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Original Article

Central Sleep Apnea in Children—10 Years Experience at a Tertiary Sleep Laboratory

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Abstract

OBJECTIVE: Central sleep apnea (CSA) is a rare condition in children; however, it can cause significant morbidity if not diagnosed early. We aimed to increase the knowledge about CSA in children by describing the clinical characteristics of children diagnosed with CSA at our sleep center.

MATERIAL AND METHODS: We retrospectively reviewed 1263 polysomnographies (PSG) performed between 2012 and 2023 at our tertiary sleep center and evaluated the clinical characteristics of the patients with CSA. Underlying diseases, clinical symptoms, sleep parameters, and short-term management of the patients were recorded.

RESULTS: Of the 1263 patients aged between 1 month and 18 years, 122 (9.65%) had CSA, with 54.9 % (n = 67) of them being female. Only 56.6% (n = 69) of the patients' parents had reported a symptom indicating sleep-disordered breathing. The most common underlying disease was genetic, including Down and Prader-Willi syndromes, followed by neurological diseases. Obstructive sleep apnea was detected in addition to CSA in 103 of the patients (84.4%). Bi-level positive airway pressure with a backup rate was the most common treatment modality.

CONCLUSION: While CSA is a rare clinical condition in children, it occurs more commonly in those with an underlying disease. Awareness of the disease and timely referral of the patients for sleep studies are critical to prevent long-term sequelae.

KEYWORDS: Sleep apnea, central apnea, children

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INTRODUCTION

Central sleep apnea (CSA) is a rare condition in the pediatric age group that occurs more commonly in children with an underlying disease. Even though central apneas can be physiological in newborns and infants, they can be an indicator of a serious condition in children, which may be related to desaturation, hypercarbia, and life-threatening arousals.[1]

A full night in-laboratory polysomnography (PSG) is the gold standard method to diagnose the disease. The central apnea index (CAI) is defined as the number of central apneas per hour of sleep and is considered pathological if higher than ≥ 5/h.[2]

Central sleep apnea is classified into 2 main groups, including primary CSA and CSA due to other conditions.[3] Primary CSA is the hallmark of congenital central hypoventilation syndrome, which is a rare genetic condition characterized by defective ventilatory control resulting in alveolar hypoventilation.[2] However, CSA is more commonly seen in children secondary to an underlying disease. Central sleep apnea can accompany a variety of diseases, including neuroanatomical diseases; genetic diseases like Prader–Willi syndrome (PWS) and Down syndrome; neuromuscular diseases; obesity; hypothyroidism; heart failure; and upper airway abnormalities including laryngomalacia and craniofacial abnormalities. Central sleep apnea may also be idiopathic or accompanied by other sleep-disordered breathing (SDB) conditions, including obstructive sleep apnea.[2-4]

Central sleep apnea is a poorly defined condition in children, with a prevalence of lower than 5% in healthy children.[1,2,5] Ghiardo et al[5] reported that the frequency of patients with CSA was 3% in their retrospective study, which included 2981 children older than 1 month over 6 years in their sleep laboratory. They also reported that Chiari malformation was the most common underlying etiology of patients with CSA, with a frequency of 13%.[5] Similarly, Felix et al[1] also reported the frequency of CSA as 4.1%, with the most common underlying etiology being neurosurgical diseases in their retrospective study, which included 441 children older than 1 year.

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The management of CSA depends on the underlying etiology, clinical findings, and complications. Surgery may be successful for neuroanatomical diseases such as Arnold–Chiari malformation and brainstem compression, craniofacial deformities, or upper airway obstructions. Some patients may benefit from nocturnal oxygen therapy, while others may require noninvasive/invasive ventilation support.[5] If CSA and OSA are not diagnosed and managed early, they can cause sympathetic nervous system activation, oxidative stress, and systemic inflammation, resulting in irreversible damage, including cardiovascular and neurocognitive complications due to chronic hypoxia and hypoventilation. Since CSA is a relatively rare condition and may be asymptomatic in some children, underdiagnosing is a major challenge.[2] Pediatricians must be aware of CSA, and sleep studies for children at increased risk of CSA should be performed timely and routinely. There are few studies investigating CSA in children. Our aim is to describe the clinical characteristics of children with CSA and demonstrate the results of sleep studies and management of the patients at a pediatric sleep laboratory.

MATERIAL AND METHODS

The study is designed as a single-center retrospective study. Children who had in-laboratory PSG between January 2012 and June 2023 and had a CAI ≥ 5/h were included. Patients had been referred for PSG because of SDB symptoms and/or an underlying disease associated with an increased risk of sleep apnea. Patients who had symptoms and/or findings of an acute infection were excluded. Demographic and clinical characteristics of the patients, including underlying diseases, comorbidities, and SDB-related symptoms, were recorded from medical records. Short-term interventions after the sleep study were also recorded.

All of the PSGs were performed in the Pediatric Sleep Laboratory with the same polysomnogram (Embla N700 PSG System®). None of the patients received any drugs or sedation during the study. Recorded parameters included airflow by a nasal flow cannula and/or thermistor, pulse oximetry by a pulse oximeter, chest and abdominal movements by inductance plethysmography, electroencephalogram, electrooculograms, submental and anterior tibialis electromyogram, and electrocardiography. The scoring and reporting were performed by experienced sleep technicians and sleep physicians. Scoring of the sleep stages and the respiratory parameters was performed according to the scoring rules of the American Academy of Sleep Medicine.[6,7]

Main Points

- Even though central sleep apnea is a rare condition in children, it can cause significant morbidity if not diagnosed and treated early.
- Children with underlying diseases, including genetic diseases and neurological conditions, have an increased risk for central sleep apnea.
- Timely referral of patients for polysomnography is critical in order to prevent long-term sequelae.

Sleep parameters including total sleep time, sleep stages, CAI, obstructive apnea–hypopnea index (oAHI), oxygen desaturation index, and minimum oxygen saturation were recorded. Central apnea was defined as a reduction in airflow of at least 90% without any respiratory effort for at least 20 seconds or more than 2 baseline respiratory cycles, associated with arousal, awakening, or oxygen desaturation of at least 3%. In addition, for infants under 1 year old, if the apnea persists for more than 2 breaths and was associated with a decrease in heart rate to less than 50/minute for at least 5 seconds or less than 60/minute for 15 seconds, it was also scored as central apnea. Obstructive apnea was defined as the absence of nasal airflow with the presence of a chest wall and abdominal movements for at least 2 breaths. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in pulse oximetry (SpO2) of at least 3% and/or arousal. The CAI was calculated as the sum of central apneas per hour of total sleep time and considered normal if <5. The oAHI was calculated as the sum of obstructive apneas and hypopneas and was considered normal if <1.[7,8]

The modified Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) and Pediatric Sleep Questionnaire (PSQ) were completed by the participants or their parents. Epworth Sleepiness Scale for Children and Adolescent is a validated, simple scale assessing daytime sleepiness, including 8 questions with 4-point Likert scale answers.[9] Pediatric Sleep Questionnaire is also a validated questionnaire used to evaluate SDB-associated symptoms.[10] Epworth Sleepiness Scale for Children and Adolescents and Pediatric Sleep Questionnaire are valid and reliable tools for use in Turkish children and adolescents.[11,12]

Written informed consent was obtained from the parents of the children. The study was approved by the Ethical Committee of Marmara University School of Medicine Approval number: 09.2024.300, date: 09.02.2024).

Statistical Analysis

Statistical analysis was carried out with the Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using graphs and normality tests. Continuous variables that were normally distributed were presented as means and standard deviations, whereas the data with asymmetrical distribution were presented as medians and percentiles. Categorical variables were presented as proportions. Spearman's rho was used for correlation analysis. Results were evaluated with 95% CIs, and statistical significance level was set at a *P* value of <.05.

RESULTS

About 1263 PSGs were reviewed retrospectively, and 122 (9.65%) of them with a CAI ≥ 5 were included. Of these, 54.9% (n = 67) were female. Patients' ages ranged from 1 month to 18 years old, with a median age of 23 months. Only 56.6% (n = 69) of the patient's parents reported a symptom indicating SDB. Witnessed apnea was the most common symptom, with a frequency of 34.4% (n = 42). Table 1 shows the baseline demographic and clinical characteristics of the patients.

Table 1. Demographic and Clinical Characteristics of the Patients (n = 122)

Age, months Median (25-75th percentile)	23 (8-96)
Sex, n (%) Female	67 (54.9)
Underlying disease* Yes, n (%) No, n (%)	 103 (84.3) 19 (15.7)
SDB-related symptoms, n (%) Witnessed apnea Mouth breathing Snoring Nighttime sweating Daytime sleepiness Dry mouth Abnormal sleep positions Difficulty in wake-ups Headache Hyperactivity	 42 (34.4) 33 (27) 30 (24.6) 16 (13.1) 15 (12.3) 9 (7.4) 8 (6.6) 6 (4.9) 5 (4.1) 5 (4.1)
Positive family history for SDB, n (%)	25 (20.5)
Prematurity, n (%)	24 (19.7)
Venous carbon dioxide level (mean ± SD)	42.48 ± 7.78

Polysomnography had been performed because of an underlying disease with a high risk of SDB in 24.6% (n = 30) of the patients. The most common underlying etiology was genetic diseases (14.8%, n = 18), including Down syndrome and PWS. Nineteen patients (15.6%) did not have a diagnosed underlying disease at the time of sleep study. Table 2 shows the underlying diseases of the patients known before PSG. Central apnea index was not correlated with age ($P > .05$), while it was positively (weakly) correlated with BMI (Spearman's $P = .398$, $P < .01$).

Table 2. Underlying Diseases of the Patients (n = 103)

Underlying disease	n (%)
Genetic syndromes *Prader–Willi, Down syndrome*	 18 (14.8)
Neurological disorders *Cerebral palsy, epilepsy*	 15 (12.3)
Neuroanatomical disorders *Arnold–Chiari, tumors, hydrocephaly*	 14 (11.5)
Metabolic diseases, n (%) *Mucopolysaccharidosis, Pompe, Krabbe, urea cycle defect*	 11 (9)
Neuromuscular diseases, n (%) *DMD, myasthenia gravis, myopathies*	 7 (5.7)
Craniofacial malformations *Nager syndrome, Pierre Robin, pycnodysostosis, Crouzon syndrome*	 7 (5.7)
Bronchopulmonary dysplasia	
Other Obstructive sleep apnea Chronic lung diseases Pulmonary hypertension Central hypoventilation Chest wall restriction (scoliosis, pectus excavatum	7 (5.7) 7 (5.7) 6 (4.9) 5 (4.1) 4 (3.3) 2 (1.6)

Table 3. Polysomnography Results of the Patients

	Median (25-75th Percentile)
TST (minutes)	203 (97.5-371)
AHI (events/h)	19.2 (9.5-35.2)
oAHI (events/h)	6.7 (2.6-17.2)
CAI (events/h)	8.4 (5.9-21.9)
Min SpO2	83 (80-87)
ODI (events/h)	23.5 (9.8-38.2)
REM sleep (%)	6.2 (0-13.2)
N1 sleep (%)	4.6 (1.9-10.4)
N2 sleep (%)	47.3 (36.4-59.8)
N3 sleep (%)	34.1 (24.1-46.2)

AHI, apnea–hypopnea index; CAI, central apnea index; oAHI, obstructive apnea hypopnea index; ODI, oxygen desaturation index; TST, total sleep time.

According to ESS-CHAD, 4 (3.3%) patients had daytime sleepiness, while 49 (40.2%) patients had SDB according to PSQ. In 103 patients (84.4%), there was accompanying obstructive sleep apnea in addition to central apnea. Table 3 shows the PSG results of the patients. There was no significant correlation between CAI and PSQ. Similarly, CAI and ESS-CHAD were not significantly correlated ($P > .05$ for both).

After PSG, bi-level positive airway pressure (BPAP) with a backup rate was initiated in 46 (37.7%) patients, while 5 (4%) patients required continuous positive airway pressure (CPAP) support. Sixteen (13.1%) patients were treated with BPAP and oxygen together, while 1 patient was treated with CPAP and oxygen together. Thirteen (10.6%) patients were treated with nocturnal oxygen support only. Two patients needed invasive ventilation support. Sixty of the patients (49.2%) needed a follow-up PSG.

DISCUSSION

The present study is one of the largest-scale studies demonstrating the demographics, clinical characteristics, and polysomnographic features of CSA in children. We evaluated the results of all PSGs performed between 2012 and 2023 (n = 1263) and found that the prevalence of CSA was 9.65%. The most common underlying etiology was genetic diseases, including Down syndrome and PWS, in the present study. While witnessed apnea was the most common symptom, more than one-third of the patients' parents had not reported a symptom indicating SDB, which shows the importance of a full-night PSG for the diagnosis of CSA.

Central sleep apnea is a poorly defined clinical condition in children. As central apneas may be accepted as a physiologic phenomenon in healthy infants and children in particular situations, it is important to distinguish between pathological and physiological central apneas.[13] Short-duration central apneas in the context of a sigh, movement, arousal, or REM (rapid eye movement) sleep are considered physiological, and with the maturation of the central nervous system, central apneas are expected to decrease.[2] Studies have reported various results regarding central apnea in healthy children. Verhulst et al[14] conducted a study including 60 healthy children (6-16 years)

without SDB-related symptoms and reported that the mean CAI was 0.85 ± 1.06, with a range between 0.0 and 5.5. Similarly, Traeger et al[15] also reported that a mean CAI was 0.08 with a range between 0 and 6/h, in their study involving 66 healthy children aged between 2 and 9 years. Although our study did not evaluate CAI values in healthy children, these results are important to demonstrate that CAI values up to 5/h can be seen in healthy children. Based on previous literature, we accepted CAI ≥ 5/h as pathological.

Different definitions of central apnea may explain the difference in frequency and severity reported across different studies. In our study, we defined central apnea as a reduction in airflow of at least 90% without any respiratory effort for at least 20 seconds or more than 2 baseline respiratory cycles, associated with arousal, awakening, or oxygen desaturation of at least 3%, according to AASM guidelines. Traeger et al accepted central apnea criteria as 20 seconds,[15] while Verhults et al. accepted 10 seconds as a threshold. This discrepancy may explain the higher median CAI results reported by Verhults study (0.85 vs. 0.08/h).[14] Felix et al[1] retrospectively evaluated 441 PSG records of children older than 12 months and reported that the frequency of patients with CAI > 5 was 4.1 % in their study. The study by Felix et al[1] has also accepted the same definition and cut-off value with our study. Kritzinger et al[13] reported the prevalence of CSA as 5.4% in their retrospective study, including patients between 3 and 156 months. The higher prevalence of CSA in our study may be related to the inclusion of patients older than 1 month. In addition, our sleep center is one of the few pediatric sleep centers in our country. We may speculate that the selected referral of patients with severe disease can be the reason for the higher prevalence of CSA in our center.

In our study, 103 of 122 (84.4%) patients had a diagnosis of an underlying disease while the sleep study was performed. Felix et al[1] reported that all patients with CSA had an underlying disease, while Ghirardo et al[5] reported that only 1 patient did not have an underlying disorder in their retrospective study, including 102 patients with a CAI > 5. As our study included a 10-year period, some of our patients may have been diagnosed during long-term follow-up. To our knowledge, our study is a retrospective study covering the longest period in this field. The most common underlying etiology was genetic diseases, including Down syndrome and PWS, in our study. Ghirardo et al[5] reported the most common underlying etiology as Chiari malformation, while upper airway malformations/dysfunctions followed. Similarly, Felix et al also reported Chiari malformation as the most common underlying etiology, in addition to ganglionoroma.[1] Kritzinger et al[13] reported that the most common risk factor was a neurological disorder. Similar to previous literature, the second most frequent underlying disease was neurological disorders, while neuroanatomical disorders, including Chiari malformation, followed in our study. The most common underlying etiology was PWS in the present study (n = 10). The relationship between PWS and central apnea is a well-known entity with a frequency as high as 43% in infants, according to previous reports. Additionally, before the initiation of growth hormone, which is a Food and Drug Administration-approved treatment for individuals with PWS, performing a sleep study is recommended due to the increased risk of obstructive apneas after the treatment.[16] The possible explanation for the relatively high frequency of PWS in our study is the need for a sleep study before growth hormone administration. In addition, we may also suggest that the awareness of clinicians regarding the relationship between central apnea and other diseases, including neuroanatomical diseases, may be less than necessary.

More than a third of the patients did not have symptoms regarding SDB in our study. Similar to our study, previous studies have also emphasized the same pattern, as opposed to patients with OSA.[1,13] Many children with a polysomnographic diagnosis of CSA were asymptomatic, including Arnold Chiari malformations, Down syndrome, and achondroplasia.[2] Thereby, it is highly important to know high-risk patient groups for CSA, mainly including neuroanatomical and neuromuscular diseases, craniofacial malformations, genetic conditions, and cardiac diseases. In addition, BMI was found to be positively correlated with CAI (weakly), similar to previous studies.[17] Clinical suspicion and referring for PSG play a key role in the diagnosis of CSA in these groups.

Interestingly, the majority of patients (85%) had concurrent OSA with CSA in our study. Several studies have demonstrated an association between OSA and CSA.[5,13] Elevated loop gain and the presence of pharyngeal narrowing have been suggested to be responsible for this association. In addition, treatment of OSA can reveal CSA, which is also called treatment emergent apnea.[18] Even though only 7 patients had a diagnosis of OSA before PSG in our study, a possible relationship between OSA and CSA should not be underestimated.[18]

Continuous positive airway pressure, oxygen support, and BPAP are the cornerstones of the treatment of central apnea. In our study, we initiated CPAP, oxygen support, and BPAP in 4%, 10.6%, and 13.1% of the patients, respectively. A combination of BPAP/CPAP together with oxygen was required in some patients. The most commonly selected treatment was BPAP in our study. BPAP with a backup rate increases ventilation independent of the patients' ventilatory drive.[18] Even though finding an appropriate interface and patient noncompliance can be a problem in pediatric patients, noninvasive ventilation support is still the most preferred treatment method for CSA. As the optimal mode for ventilation support is not clear in the pediatric age group and the studies have mostly been performed in adult patients, further studies are urgently needed in this area.[19] Additionally, the heterogeneity of the disease and the wide spectrum of underlying diseases make the management of CSA more complex, and an individualized approach is required to find optimal treatment.

The present study has some limitations. First, our study was designed as a retrospective single-center study. We could not evaluate the progress of the patients as we did not include the following PSG results of the patients. Additionally, there may be some patients who may receive a new diagnosis in the long-term follow-up. We could not measure carbon dioxide levels of the patients during sleep due to technical issues, which is necessary to diagnose hypoventilation. It is possible that the number of patients with hypoventilation may be underestimated. Lastly, as our center is one of the

few reference centers regarding SDB in children, a higher prevalence of CSA may be overestimated by the priority of high-risk patients.

CSA is not a well-defined clinical condition in children. Patients may be asymptomatic, and thereby late diagnosis is a major clinical problem. Awareness of CSA, close monitoring of high-risk patients with an underlying disease, and timely referral of patients for PSG are highly critical to prevent long-term sequelae. The heterogeneity of the underlying etiology, the complex course of the disease, and the lack of a standard pediatric treatment protocol make the management of the disease difficult. There is an urgent need for a universal clinical protocol for the optimal management of the disease.

Ethics Committee Approval: This study was approved by the Ethics Committee of Marmara University (approval number: 09.2024.300; date: 09.02.2024).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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