Research Article

Polysomnographic Characteristics of Patients with Mucopolysaccharidosis VI Undergoing Enzyme Replacement Therapy

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Abstract

Aim: To compare the sleep architecture and polysomnographic respiratory profile of patients with mucopolysaccharidosis (MPS) VI before and after enzyme replacement therapy.

Methods: Observational, retrospective cohort study based on data collected from the clinical records of 14 patients with MPS VI cared for at a university hospital referral outpatient service.

Results: The mean ± standard deviation of the age of the patients at diagnosis was 4.5±5.1 years old; the mean ± standard deviation of the time elapsed until initiation of enzyme replacement therapy was 6.9±4.9 years. Obstructive sleep apnea was detected in 100% of the patients at baseline polysomnography and was severe in 78.6% of them. By the time of the second polysomnography, the mean ± standard deviation of the duration of enzyme replacement therapy was 1.9±0.7 years, and 77.8% of the patients met the diagnostic criteria for obstructive sleep apnea.

Conclusion: The assessed population of children with MPS VI exhibited a high prevalence of obstructive sleep apnea. Despite considerable individual variation, we did not detect a statistically significant improvement in the patients’ polysomnographic indexes after initiating enzyme replacement therapy. Possibly such findings are related to the sample size and the study design.

INTRODUCTION

Mucopolysaccharidosis (MPS) VI is an autosomal recessive lysosomal storage disease in which mutations of the gene that encodes N-acetylgalactosamine-4-sulfatase lead to reduced or absent enzyme activity [1,2]. As a result, dermatan sulfate, the substrate of that enzyme, is not completely degraded and accumulates in several tissues, giving rise to a multisystem chronic degenerative disorder [2,3].

The incidence of MPS VI in the scientific literature is quite variable, ranging from 1:248,000 to 1:1,300,000 [4]. Data on the incidence of MPS VI in Brazil have not yet been published; surveys performed by the Brazil MPS Network indicate that it...
occurs more often in Brazil than in other countries, and type VI is the most frequent type. Monte Santo, a town in the interior of Bahia, exhibits a considerable cluster of cases of MPS, with an estimated incidence of 1:5,000 live births. Such an incidence is due to a high index of endogamy in that area, which is the highest in the world [5].

In individuals with MPS, dermatan sulfate is also deposited in the upper airways (UA) and tracheobronchial tree [6], with consequent narrowing of the UA and increased airway resistance. In association with the reduction in muscle tone that occurs during sleep, this deposition phenomenon contributes to the occurrence of obstructive sleep apnea (OSA) [7]. To assess sleep-related breathing disorders and sleep architecture, a full-night polysomnograph at a sleep laboratory under normal sleep conditions and without sedation is recommended [8].

The prevalence of OSA in patients with MPS is reported to be 40%, i.e., ten times higher compared with the overall pediatric population [7,9]. In addition to impairing their physical development and inducing behavioral and learning disorders, OSA is a significant cause of morbidity and mortality in these patients because it causes chronic hypoxemia, which may lead to systemic arterial hypertension and pulmonary hypertension, eventually resulting in cor pulmonale and death [1,7].

Because MPS affects several body systems, the promotion of integral care by means of multidisciplinary teams is highly relevant. A specific therapy for this disease has recently been formulated, namely, enzyme replacement therapy (ERT) [1]. In MPS VI, ERT with galsulfase has been shown to be safe and well tolerated, to reduce urine Glycosaminoglycans (GAG) levels, to improve respiratory function and to induce positive effects on patients’ growth and quality of life [10-12].

Few publications discuss the effects of ERT on OSA indexes, and its effects on the sleep architecture and polysomnographic respiratory profile still require more thorough investigation [6]. Therefore, our aim was to compare the sleep architecture and polysomnographic respiratory profile in individuals with MPS before and after initiating ERT.

**MATERIALS AND METHODS**

The present study was an observational, descriptive, retrospective cohort study that compared polysomnography variables before and after initiating ERT. The non-probabilistic sample included 14 individuals cared for at a referral outpatient clinic at the Edgard Santos University Hospital (Hospital Universitário Professor Edgard Santos - HUPES), in Salvador, Bahia, Brazil. The sample comprised patients of both genders with a laboratory-confirmed diagnosis of MPS VI whose clinical records included the results of at least one polysomnograph before or up to six months after starting ERT. All patients had progressive, debilitating effects including skeletal dysplasia, impaired growth and facial dysmorphism.

The full-night polysomnographs were performed at a sleep laboratory without sedation and according to the latest recommendations by the American Academy of Sleep Medicine [13], as well as analysis of sleep stages, analysis of micro arousals, and scoring of respiratory events during sleep, using a computerized system (Brain Net BNT; LYNX Tecnologia Eletrônica, Rio de Janeiro, Brazil).

A single, highly experienced sleep technologist scored all polysomnograms. The proportion of time spent in each stage was expressed as a percentage of total sleep time (%TST). The following were calculated: (1) sleep efficiency (SE), defined as TST divided by total recording time and expressed as a percentage; (2) first stage sleep latency, defined as the time elapsed between turning off the lights and the onset of sleep; and (3) REM sleep latency, defined as the time elapsed between the onset of sleep and the first REM sleep period. The numbers of EEG arousals per hour (according to the arousal index) as well as the periodic limb movement in sleep (PLMS)/hour index were calculated and reported [13]. An arousal index greater than 10 was considered abnormal. Obstructive apnea was defined as the presence of abdominal and thoracic wall movement in the absence of oral-nasal airflow, with a minimum time of two respiratory cycles. Hypopnea was defined as a reduction of 50% or more in the airflow signal amplitude and was quantified if an episode lasted more than two respiratory cycles, with a decrease of 4% or more in oxyhemoglobin saturation and/or arousal. Mixed apneas were also recorded. The apnea and hypopnea index (AHI) was defined as the total number of obstructive apneas and hypopneas plus mixed apneas, divided by the TST. The obstructive apnea index (AI) was defined as the total number of obstructive apneas and mixed apneas, divided by the TST [13]. OSAS was deemed to be present when AI ≥ 1. OSAS was considered mild when AI was between one and five events/h of sleep, moderate with AI greater than five and up to 10 events/h of sleep, and severe in cases with AI > 10 events/h of sleep [14].

The baseline was defined as the period up to six months after initiating ERT. All the data analyzed in the present study were collected from the patients’ medical records.

We used the statistical software Statistical Package for the Social Sciences (SPSS, version 13 (SPSS Inc., Chicago, IL, USA) to elaborate a database and perform the analyses. Descriptive statistics were used, and the results were expressed as the mean ± standard deviation (SD) or median and inter quartile range (IQR) in addition to the absolute and relative frequencies. Being dependent samples, to compare the means of the polysomnography variables before and after initiating ERT, we used the paired t- or the Wilcoxon test according to the normality of the data distributions. We used Spearman’s correlation to investigate the relationship between two or more variables: a strong correlation was defined by coefficient values close to -1 or +1, and a weak correlation was defined as values close to zero. We used McNemar’s test to analyze the proportions between two related samples. The significance level was set as a p-value < 0.05.

This study was approved by the HUPES research ethics committee (Comité de Ética em Pesquisa - CEP/HUPES) on November 29th, 2013.
RESULTS AND DISCUSSION

The sample comprised 14 patients, nine of whom were male (64.3%); eight (57.1%) came from Monte Santo (Bahia), and the remainder came from other towns in the interior of Bahia. The mean ± SD and median (IQR) of the age at initiation of ERT were 6.9 ± 4.9 and 6.6 (3.0-10.5) years old, respectively. The mean ± SD and median (IQR) of the age at diagnosis were 4.5±5.1 and 2.5 (1.2-4.5) years old, respectively.

The mean ± SD and median (IQR) of the patients’ age at baseline polysomnography were 6.5±3.9 and 6.7 (3.3-9.7) years old, respectively. One participant was treated with continuous positive airway pressure (CPAP) of 14 cmH2O during sleep. All the participants met the diagnostic criteria for OSA. According to the apnea-hypopnea index (AHI), one participant (7.1%) was diagnosed with mild OSA, two (14.3%) with moderate OSA, and 11 (78.6%) with severe OSA (Tables 1 & 2).

The participant exhibited considerable variation in their polysomnographic respiratory variables and on polysomnography at baseline, and the prevalence of OSA was higher than the prevalence reported in the literature. In a prospective study conducted with 28 individuals with MPS VI in Brazil, John et al. found that the prevalence of OSA was lower, 85%, of which 50% were diagnosed with severe OSA [7]. Another Brazilian retrospective study that analyzed 12 individuals with MPS VI found an even lower prevalence of OSA (66.7%), of which 50% were diagnosed with severe OSA [15]. In one study conducted in Asia with 24 individuals with MPS, four of whom exhibited type VI, all the participants were diagnosed with OSA based on the polysomnography results, and 59% of the cases were severe OSA [16]. The elevated frequency of OSA in the Asian population was similar to the frequency found in the present study (100%).

The mean and nadir peripheral oxyhemoglobin saturation values were lower compared with the results reported by other studies conducted on individuals with MPS VI [7,15]. Our findings possibly reflect greater UA obstruction during sleep or involvement of the central ventilator drive. Our results show that individuals with MPS VI exhibit a strong tendency to hypoxemia, and together with the findings of other studies, they suggest that the level of hypoxemia combined with the AHI may be useful for the diagnosis of OSA and to guide subsequent therapeutic intervention [15].

One prior study subjected 60 healthy children and adolescents to polysomnography to establish normal patterns for the sleep architecture variables, and the results were as follows: total sleep time (TST) 7.8±0.8 hours; sleep efficiency 80.5±8.5%; sleep latency 45.6±29.4 min; and REM sleep latency 118.4±49.9 min [17]. In comparison with our results, the average TST and sleep latency were longer in that study. The shorter TST exhibited by the patients in our study may be explained by the first-night effect, i.e., alterations that occur on the first night a person spends at a sleep laboratory. However, the shorter sleep latency may reflect the state of sleepiness of the children due to their poor sleep quality. The mean sleep efficiency value was considered normal; however, the REM sleep latency was longer compared with the values described above due to the sleep fragmentation exhibited by children with MPS that hinders the entrance into REM sleep.

Based on the reference values for sleep architecture in healthy non-snoring children (i.e., stage N1 5±3%, N2 42±8%, N3 (slow-wave sleep) 26±8%, and REM 20±5% [18]), the percentages of stage N2 and REM time exhibited by the participants in the present study were similar to the healthy pediatric population, while the percentages in stages N1 and N2 were slightly shorter; this difference did not appear to be relevant.

Few studies have sought to characterize the sleep architecture of individuals with MPS [16]. Comparison of our results with data collected from healthy children showed that the sleep architecture of the participants in the present study was quite normal. According to some reports in the literature, the sleep architecture may be preserved in children who exhibit obstructive respiratory events during sleep [19]. The polysomnography data on sleep efficiency were similar to the results reported in a study conducted with individuals with MPS VI; however, the sleep latency was longer, and the REM sleep latency was shorter [7].

Ten of the 14 children analyzed in the present study underwent a second polysomnography after initiating ERT. The
mean ± SD and median (IQR) of the duration of ERT at the time of the second polysomnography were 1.9 ±0.7 and 2.1 (1.39-2.39) years, respectively.

The mean ± SD and median (IQR) of the age of those 10 children at the time of the second polysomnography were 7.8 ±3.8 and 8.3 (4.8-10.9) years old, respectively. One patient was using CPAP during sleep, but it was not the same patient as the one who had been using CPAP at the baseline polysomnography. Seven children (77.8%) met the diagnostic criteria for OSA; two (28.6%) were diagnosed with mild OSA (AHI 1-5 events/hour), two (28.6%) with moderate OSA (AHI 5-10 events/hour) and three (42.8%) with severe OSA (AHI above 10 events/hour). The comparison between the mean values of the sleep architecture and polysomnographic respiratory variables before and after initiating ERT is described in Table 3.

Comparison of the polysomnography tests before and after initiating ERT on an individual level revealed considerable variations. The AHI decreased on the second test in 80% of the participants, with six patients showing improvement in the degree of severity of their OSA. Three participants exhibited abnormalities on the first polysomnography, but the second test was normal. The AHI values for each participant before and after initiating ERT and their ages at both polysomnography tests are described in Table 4.

A previous prospective study assessed the long-term effect of ERT on 11 individuals with MPS VI aged 2 to 18 years old whose treatment outcomes were followed for 1.4 to 5.4 years. A second polysomnography was performed in eight of the patients after 2.1 to 4 years of treatment. Six children who did not exhibit OSA at baseline remained without abnormalities at the second assessment; one child progressed into mild OSA; and one child with moderate OSA progressed to mild OSA [20]. It is possible that the second polysomnography was performed too early in the present study, and thus, no significant improvement was detected in the respiratory parameters after initiating ERT.

In 2013, Horovitz et al. assessed 34 Brazilian children with MPS who started ERT before age 5. Twelve children had been diagnosed OSA at their first polysomnography; five children continued to exhibit normal results at the second test, one child with severe OSA remained stable, one child with mild OSA at baseline exhibited normal results at the second polysomnography, and one child each progressed into mild and severe OSA. Those authors did not infer any conclusions regarding the effect of ERT on the participants’ sleep respiratory disorders because of the limited data available [21]. Lin et al. assessed nine individuals with MPS VI and found a reduction in the prevalence of sleep apnea but only after at least 2 years of ERT [3]. These promising results notwithstanding, the possibility of drawing conclusions regarding the effect of ERT on obstructive respiratory events during sleep was hindered in the present study by the small sample size.

We found snoring in 100% of the sample at baseline and in 55.6% of the sample at the polysomnography performed after initiating ERT; this difference was not statistically significant. Nevertheless, this finding may indicate a positive impact of ERT on the patients’ respiratory pattern. Romero et al. showed that snoring is predictive of OSA with a sensitivity of 82.6%, a specificity of 43%, a positive predictive value of 84.7% and a negative predictive value of 39.6% [22].

Upon investigating the relationship between the patients’ age before ERT and the AHI on both polysomnography tests, we found moderate and non-significant correlations relative to

### Table 4: Apnea-hypopnea index before and after initiating enzyme replacement therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>AHI baseline Mean (SD)</th>
<th>AHI after ERT Mean (SD)</th>
<th>ERT duration</th>
<th>AHI after ERT Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.6</td>
<td>28.54</td>
<td>7.75</td>
<td>1.17</td>
<td>21.88</td>
</tr>
<tr>
<td>2</td>
<td>10.4</td>
<td>22.63</td>
<td>13.41</td>
<td>2.58</td>
<td>0.85 (CPAP)</td>
</tr>
<tr>
<td>3</td>
<td>4.3</td>
<td>5.0</td>
<td>6.75</td>
<td>2.62</td>
<td>4.2</td>
</tr>
<tr>
<td>4</td>
<td>9.5</td>
<td>18.06</td>
<td>11.0</td>
<td>1.98</td>
<td>5.2</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
<td>11.72</td>
<td>10.0</td>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td>6</td>
<td>9.22</td>
<td>32.82</td>
<td>10.83</td>
<td>2.16</td>
<td>39.9</td>
</tr>
<tr>
<td>7</td>
<td>6.9</td>
<td>12.25</td>
<td>8.83</td>
<td>2.33</td>
<td>7.4</td>
</tr>
<tr>
<td>8</td>
<td>0.76</td>
<td>3.29</td>
<td>1.91</td>
<td>1.46</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>3.7</td>
<td>36.48</td>
<td>5.75</td>
<td>2.32</td>
<td>62.9</td>
</tr>
<tr>
<td>10</td>
<td>1.25</td>
<td>10.15</td>
<td>3.6</td>
<td>2.3</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Abbreviations:** CPAP: Patient Using Continuous Positive Airway Pressure During the Test
the baseline test only (rs = 0.42, p = 0.13 vs. rs = -0.02, p = 0.97). No association was found between the time until initiating ERT and the sleep architecture or polysomnographic variables on the second assessment (i.e., AHI, rs = -0.10, p = 0.80; TST with SpO₂ < 91%, rs = -0.21, p = 0.61; mean SpO₂ rs = 0.02; p = 0.97; minimum SpO₂ rs = -0.20, p = 0.96) except for sleep efficiency, which exhibited a strong and significant negative correlation (rs = -0.78, p = 0.01).

We did not find a significant correlation between the participants’ age and the AHI. However, Lin et al. (2010) found that the frequency of sleep disorders was higher among pubescent and post pubescent patients compared with prepubescent patient, and there was a positive correlation between the frequency of desaturations and older age (r = 0.508, p < 0.01) [16], which may merely reflect the neurological involvement characteristic of MPS. Santamaria et al. found contrasting results in a study conducted with 11 individuals with MPS aged 2.9 to 29.6 years allocated to two groups: children (5 participants) and adults (6 participants). The participants underwent polysomnography, which revealed a higher prevalence and increased severity of OA among the children compared with the adults (p = 0.04). Those authors explained these findings by adducing that children with the most severe phenotypes exhibit greater UA abnormalities and thus usually do not reach adulthood because they die before the second decade of life [23].

The strength of our study included the evaluation of patients with a rare progressive disorder where the use of Enzyme replacement therapy (ERT) although long-term, has been modifying the natural course of this disease. However, there are limitations that need to be considered. The study was retrospective in design, which precludes causal inferences. In addition, we identified the need for a larger sample as well as a control group in order to correct all potential confounding factors; the small sample size is an important limitation of this study, although justified by the difficulty in enrolling such patients.

CONCLUSION

On the first polysomnography, the participants exhibited shorter sleep latency and longer REM sleep latency, a high number of micro-arousals, an elevated AHI in 100% of the participants, and desaturations and hypoxemia during sleep, while the remainder of the sleep architecture variables was similar to children with normal sleep. The considerable individual variations notwithstanding, we did not find a statistically significant improvement in the polysomnographic respiratory indexes after initiating ERT. This apparent lack of efficacy may be partially accounted for by the small sample size and the lack of standardization of the second polysomnography. The second test was performed after an interval of less than 1 year in one case and 1 to 2 years after the first test in the remainder of the participants. In the case of the polysomnography tests performed after the first six months of ERT, the time elapsed was potentially insufficient to detect the beneficial effects of ERT on the UA. Other studies with larger samples should be performed to achieve more precise results regarding the impact of ERT on the sleep of individuals with MPS VI.

REFERENCES


