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Pulmonary functions and sleep-related breathing disorders in lipid storage disease

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Abstract

Purpose Pulmonary function abnormalities and sleep-related breathing disorders (SRBD) are frequent in subjects with several neuromuscular diseases but there is no data about lipid storage diseases (LSD). Therefore, we aimed to evaluate pulmonary functions and SRBD in adults with LSD.

Methods Pulmonary functions (forced expiratory volume (FEV_1), forced vital capacity (FVC), supine FVC, upright-supine FVC% change, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), peak cough flow (PCF)), arterial blood gases, and polysomnographic data of all subjects were evaluated.

Results Twenty-five subjects with LSD were evaluated [17 males, 8 females; age 34.9 ± 15 years; BMI 26.5 ± 3.4 kg/m^2]. MIP was − 72.2 ± 32.7 cmH_2O (< − 80 cmH_2O in 13 subjects), MEP was 80.9 ± 39.1 cmH_2O (< 80 cmH_2O in 9 subjects, < 40 cmH_2O in 6 subjects), and PCF was 441.3 ± 190.9 L/min (< 360 L/min in 11 subjects). FVC was 87.8% ± 25.7 and 6 subjects had FVC < 80%. Seven subjects had diaphragm dysfunction (four upright-supine FVC% ≥ 15, three dyspnea in supine position with paradoxical abdominal respiration). Five subjects had hypoxemia (PaO_2 < 80 mmHg) and 8 subjects had hypercapnia ($PaCO_2$ > 45 mmHg). REM sleep had decreased in all subjects (10.2% ± 6.1). Obstructive sleep apnea (OSA) was found in 80% of the subjects (n = 20; 9 mild, 9 moderate, 2 severe). For subjects with OSA, apnea-hypopnea index (AHI) was 20.8 ± 15.9/h, oxygen desaturation index (ODI) was 11.9 ± 15.4/h, AHI_{REM} was 30.6 ± 19.7/h, AHI_{NREM} was 19.7 ± 16.6/h, ODI_{REM} was 27.2 ± 26.1/h, and ODI_{NREM} was 11.4 ± 15/h. Five subjects (20%) diagnosed as REM-related OSA. Nocturnal mean SpO_2 was 94.9% ± 1.7, lowest SpO_2 was 73.3% ± 13.9, and time spent with SpO_2 < 90% was 2.4% ± 7.2.

Conclusion In subjects with LSD, pulmonary function impairment, daytime hypercapnia and hypoxemia, and OSA, especially REM-related OSA, are frequent. Therefore, pulmonary functions and polysomnography should be performed routinely.

Keywords Lipid storage disease · Neuromuscular disease · Obstructive sleep apnea · Pulmonary functions

Introduction

Lipid storage diseases (LSD) develop due to lipid dysmetabolism and are characterized by the accumulation of abnormal amounts of neutral fat in muscle fibers. Lipid metabolism is an energy pathway necessary for body movements. This pathway, which is blocked during transport or destruction of neutral lipids in muscle fibers, reveals both energy deficit and causes the undiluted lipids to accumulate in the cells [1]. LSD are characterized by progressive muscle weakness and exercise intolerance, occasionally accompanied with systemic findings [1]. Several LSD such as carnitine deficiencies, acyl-coenzyme A dehydrogenase deficiencies, electron transfer flavoprotein defects, and coenzyme-Q deficiency may cause myopathy [1, 2]. Clinical presentation of LSD is heterogeneous, but generally, there are two major clinical phenotypes, especially in late-onset subjects [3]. The most common type is LSD with progressive muscle weakness associated with or without metabolic crisis. The second type is characterized with

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recurrent rhabdomyolysis triggered by infections, hunger, fasting, or vigorous exercise. Respiratory muscles may be involved in LSD with progressive muscle weakness [4–8]. Deposition of lipids in the upper airway muscles and respiratory muscles especially the diaphragm is likely which may lead to sleep-related disordered breathing (SRBD), obstructive sleep apnea (OSA), nocturnal hypoventilation, or pulmonary dysfunction. However, impairment in pulmonary functions and SRBD in subjects with LSD is unknown. There are only case reports in the literature [4–8]. We aimed to evaluate the pulmonary functions and SRBD in adult subjects with LSD.

Materials and methods

This prospective study was conducted in Istanbul University, Istanbul Medical Faculty, Department of Pulmonary Diseases Sleep Laboratory, from September 2016 to December 2016. All subjects voluntarily signed their informed consent. The study was carried out according to the principles of the Helsinki Declaration. It was approved by the Istanbul University Istanbul Medical Faculty Institutional Board (Ethic No. 2016/905).

This study included all adult subjects referred from Neurology Department, who had the diagnosis of LSD which was confirmed clinically and histopathologically. Subjects with severe pulmonary parenchymal diseases, cardiac disorders, renal or hepatic dysfunction, uncontrolled hypothyroidism, active inflammatory diseases, acute infections, malignancy, and medication which may affect sleep architecture were excluded. We categorized our subjects into two clinical phenotype: (1) subjects with progressive muscle weakness and (2) subjects with previous recurrent rhabdomyolysis attacks.

Demographics, body mass index (BMI), smoking history, comorbidities, and duration of the LSD were recorded. The BMI was calculated using Khosla and Lowe's formula (weight[kg]/height^2[m^2]). Characteristic symptoms of OSA (apnea, snoring, daytime sleepiness) and other respiratory symptoms were recorded.

Assessment of pulmonary functions

Spirometry is performed in the upright and supine positions in accordance with the ATS/ERS standards [9]. Spirometric parameters were measured using a ZAN-GPI 3.00 (Nspire Health GmbH, Germany). Measurement of forced expiratory volume (FEV_1) and forced vital capacity (FVC) and FEV_1/FVC ratio were recorded. Results were expressed as a percentage of predicted normal values [10]. A measured value below 80% of the predicted value was considered to be abnormally low. A drop of 15% and more in FVC from sitting to supine position or dyspnea in supine position with paradoxical abdominal respiration was considered as diaphragm dysfunction [11, 12]. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured by a Micro Medical MicroRPM (Carefusion Micromedical, Micro RPM, USA) [13]. Black and Hyatt reference values were used for MIP and MEP data as percent was predicted [14]. For peak cough flow (PCF), three measurements were taken using a peak expiratory flow meter, and the highest level was recorded [15, 16]. PCF < 360 L/min was considered as abnormal [17]. In order to investigate hypercapnic respiratory failure, arterial blood gases (ABG) were taken. PaO_2 < 80 mmHg was considered as hypoxemia and $PaCO_2$ > 45 mmHg was considered as hypercapnia.

Assessment of polysomnographic findings

Polysomnography was performed using the Compumedics E device. Sleep stages and respiratory events were scored according to the AASM 2012 guidelines [18]. OSA was defined as a cessation of airflow ≥ 90% compared with baseline for ≥ 10 s while there was evidence of persistent respiratory effort. Hypopnea was defined as an amplitude reduction of ≥ 30% in airflow lasting for ≥ 10 s that was associated with an oxygen desaturation of ≥ 3% or with arousal [18]. Polysomnography records were scored by a trained technician and interpreted by a sleep specialist. OSA was diagnosed if the AHI was ≥ 5/h and the presence of clinical symptoms or AHI ≥ 15/h without any symptoms. The OSA severity was graded as mild (AHI 5–14/h), moderate (AHI 15–29/h), or severe (AHI ≥ 30/h) [18]. According to the previously reported definition of REM-related sleep sleep-disordered breathing in the literature, we defined REM-related sleep-disordered breathing as follows: (1) overall AHI ≥ 5, (2) $NREM_{AHI}$ < 15, and (3) REM_{AHI} to $NREM_{AHI}$ ratio > 2 [19, 20].

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (AIMS, Istanbul, Turkey). The patient characteristics were presented with descriptive statistics as the means ± SD or median (interquartile ranges) for non-normally distributed variable or frequency (percentage) for categorical variables. The concordance of normal distribution of all variables was calculated using the Shapiro-Wilk test. If the data were not normally distributed, we used nonparametric tests for the dependent variables. Comparisons between groups were carried out using the Mann-Whitney *U* test or Student's *t* test. Categorical variables were compared using the chi-square test. A *p* value less than or equal to 0.05 was considered statistically significant.

Results

Twenty-five subjects with LSD were evaluated [17 males, 8 females; age 34.9 ± 15 years; BMI 26.5 ± 3.4 kg/m^2 (19–31 kg/m^2)]. BMI of one patient was 31 kg/m^2. Mean disease duration was 142.3 ± 86.9 months (36–360 months). Fourteen (56%) subjects had progressive muscle weakness phenotype and 11 (44%) had LSD with previous recurrent rhabdomyolysis attacks. Of 14 subjects with progressive muscle weakness, six had lower extremity muscle myopathy, three had only upper extremity muscle myopathy, three had both upper and lower extremity muscle myopathy, and the remaining two had quadriplegia. Two of them lost their ability to walk (8%) and five (20%) of them could walk only with support. Subjects with previous recurrent rhabdomyolysis attacks were stable during the study period. Pulmonary symptoms were dyspnea at upright position (n = 2, 8%), dyspnea at supine position (n = 7, 28%), and ineffective cough (n = 6, 24%).

Pulmonary functions

Maximal inspiratory pressure was − 72.2 ± 32.7 cmH_2O (< 80cmH_2O in 13 subjects), MEP was 80.9 ± 39.1 cmH_2O (< 80cmH_2O in 9 subjects, < 40cmH_2O in 6 subjects), and PCF was 441.3 ± 190.9 L/min (< 360 L/min in 11 subjects). FVC of the subjects was 87.8% ± 25.7 and six of them had FVC < 80%. There was no subject with obstructive pattern. FEV_1 was 90.1% ± 24.9 (21–127). Seven subjects had diaphragm dysfunction (n = 7, 28%). Four subjects had ≥ 15% supine fall in FVC. Three subjects did not have supine fall in FVC but had complained of dyspnea in supine position and paradoxical abdominal respiration. Five subjects had hypoxemia (PaO_2 < 80 mmHg, range 51–76 mmHg); 8 subjects had hypercapnia ($PaCO_2$ > 45 mmHg, range 46–58 mmHg). Pulmonary functions and ABG of subjects with LSD are given in Table 1.

Polysomnographic findings

Characteristic OSA symptoms were reported in 17 (68%) subjects [snoring 48% (n = 12), witnessed apnea 28% (n = 7), daytime sleepiness 44% (n = 11), headache in the morning 8% (n = 2)]. REM sleep had decreased in all subjects (10.2% ± 6.1). OSA was found in 80% of the subjects (n = 20; 9 mild, 9 moderate, 2 severe). For subjects with OSA, apnea-hypopnea index (AHI) was 20.8 ± 15.9/h, apnea index was 8.4 ± 17.6/h, hypopnea index was14.1 ± 9/h, AHI_{REM} was 30.6 ± 19.7/h, AHI_{NREM} was 19.7 ± 16.6/h, oxygen desaturation index (ODI) was 11.9 ± 15.4/h, ODI_{REM} was 27.2 ± 26.1/h, and ODI_{NREM} was 11.4 ± 15/h. Five subjects (20%) diagnosed as REM-related sleep apnea. Nocturnal mean SpO_2 was 94.9% ± 1.7, lowest SpO_2 was 73.3% ± 13.9, and time spent with SpO_2 < 90% was 2.4% ± 7.2. Time spent with nocturnal SpO_2 < 90% was found to be ≥ 30% in only one subject. Characteristics and polysomnographic data of subjects with OSA are given in Table 2.

Polysomnographic parameters and frequency of OSA and REM-related sleep apnea were not different between subjects with progressive muscle weakness and LSD with previous recurrent rhabdomyolysis attacks. MEP was significantly lower in subjects with progressive muscle weakness (62 ± 37.8 cmH_2O vs 102.2 ± 32.5 cmH_2O, p = 0.049). Upright and supine FVC were significantly lower in subjects with progressive muscle weakness ($FVC_{upright}$ 76.6% ± 27.9 vs 100.1% ± 13.5, p = 0.019; FVC_{supine} 71.9% ± 26.8 vs 98.1 ± 11.6, p = 0.007). Arterial blood gases were not different between groups. Comparison of subjects with progressive muscle weakness and subjects with previous recurrent rhabdomyolysis attacks is given in Table 3. Six subjects (two with hypoxemic and hypercapnic respiratory failure and four with hypercapnia and diaphragm dysfunction) were advised to use nocturnal BIPAP. Subjects with OSA were advised to use nocturnal CPAP (five subjects with REM-related sleep apnea and three subjects with OSA).

Table 1 Pulmonary functions and arterial blood gases of subjects with LSD

Test	Mean	Range
FEV_1 (%)	90.1 ± 24.9	21–127
FVC (%)	87.8 ± 25.7	18–122
FEV_1/FVC	92.9 ± 11.2	79–117
MIP (cmH_2O)	− 72.2 ± 32.7	− 13–122
MEP (cmH_2O)	80.9 ± 39.1	9–170
PCF (L/min)	441.3 ± 190.9	90–850
PaO_2 (mmHg)	90.7 ± 15.6	51–108
$PaCO_2$ (mmHg)	42.4 ± 4.4	36–58
pH	7.39 ± 0.02	7.34–7.44
HCO_3	25.4 ± 1.9	22–29
Base access	1.4 ± 2.6	− 3–7
SaO_2 (%)	96.1 ± 3.2	82–99

Table 2 Clinical and polysomnographic data of OSA subjects with LSD

Subjects with OSA (n = 20)	Mean ± SD	Range
Age	37.5 ± 15.6	16–79
Gender (female/male)	15/5	
BMI (kg/m^2)	27.1 ± 3.2	21–31
Comorbidities (%)	45	
Hypercapnia (%)	40	
AHI/h	20.7 ± 15.9	7–77
REM AHI/h	30.6 ± 19.7	0–73
ODI/h	11.9 ± 15.4	0–72
REM ODI/h	27.2 ± 26.1	0–77
Mean SpO_2 (%)	94.9 ± 1.7	91–98
Lowest SpO_2 (%)	73.3 ± 13.9	49–96
Sleep time with SpO_2 < 90% (%)	2.4 ± 7.2	0–33

Table 3 Comparison of subjects with progressive muscle weakness and subjects with recurrent rhabdomyolysis attacks

	LSD with progressive muscle weakness $N = 14$	LSD with recurrent rhabdomyolysis attacks $N = 11$	p value
Age	37.9 ± 17.5	30.7 ± 9.7	NS
Gender (female/male)	4/10	3/6	NS
BMI (kg/m^2)	26.1 ± 3.6	27.7 ± 2.6	NS
$FVC_{upright}$ (%)	76.6 ± 27.9	100.1 ± 13.5	0.019
FVC_{supine} (%)	71.9 ± 26.8	98.1 ± 11.6	0.007
$FVC_{upright}$–FVC_{supine} (%)	− 5 ± 10.9	− 0.9 ± 5.2	NS
MIP (cmH_2O)	− 61.3 ± 39.5	− 87 ± 18.9	NS
MEP (cmH_2O)	62 ± 37.8	102.2 ± 32.5	0.049
PCF (L/min)	402.5 ± 194.9	500 ± 196.7	NS
PaO_2 (mmHg)	88.2 ± 18.9	90.5 ± 10.1	NS
Hypoxemia (%)	28.6	11.1	NS
$PaCO_2$ (mmHg)	44 ± 6.2	41.7 ± 3.8	NS
Hypercapnia (%)	42.9	22.2	NS
OSA symptom (%)	28.6	11.1	NS
AHI/h	15.7 ± 11.3	17.4 ± 23.7	NS
REM AHI/h	30.7 ± 18.1	17.9 ± 24.6	NS
ODI/h	8.5 ± 6.5	13.6 ± 22.7	NS
REM ODI/h	20.7 ± 20.8	21.9 ± 29.2	NS
Mean SpO_2 (%)	95.1 ± 1.8	95.4 ± 2.1	NS
Lowest SpO_2 (%)	71.9 ± 12.3	75.3 ± 16.1	NS
Sleep time with $SpO_2 < 90\%$ (%)	0.9 ± 1.4	3.8 ± 10.8	NS

Discussion

To the best of our knowledge, our study is the first which evaluated impairment in pulmonary functions and SRBD in patients with LSD. According to our findings, pulmonary functions and nocturnal parameters are adversely affected in patients with LSD. The most remarkable findings were impairment of pulmonary functions, daytime hypercapnia, hypoxemia, OSA, and REM-related OSA.

In the literature, there is only one study and four case reports in which respiratory problems or SRBD were mentioned in LSD [4–8]. However, the primary aim was not evaluating respiratory functions or SRBD in patients with LSD in these reports. Ohkuma et al. evaluated causative genes in lipid storage myopathies in 47 subjects [5]. Ten of their subjects had respiratory failure but only one of them was an adult (59 years old) and details of respiratory failure were not given in that study. Olsen et al. reported a subject with lipid storage myopathy who developed respiratory insufficiency at age 14 years and required long-term overnight ventilation [4]. Sleep study of that subject revealed nocturnal hypoventilation with some episodes of central apnea. Nocturnal saturation was very low (median < 70%) and $PaCO_2$ (80 mmHg) was very high. Spirometry showed severe restrictive patterns compatible with muscle weakness (FEV_1 37% predicted; FVC 34% predicted). Radiography did not show diaphragmatic paralysis. Electromyography revealed chronic myopathy with fiber loss, more marked in the intercostals than limb muscles [4]. DiDonato et al. reported a 12-year-old girl with LSD who had paradoxical abdominal breathing and generalized muscle weakness [7]. The oropharyngeal and upper trunk muscles were predominantly affected in their case. In the other two case reports, involvement of respiratory muscles was mentioned but no more details were given [6, 8].

In our study, the most common respiratory symptoms were dyspnea at supine position and ineffective cough. Mouth pressures (MIP, MEP) and PCF were affected in majority of the subjects. Decrease of FVC (< 80%) in spirometry (24%) and diaphragm dysfunction (28%) were also common. Nearly half of them had daytime hypercapnia and/or hypoxemia. There are similar results which reported impairment of pulmonary functions in several neuromuscular diseases such as Pompe disease, amyotrophic lateral sclerosis, myasthenia gravis, Duchenne muscular dystrophy, and myotonic dystrophy [21–23].

SRBD are common in several neuromuscular diseases [24–26]. Most common SRBD are sleep-related hypoventilation and/or hypoxemia, OSA, central sleep apnea, and Cheyne-Stokes breathing [24–26]. SRBD adversely affect the prognosis. Therefore, it is very important to diagnose and

treat SRBD in neuromuscular diseases. Upper airway muscle weakness, respiratory muscle weakness especially diaphragm weakness, orofacial abnormalities, impairment of respiratory drive, and, in some cases, weight gain from limited physical activity or corticosteroid usage are risk factors for SRBD. Some of these risk factors are more preliminary in different types of neuromuscular diseases such as upper airway muscle weakness in amyotrophic lateral sclerosis, diaphragm dysfunction in Pompe disease and amyotrophic lateral sclerosis, and impairment of respiratory drive in myotonic dystrophy and Duchenne muscular dystrophy [22, 24–26]. There is no study about SRBD in LSD. One possible mechanism for SRBD in LSD may be lipid deposition in upper airway muscles and/or diaphragm. Similar mechanisms for SRBD were reported in other metabolic storage diseases such as Fabry and Pompe diseases [27–30]. Unfortunately, we cannot comment on this issue because we could not perform magnetic resonance imaging of the upper airway and/or diaphragm. Another possible mechanism may be lipid deposition in the central nerve system which may cause impairment in respiratory drive. There is only one case with LSD who had central apnea and nocturnal hypoventilation [4]. But neither this case nor our subjects had magnetic resonance imaging of the central nerve system.

In our study, most of the subjects had characteristic OSA symptoms and OSA frequency was very high (80%). OSA severity was mostly mild and moderate. REM sleep decreased in all patients. REM AHI and REM ODI were significantly higher than non-REM sleep. Of the subjects, 20% had REM-related sleep apnea. Although we do not have a healthy control group, it is known that OSA frequency is very low in the normal population of third decade. We cannot explain this high rates with obesity because only one of our subjects was obese.

Clinical presentation of LSD is heterogeneous. Generally, there are two phenotypes [8]. One is LSD with progressive muscle weakness and the other is LSD with recurrent rhabdomyolysis. Majority of our subjects had progressive muscle weakness (56%). Polysomnographic parameters and frequency of OSA and REM-related sleep apnea were not different between the two phenotypes. However, MEP and upright and supine FVC were significantly lower in subjects with progressive muscle weakness.

There are several genetic subgroups of LSD. Clinical presentation may be different in the subgroups. For example, primary carnitine deficiency, multiple acyl-coenzyme A dehydrogenase deficiency, and neutral lipid storage disease usually have significant myopathy compared to the others [3–5]. Although all of our subjects were clinically and histopathologically diagnosed, we do not have genetic subgroup analysis. Respiratory functions and SRBD may differ according to subgroups. Unfortunately, we cannot comment about this issue. Therefore, in further studies, respiratory problems and SRBD should be investigated for different subgroups of LSD.

The present study has some limitations. First, it has a small sample size. But LSD is not a common disease. Although not having genetic analysis seems to be a limitation, it was reported that known mutations in causative genes were found in only 24% of the cases [4]. On the other hand, mutation analyses are usually helpful for making the final diagnosis especially when clinical phenotype and muscle biopsy show indistinguishable findings. The other limitations are lack of a healthy control group and not performing any imaging to show the deposition of lipid in upper airway muscles and in the diaphragm.

In conclusion, in subjects with LSD, pulmonary function impairment, daytime hypercapnia and hypoxemia, and OSA, especially REM-related OSA, are frequent. In LSD, ABG analysis, pulmonary function tests, and nocturnal evaluations should be performed periodically. Additionally, more researches are needed to clarify the prevalence of SRBD in LSD and also in subgroups.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Istanbul University Istanbul Medical Faculty Institutional Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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