0 to 5 years old.

<sup>b</sup> $P < .05$  vs controls.

<sup>c</sup>Body mass index (BMI) for children 6 years old or older.

<sup>d</sup>Spirometry obtained in 19 children 6 years old or older.

<sup>e</sup> $P < .001$  vs controls.

**Table 2. Sleep Variables**

Variable	Mean (SE)	
	Children With CF (n = 40)	Controls (n = 18)
TST, min	421 (113) <sup>a</sup>	442 (73.3)
Sleep efficiency, %	80.4 (40.9) <sup>b</sup>	87.8 (13.1)
NREM		
Stage 1, % of TST	4.2 (2.5)	5.2 (5.5)
Stage 2, % of TST	49.6 (20.2)	48.5 (17.8)
Stage 3, % of TST	24.2 (13.9)	27.1 (14.4)
Stage 4, % of TST	9.7 (6.9)	9.4 (8.9)
REM		
% of TST	11.7 (5.6) <sup>a</sup>	13.1 (8.0)
Arousals per hour, No.	11.0 (10.6) <sup>b</sup>	8.2 (0.7)

Abbreviations: CF, cystic fibrosis; NREM, nonrapid eye movement; REM, rapid eye movement; TST, total sleep time.

<sup>a</sup> $P < .05$  vs controls.

<sup>b</sup> $P < .001$  vs controls.

### GAS EXCHANGE AND NOCTURNAL RESPIRATORY VARIABLES

Although both groups had similar daytime values of SaO<sub>2</sub> (98% for both groups), the mean nocturnal values were significantly lower in all the children with CF compared with the controls ( $P < .001$ ) and compared with wakefulness ( $P < .05$ ) (Table 1). None of the patients had nocturnal hypoventilation defined as an SaO<sub>2</sub> less than 90% for more than 5% of the night. In both groups mean sleep SaO<sub>2</sub> values significantly correlated with awake SaO<sub>2</sub> values (CF group vs controls,  $r^2 = 0.29$  vs  $0.31$ ,  $P < .001$  for both). No correlation was found between mean sleep SaO<sub>2</sub> and FEV<sub>1</sub> in

**Table 3. Demographic and Respiratory Functional Data in Patients With CF With or Without OSA**

Variable	Mean (SE)	
	Children With CF and OSA (n = 29)	Children With CF Without OSA (n = 11)
Age, y	4.5 (2.2) <sup>a</sup>	7.3 (3.3)
Male, %	53	50
Height, centile <sup>b</sup>	32.0 (23.7)	28.0 (7.0)
Weight, centile <sup>b</sup>	26.5 (21.2) <sup>a</sup>	14.7 (5.0)
BMI <sup>c</sup>	16.6 (1.8)	15.9 (2.0)
FEV <sub>1</sub> , % predicted <sup>d</sup>	76.6 (7.8) <sup>a</sup>	82.3 (4.8)
FVC, % predicted	82.5 (6.1)	84.3 (3.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; OSA, obstructive sleep apnea.

<sup>a</sup> $P < .05$ .

<sup>b</sup>Height and weight in centiles for children 0 to 5 years old.

<sup>c</sup>Body mass index for children 6 years old or older.

<sup>d</sup>Spirometry obtained in children 6 years old or older.

**Table 4. Respiratory Variables**

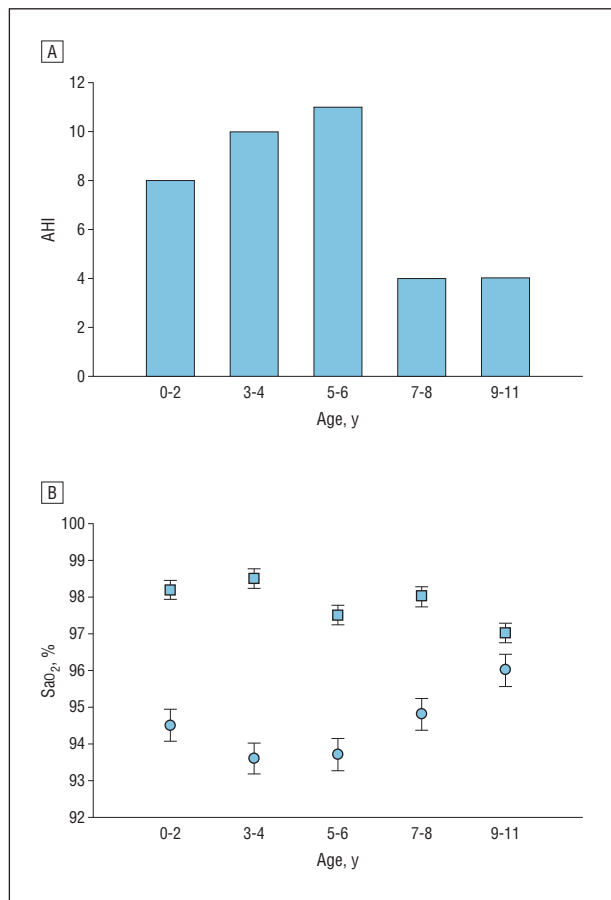
Variable	Mean (SE)		
	Children With CF and OSA (n = 29)	Children With CF Without OSA (n = 11)	Controls (n = 18)
Awake SaO <sub>2</sub> , %	97.8 (0.6)	98.6 (0.6)	98.9 (0.6)
Mean sleep SaO <sub>2</sub> , %	94.1 (1.1) <sup>a</sup>	96.0 (1.0)	97.0 (2.1)
Lowest NREM SaO <sub>2</sub> , %	86.2 (9.1) <sup>a</sup>	93.1 (3.0)	94.1 (0.9)
Lowest REM SaO <sub>2</sub> , %	85.1 (7.1) <sup>a</sup>	93.2 (1.0)	94.1 (0.5)
AHI	9.2 (6.5) <sup>a</sup>	0.8 (0.7)	0.5 (0.4)
Mean duration of the apnea/hypopnea, s	21.1 (2.7)		

Abbreviations: AHI, apnea/hypopnea index; CF, cystic fibrosis; REM, rapid eye movement; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; SaO<sub>2</sub>, oxyhemoglobin saturation.

<sup>a</sup> $P < .001$  children with CF and OSA vs children with CF without OSA. No statistical difference between CF without OSA and controls.

either the group with CF ( $r^2 = 0.03$ ,  $P = .14$ ) or controls ( $r^2 = 0.08$ ,  $P = .17$ ).

Children with CF had a high number of obstructive respiratory events (both apneas and hypopneas) whereas central apneas were rare in both groups. The mean (SE) AHI value was 7.3 (1.3) in the CF group vs 0.5 (0.4) in the control group ( $P < .001$ ) (Table 1 and **Table 3**). Within the CF group, 28 children with CF (70%) had an AHI greater than 2, considered the cut-off value to define OSA. Among these 28 children, 15 (53%) exhibited a mild degree of OSA (AHI < 5), whereas all the others, except 1 with severe CF, had moderate OSA. Children with CF and OSA, compared with children with CF without OSA, also had significantly lower values of mean nocturnal SaO<sub>2</sub> and mean lowest SaO<sub>2</sub> during REM and NREM sleep (**Table 4**). Children with CF but without OSA exhibited a nocturnal respiratory profile similar to healthy



**Figure.** Age-related distribution of apnea/hypopnea index (AHI) (A) and daytime (squares) and sleep (circles) mean (SE) oxyhemoglobin saturation (SaO<sub>2</sub>) (B) in children with cystic fibrosis and normal or mildly impaired lung function in stable clinical condition.

children (Table 4). In all the children with CF, age-related distribution of AHI values indicated a more severe degree of OSA in children younger than 6 years, with the highest AHI and the lowest mean SaO<sub>2</sub> reached in children aged 5 to 6 years (**Figure**). In the group of children with CF, all but 1 child with adenotonsillar hypertrophy and/or rhinosinusitis had OSA (AHI > 2), and overall, the mean AHI was slightly higher in children with UA abnormalities compared with those without UA abnormalities (9.7 [1.2] vs 6.7 [0.9], respectively;  $P < .05$ ).

#### COMMENT

This study provides evidence, to our knowledge for the first time, that sleep-disordered breathing, mainly obstructive apnea/hypopnea, may occur in an early stage of the life in children with CF and mild lung disease in stable clinical condition (out of exacerbation episodes). Using a cut-off value of 2 apneas-hypopneas per hour, 28 (70%) of 40 children with CF were affected by mild to moderate OSA. Different from most other sleep studies about CF, including adolescents and adults, our study included a relevant number of children aged from 6 months to 5 years. It was interesting that OSA was more severe within this age range. It was further found that, although in stable clinical condition, children with CF

exhibited a poorer sleep quality compared with healthy children.

Little is known about the role of UA obstruction in determining nocturnal apnea in infants and children with CF. This is due, at least in part, to the fact that many of the earlier studies were performed using nocturnal oxymetry, rather than full polysomnography, and that most of the cohorts did not include preschool-aged children. In a sample of adults patients (mean age, 27 years), Milross et al<sup>3</sup> found rare episodes of nocturnal apnea (0.1 apnea per hour and 3.1 hypopneas per hour) with a mild degree of oxygen desaturation. Only one previous report about nocturnal breathing in infants with CF is available, including 3- to 36-months-old infants, although these infants were not in stable condition.<sup>4</sup> Villa et al<sup>4</sup> found that all the infants with symptomatic mild airway inflammation exhibited OSA, with an AHI value lower compared with our patients in that age range. However, in the study by Villa et al abnormalities of the upper respiratory tract were not documented.

In children with OSA, the most common site of airway obstruction is the oropharyngeal tract (tonsillar hypertrophy, increased size of the uvula, or enlargement of lateral pharyngeal walls), followed by rhinopharynx.<sup>11</sup> Chronic rhinosinusitis has been reported in about 70% of the patients with CF and, in up to 44% of the cases, nasal polyps have been shown.<sup>2</sup> Ramos et al<sup>12</sup> in 2009 found that in children with CF (age range, 2-14 years), there was a close relationship among the occurrence of oropharynx structural alteration, chronic rhinosinusitis, and OSA. Accordingly, we found UA obstruction (nasal and/or pharyngeal) in about half of the cohort, and in these patients, OSA was slightly more severe. While tonsillar hypertrophy is a well-established cause of OSA, the mechanism by which nasal obstruction may cause nocturnal apneas is less clear. It has been speculated that nasal obstruction may increase UA collapsibility, by inhibiting the nasal afferents reflex that contributes to maintain the muscular tone.<sup>13</sup> Nasal obstruction may favor mouth-breathing that favors airway inflammation and destabilizes the upper respiratory tract.<sup>14</sup> Secretions from sinuses are also a cause of airway inflammation and occlusion.<sup>14</sup> The higher apnea index, found in children younger than 6 years, is somehow not surprising, as in the general pediatric population the nadir for OSA prevalence, perhaps due to the commonness of adenotonsillar hypertrophy, has been reported in preschool-aged children.<sup>15</sup> However, the prevalence of OSA found in the present group of children younger than 6 years is definitely higher than coetaneous general population (2%-3% of the children), thus, it is likely that factors, other than tonsil hypertrophy, more strictly associated with CF (eg, increased mucus secretion in the respiratory tract or UA inflammation) may determine/worsen UA occlusion in these patients.

Another major finding of the present study is that OSA may be a significant cause of sleep disruption. Alteration of sleep structure has been reported during infective exacerbation in adults with CF.<sup>16</sup> Clashing results have been reported in stable conditions although more recently an increased number of arousals and changes in REM sleep duration have been reported in adults and

adolescents with severe lung disease.<sup>17,18</sup> Indeed, the high number of respiratory events that we found in our study population, with mild lung disease, may be a major factor determining sleep disruption. As it is well known that OSA may adversely affect many aspects of children's life and development,<sup>11</sup> it is possible to discuss some potential clinical implication of our finding. In children, OSA has been associated with several neurocognitive and behavioral abnormalities.<sup>19,20</sup> In 5- to 9-year-old children, these include lack of memory, reduced executive functioning, learning disability, language dysfunction, and a lower intelligence quotient.<sup>21</sup> In a group of snoring infants, a negative correlation between the AHI and the Mental Development Index has also been shown.<sup>21</sup> In adults with CF, sleep disruption negatively affects tests of neurobehavioral performance regardless of the disease severity,<sup>18</sup> although there are no data about children with CF. Moderate to severe OSA in early childhood can also trigger relevant cardiovascular consequences. When awake, children with moderate to severe OSA exhibit higher systolic blood pressure compared with controls, while both mean diastolic and systolic blood pressures are increased during sleep.<sup>22</sup> Left ventricular hypertrophy, abnormal ventricular geometry, and altered heart rate autonomic control have also been shown in children and adolescents with OSA.<sup>21-23</sup> Finally, in childhood, OSA may lead to the activation of a systemic inflammatory response and an altered glucose metabolism.<sup>21</sup> However, we can only speculate on the potential adverse effects of sleep disruption and OSA in children with CF because no data are available to confirm this assumption.

In conclusion, our study demonstrated an early occurrence of OSA in infants and children with CF in stable clinical condition associated with a mild level of sleep disruption. Although further studies are necessary to assess the effect of sleep disorders on clinical outcomes, these data advise an early inclusion of nocturnal cardiorespiratory monitoring in the routine evaluation of these patients.

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*tistical analysis:* Spicuzza. *Administrative, technical, and material support:* Spicuzza. *Study supervision:* Spicuzza, Leonardi, and La Rosa.

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