Original Research

Clinical Symptoms and Polysomnographic Findings in Children and Adolescents with Neuromuscular Disorders Referred to the Sleep Center of Qazvin Children's Hospital, Iran

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Abstract

Background and Objective: Patients with neuromuscular diseases (NMDs) are at high risk for sleep problems, may lead to significant morbidity. Central sleep apnea (CSA), obstructive sleep apnea (OSA), hypopnea, and nocturnal hypoventilation are common in children with NMDs. Polysomnography (PSG) is the gold standard for evaluating and diagnosing sleep breathing disorders in children and adolescents with NMDs. This study aimed to evaluate clinical symptoms and PSG findings among them.

Materials and Methods: This retrospective cross-sectional study included 22 children and adolescents aged 18 years or younger referred to the sleep department of Qods Children's Hospital, Qazvin, Iran, between 2017 and 2022.

Results: PSG was performed in 22 children with NMD, with a mean age of 65 months. Spinal muscular atrophy (SMA) was the most common diagnosis (45.4%). The most common sleep problems were sleep-disordered breathing (SDB) (86.4%), followed by restless sleep (9%). The mean sleep efficiency was 79.2%, and the mean apnea-hypopnea index (AHI) was 22.2 events per hour of total sleep time (TST). Hypopnea, OSA, and CSA were observed in 36%, 22%, and 7% of patients, respectively. The mean oxygen desaturation index (ODI) was 12.5, and the mean arousal index was 22.7. The sleep architecture was mildly disturbed with a reduction in rapid eye movement (REM) sleep.

Conclusion: SDB is prevalent among children and adolescents with NMDs. Based on the severity of symptoms, noninvasive ventilation (NIV) and medical treatments were initiated. PSG is essential for early diagnosis and management and may reduce morbidity and mortality of patients with NMDs.

Keywords: Child; Neuromuscular diseases; Polysomnography; Sleep-disordered breathing

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Introduction

Neuromuscular diseases (NMDs) comprise a broad spectrum of conditions, including more than 400 distinct diseases (1) that impair muscle function due to pathology of nerves, muscles, or the neuromuscular junction. These disorders may be acquired or inherited (2), and are diagnosed using electromyography (EMG), nerve conduction velocity (NCV), magnetic resonance imaging (MRI), and next-generation sequencing (NGS) (3).

Patients with NMD exhibit inspiratory and expiratory muscle weakness, ineffective cough, progressive reduction in lung volumes, and ventilation dysfunction (4). It is estimated that approxi-

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mately 40% of patients with NMD have sleep-disordered breathing (SDB) (5), which leads to significant daytime symptoms, decreasing quality of life (QOL) and survival (6).

The clinical manifestation of SDB in patients with NMD may be subtle. Common features include sleep fragmentation, daytime sleepiness, and morning headaches. In advanced stages of the disease, obstructive sleep apnea (OSA) and hypoventilation occur more frequently (5). Other sleep problems, such as disturbed sleep architecture (1) and restless legs syndrome (RLS), have also been reported in this population (7).

Physiologically, ventilatory effort decreases during sleep, especially during the rapid eye movement (REM) stage. This reduction leads to a decline in minute ventilation by 1-2 l/min, a decrease in partial pressure of oxygen (PaO_2) by 2-8 mmHg, and an increase in partial pressure of carbon dioxide ($PaCO_2$) by 2-8 mmHg (8). In patients with NMD, alveolar hypoventilation due to respiratory muscle weakness, together with increased upper airway resistance secondary to pharyngeal dilator muscle atonia (causing OSA), are key mechanisms contributing to the progression of SDB (9, 10).

Diaphragmatic weakness and reduced alveolar ventilation are further exacerbated during sleep, increasing the risk of complications related to nocturnal hypoxemia, including pulmonary hypertension (PHTN), cor pulmonale, and neurocognitive dysfunction. Restrictive thoracic disorders, chest wall deformity, and nervous system impairment may also be aggravated by SDB (11).

The earliest manifestation of respiratory muscle weakness is oxygen desaturation during REM sleep, resulting from reduced rib cage contribution to ventilation and subsequently, a reduction in tidal volume. Important predisposing factors for sleep ventilation events include pharyngeal muscle weakness, bulbar disorders, macroglossia, and reduced lung volumes. Despite an intact central respiratory drive, patients with NMD demonstrate a reduced ventilatory response to hypercapnia (1). With disease progression, respiratory symptoms may also occur in non-REM (NREM) sleep and wakefulness in addition to the REM stage (6).

Several studies suggest that cardiorespiratory polygraphy is a useful screening method for OSA in children with chronic diseases, offering advantages over questionnaires (12). However, polysomnography (PSG) remains the most effective tool for detecting SDB in patients with NMD, whether performed in a sleep clinic or at home (13). PSG is the gold standard for diagnosing SDB before the onset of daytime respiratory abnormalities (14) and allows accurate classification of breathing and titration of noninvasive ventilation (NIV) (2).

Materials and Methods

This retrospective cross-sectional study evaluated the demographic and clinical characteristics, sleep-related symptoms, Children's Sleep Habit Questionnaire (CSHQ) scores, and PSG findings of 22 children and adolescents (< 18 years) with NMD who were referred to the sleep ward of Qods Children's Hospital, Qazvin, Iran, between 2017 and 2022.

The study protocol was approved by the Ethics Committee of Qazvin University of Medical Sciences (Ethics Code: IR.QUMS.REC.1401.046).

The diagnosis of NMD was confirmed by a neurologist and geneticist based on the relevant tests.

Participants' age, sex, height, weight, body mass index (BMI), PSG indicators, underlying diagnoses, referral sources, and sleep-related symptoms, including snoring and apnea during sleep, were extracted from medical records. Information regarding current illness, primary complaints, and background illness was also reordered.

Sleep habits and patterns were assessed using the validated Persian version of the CSHQ (15), completed by parents according to the child's age. The questionnaire evaluates multiple domains, including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, SDB, and daytime sleepiness.

PSG was performed under standardized conditions. The sleep environment was adjusted according to the child's age, including room temperature, lighting, noise level, and bed size to approximate the child's sleeping conditions at home.

A nurse described the test, electrodes, and PSG devices to the child's parents. All PSGs were performed using the Devilbiss device (Germany).

A trained nurse applied gold electrodes and sensors, including eight standard electroencephalography (EEG) electrodes, six common EMG electrodes for the chin and leg, and at least two standard electrocardiography (ECG) electrodes. Nasal pressure and temperature sensors were placed in front of the nose and mouth. Thoracic

and abdominal belts with the corresponding sensors were used to record breathing movements. Pulse oximetry was placed on the child's finger to record arterial oxygen saturation. Due to limitations, capnography was performed only in six children with a high suspicion of hypoventilation. Audio and video monitoring were used to document snoring and body movements. After all the electrodes and sensors were connected, the PSG recording began after lights-off and continued for 7-8 hours. Electrodes were moved around 7:00 AM. The following day, PSG data were scored and analyzed by a pediatric sleep disorders fellow according to standard criteria (13).

Recorded variables included sleep time, sleep efficiency, sleep architecture, respiratory events, apnea-hypopnea index (AHI), arousal index (AI), and oxygen desaturation index (ODI).

Statistical analysis was performed using SPSS software (version 21, IBM Corporation, Armonk, NY, USA).

Data normality was assessed using the Kolmogorov-Smirnov test, which indicated a non-normal distribution. Therefore, results were presented as medians and interquartile ranges (IQRs) (25^{th} percentile-75^{th} percentile). Pearson correlation analysis was applied where appropriate. A P-value less than 0.05 was considered statistically significant.

Results

Of the 50 children and adolescents (< 18 years) with NMD who were referred to the sleep clinic of the children's hospital over a five-year period, 22 patients had a confirmed diagnosis of NMDs and were included in the study.

Among the included participants, 12 were boys (54.5%). The age range was 4 months to 13 years, with a mean age of 5.5 years. Based on height and weight measurements, the mean BMI was 15.80 ± 5.34 kg/m^2.

Ten patients (45.4%) were diagnosed with spinal muscular atrophy (SMA) types I-III. Myopathies were the second most frequent diagnostic category in 10 patients (45.4%), including four cases of muscular dystrophy and six cases of other myopathies. In addition, one patient had Charcot-Marie-Tooth (CMT) disease and one patient had congenital myasthenia gravis (Table 1).

Table 1. The prevalence of patients with neuromuscular disease (NMD) referring to the sleep clinic of Qods Children's Hospital, Qazvin, Iran, 2017-2022

Disease	n (%)
SMA	10 (45.4)
Myopathy	6 (27.3)
Muscular dystrophy	4 (18.1)
Others (congenital myasthenia gravis and CMT disease)	2 (9.0)

SMA: Spinal muscular atrophy; CMT: Charcot-Marie-Tooth

According to clinical history, the most common reason for referral to the sleep clinic was a recommendation from a neurologist or pulmonologist for PSG evaluation.

The main complaint in 19 patients (86.4%) was breathing problems during sleep, including witnessed apnea, cyanosis, and dyspnea. Restless sleep with or without nocturnal sweating was reported in two patients. One patient was referred for evaluation prior to tracheostomy decannulation, and in one case, seizure activity during sleep was suspected.

PSG findings related to sleep structure and respiratory events are presented in tables 2 and 3. The median sleep efficiency was 77.9%, and the median AHI was 22.7/hour. Sleep architecture in N1, N2, and N3 stages was almost standard, whereas a decrease in the REM stage was observed (median = 11.4%).

Table 2. Sleep architecture of patients with neuromuscular disease (NMD) referring to the sleep clinic of Qods Children's Hospital, Qazvin, Iran, 2017-2022

Variable	Median	Percentile 25	Percentile 75
TST (minute)	315.000	271.500	378.750
N1 (%)	7.000	5.200	13.950
N2 (%)	54.800	49.775	69.275
N3 (%)	19.850	13.875	27.850
REM (%)	11.400	5.925	15.950
Sleep efficiency (%)	79.200	70.725	88.725
AHI	22.700	9.675	34.500
PLMs index	7.550	5.375	15.475
Bruxism index	27.100	23.425	52.200

TST: Total sleep time; REM: Rapid eye movement; AHI: Apnea-hypopnea index; PLMs: Periodic limb movements

Table 3. Respiratory events of patients with neuromuscular disease (NMD) referring to the sleep clinic of Qods Children's Hospital, Qazvin, Iran, 2017-2022

Variable	Median	Percentile 25	Percentile 75
CSA	7.00	2.00	20.00
OSA	22.00	6.00	78.50
Hypopnea	36.00	9.50	90.25
Mixed apnea	4.00	2.50	11.25
AHI	27.50	10.20	86.40
AHI (REM)	37.85	8.20	56.17
AHI (NREM)	22.20	3.37	41.25
Baseline O_2	90.50	81.25	95.00
Lowest O_2	83.50	67.00	95.00
ODI	12.50	9.70	34.30
$PaCO_2$	50.60	40.10	80.62

CSA: Central sleep apnea; OSA: Obstructive sleep apnea; AHI: Apnea-hypopnea index; REM: Rapid eye movement; NREM: Non-rapid eye movement; ODI: Oxygen desaturation index; PaCO2: Partial pressure of carbon dioxide

The AHI was analyzed separately for REM and NREM stages. The mean AHI was 22.2 events/hour during NREM stage and 37.8 events/hour during REM stage, indicating a significantly higher AHI during REM sleep. No significant association was found between total AHI and REM AHI (P = 0.996). However, a significant association was found between total AHI and NREM AHI (P = 0.009). ODI, a vital sign of nocturnal desaturation, was 12.5 events/hour. A significant positive correlation was found between ODI and AHI (P = 0.026), as well as between AI and AHI (P = 0.006) (Table 4).

Capnography was performed in six patients with suspected hypoventilation, confirming hypoventilation in three cases.

Discussion

Given the high prevalence of SDB in patients with NMDs (16), sleep assessment is essential in this population, as early diagnosis and timely initiation of NIV can improve survival (17).

In this study, the mean age of patients with NMD referred to the sleep clinic was 5.5 years, with a predominance of boys. SMA was the most common diagnosis. The primary reason for referral was severe breathing problems during sleep, most commonly witnessed apnea, cyanosis, and dyspnea. Total sleep time (TST) was reduced compared with age-related norms. This reduction may be explained by unfamiliar sleep laboratory environment and inadequate adaptation of the children during the test night; however, sleep fragmentation due to frequent breathing problems during sleep appears to be more important contributing factor. Accordingly, the AI of the study sample was markedly elevated, with a median value of approximately 23. These arousals typically occurred after respiratory events, returning blood gases to normal levels, causing fragmented sleep (18).

Table 4. Pearson's correlation matrix of important data obtained from polysomnographic (PSG) studies of the studied subjects, 2017-2022

		Age	AHI (total)	AHI (REM)	AHI (NREM)	Sleep efficiency	ODI	AI
Age	R	1						
	P-value	-						
AHI (total)	R	0.014	1					
	P-value	0.950	-					
AHI (REM)	R	0.292	0.001	1				
	P-value	0.187	0.996	-				
AHI (NREM)	R	0.009	0.546	0.104	1			
	P-value	0.969	0.009	0.645	-			
Sleep efficiency	R	-0.016	0.342	0.142	0.432	1		
	P-value	0.944	0.119	0.530	0.045			
ODI	R	0.251	0.473	0.416	0.487	0.407	1	
	P-value	0.260	0.026	0.054	0.022	0.060	-	
AHI	R	0.193	0.568	0.448	0.464	0.228	0.468	1
	P-value	0.390	0.006	0.036	0.030	0.309	0.028	-

AHI: Apnea-hypopnea index; REM: Rapid eye movement; NREM: Non-rapid eye movement; ODI: Oxygen desaturation index

In a study by Shinde and Kinimi, involving 46 children with NMD (mean age: 8 years and nine months), the reported mean AI was 10.76 ± 8.20/hour (19), which is significantly lower than that observed in our study. This is likely due to referral at more advanced stages and the younger age of our cohort. Similarly, Aboussouan's study reported that 71% of patients with NMD had an AHI greater than 2.1 events/hour (2).

Sleep architecture analysis in our patients revealed relatively preserved N1, N2, and N3 stages, accompanied by a significant reduction in REM sleep. Considering the blood oxygen depletion attacks in REM sleep, instability and a decrease during REM sleep are seen in a similar study conducted by Bourke and Gibson on patients with NMD who underwent a PSG. Consistent with our findings, they also reported a reduction in TST, frequent arousals, increased N1 stage, and reduction or complete suppression of REM stage (20). These alterations contribute to poor sleep quality and sleep deficiency in these children, which was significantly decreased in our cohort compared with normal reference value of approximately 90%.

In the study by Shinde and Kinimi, sleep efficiency was also reduced, with a mean value of 82.72 ± 12.82, and severe OSA was identified as the most common respiratory disorder with a prevalence of 60.86% (19). Shneerson et al. similarly demonstrated that OSA was more common in patients with NMD due to reduced upper airway dilator muscle tone, while central sleep apnea (CSA) was an important diagnostic feature in this population (17).

In our study, hypopnea and OSA were the most frequently observed respiratory events, followed by CSA.

In patients with CMT disease, OSA and hypoventilation are commonly reported due to pharyngeal and larynx muscles neuropathy and hypoglossal nerve dysfunction, contributing to increased morbidity and mortality (21). In Duchenne muscular dystrophy (DMD), frequent night awakenings, OSA, and hypoventilation may occur in early stages, with progressive worsening in later stages of the disease (22).

AHI in our patients was significantly elevated, with a mean of 25 events/hour, and was significantly higher during REM sleep than during NREM sleep. These findings are consistent with the study by Aboussouan, which showed that the first manifestation of respiratory muscle weakness in patients with NMD was oxygen desaturation in the REM stage, attributed to the limited chest wall movement. Hypoventilation first appears in the REM phase and then in the NREM phase (2). Accordingly, SDB and nocturnal desaturation are more severe during REM sleep in patients with NMD (20). In another similar study, the majority of respiratory events among these patients occurred during the REM stage (88.37%) (19).

In general, most breathing problems occur first in REM, then NREM, and finally in the wake (18). We observed a positive correlation between AHI and AI, indicating that more severe breathing problems during sleep are associated with more arousals and sleep fragmentation. Additionally, a significant association was found between AHI in NREM and sleep efficiency, a finding not consistently reported in previous studies. Delayed referral and more severe SDB at the time of PSG may partly explain this observation.

In a study by Falsaperla et al., the ODI of patients with NMD before NIV initiation was slightly lower than that in our study (20.7 ± 13.9), and no significant relationship between ODI and AHI was identified (23). In contrast, we found a significant positive relationship between these variables. Elevated ODI has been linked to increased interleukin-6 (IL-6) and a higher risk of inflammation and cardiovascular events in patients with NMD (24).

Aboussouan's study reported that the most common indicator of respiratory dysfunction in 80% of patients with NMD was O_2 saturation below 85% (2). In our study, 50% of patients experienced oxygen desaturation below this threshold; notably, the lowest recorded O_2 saturation in one patient reached 34%. The lower prevalence in our study may be related to the smaller sample size and the younger participants.

We performed capnography only for less than a third of our patients, limited to those with a strong suspicion of nocturnal hypoventilation, and confirmed hypoventilation in three cases based on the American Academy of Sleep Medicine (AASM) reference. Technical challenges in young children and the high cost of capnography limited its broader use for all of our patients.

Kotterba et al. emphasized the importance of nighttime capnography and pulse oximetry in diagnosing respiratory failure in patients with NMD, noting that capnography was more sensi-

tive than pulse oximetry in these patients (25). Measurement of $PaCO_2$ in patients with NMD is an essential indicator for diagnosing hypoventilation and the decision to initiate NIV (26).

PSG remains the diagnostic and therapeutic standard for diagnosing SDB and starting NIV (2). However, high costs, limited access to PSG devices across medical centers, and a shortage of pediatric sleep specialists to conduct accurate analyses pose significant barriers to early patient examinations and intervention in patients with NMD.

Conclusion

Sleep-related breathing disorders are highly prevalent in children with NMD, typically manifesting first during sleep and later extending into wakefulness. These disturbances significantly impair sleep quality and quantity and may have long-term irreparable effects on the child's QOL. Therefore, PSG is essential for timely diagnosis and appropriate management, enabling early intervention that can substantially reduce morbidity and mortality and improve QOL in this population.

Conflict of Interests

Authors have no conflict of interests.

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