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Obstructive sleep apnea syndrome after hematopoietic stem cell transplantation in children with mucopolysaccharidosis type I

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ABSTRACT

Background: Obstructive sleep apnea syndrome (OSAS) is very common in mucopolysaccharidosis I (MPS I). Hematopoietic stem cell transplantation (HSCT) is the preferred treatment for patients with severe MPS I diagnosed early in life. The protective effect of HSCT on the development of long term OSAS is not known.
Methods: Overnight polysomnography (PSG) and biomarker data were analyzed during the annual follow-up in consecutive MPS I patients treated with HSCT.
Results: The data of 13 patients (6 boys) were analyzed. Median age at HSCT was 17 (range 14–19) months, median age at PSG was 9.0 (4.5–14.5) years, and median time elapsed since HSCT was 7.6 (2.4–13.2) years. A significant correlation was observed between time elapsed since HSCT and the apnea–hypopnea index (AHI, $r^2 = 0.493$, $p = +0.003$) and the oxygen desaturation index ($r^2 = 0.424$, $p = +0.02$). Patients older than 10 years of age had a higher mean AHI (25.8/h vs 1.4/h, $p = 0.0008$), a lower mean pulse oximetry (94.7% vs 97.2%, $p = 0.01$) and a higher mean hypopnea index (18.8 vs 0.71/h, $p = 0.016$) as compared to those younger than 10 years of age. No correlation was observed between the AHI and the metabolic clearance, assessed by urine glycosaminoglycan (GAG) excretion and residual enzyme activity, although there was a positive trend for the urinary GAG/higher normal value for age ratio ($p = 0.09$).
Conclusion: HSCT does not offer long term protection against OSAS in MPS I with OSAS being documented in all patients after a time elapse since HSCT exceeding 10 years. The potential benefit of additional enzyme replacement therapy needs to be assessed.

1. Introduction

Mucopolysaccharidosis I (MPS I) is a chronic, progressive, debilitating and life-threatening lysosomal storage disorder with an incidence of approximately 1 in 100,000 live births. MPS I is an autosomic recessive and panethnic disease, due to the deficient activity of the enzyme a-L-iduronidase (IDUA), leading to the multi-organ accumulation of the glycosaminoglycans (GAG), dermatan sulfate and heparin sulfate, ultimately compromising all organs and tissues [14].MPS I presents across a broad phenotypic continuum from the early onset severe, multivisceral and neurocognitive phenotype also called Hurler syndrome (MPS I-H) to the later onset, essentially skeletal, multivisceral and non-neuropathic phenotype, also known as Scheie syndrome (MPS I-S).

Sleep disordered breathing (SDB), and in particular obstructive sleep apnea syndrome (OSAS), is a common feature in patients with MPS I

Abbreviations: OSAS, obstructive sleep apnea syndrome; MPS I, mucopolysaccharidosis I; HSCT, hematopoietic stem cell transplantation; PSG, polysomnography; AHI, apnea–hypopnea index; GAG, glycosaminoglycan; IDUA, a-L-iduronidase; MPS I-H, Hurler syndrome; MPS I-S, Scheie syndrome; SDB, sleep disordered breathing; ERT, enzyme replacement therapy; DQ, developmental quotient; IQ, intellectual quotient; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence; WISC III, Wechsler Intelligence Scale for Children; NEMI, New Intelligence Metrical Scale; SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide pressure; OA, obstructive apnea; CA, central apnea; CAI, central apnea index; OAHI, obstructive apnea–hypopnea index; ODI, oxygen desaturation index; REM sleep, rapid eye movement sleep.

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occurring in approximately 80% of patients [2,6–9]. OSAS is mainly explained by upper airway obstruction due to cranio-facial skeletal abnormalities such as a flattened nasal bridge, a short neck, abnormal cervical vertebrae, and the deposition of GAG in the mouth, nose, throat and tracheobronchial airway [1]. A restrictive component, causing a reduction of the ventilatory capacity, is the consequence of the organomegaly, with hepatomegaly and splenomegaly, and skeletal abnormalities with a short stature, skeletal dysplasia, kyphoscoliosis and pectus carinatum [2].

Enzyme replacement therapy (ERT) reduces GAG storage and is associated with moderate improvements in some clinical manifestations and in particular respiratory function and physical capacity [5]. Positive results have also been observed in clinical trials with laronidase with regard to sleep apnea and hypopnea [14].

Hematopoietic stem cell transplantation (HSCT) is currently recognized as a more efficient therapy with respect to the neurocognitive aspects of the disease and represents the preferred treatment for patients with severe MPS I-H when it is performed at an early age [4]. All MPS I patients, including those who have not been transplanted or whose graft has failed, may benefit from ERT. Finally, ERT should also be started at diagnosis and may be of value in patients awaiting HSCT [4].

However, studies on long term evolution after HSCT are scarce with few data being available on the long term efficacy of HSCT on OSAS [9]. The aim of the present study was to describe the polysomnographic (PSG) characteristics in a group of children treated with HSCT for MPS type I in infancy and to analyze the association between OSAS and metabolic function.

2. Material and methods

2.1. Patients

An overnight PSG is routinely performed in all patients affected with MPS as part of their annual follow-up. In this study, we present the PSG data of all consecutive children with MPS I studied between September 2013 and July 2014 and treated with HSCT in infancy. Genotype was established at diagnosis in 7 patients and p.W402X homozygous was largely preponderant. This homozygous mutation is known to be correlated with MPS I Hurler phenotype [11]. Donor chimerism was established (in %) one year after HSCT and at last follow-up.

For all patients, gender, age, anthropometric data, time elapsed since HSCT, and history of upper airway surgery (adenoidectomy, tonsillectomy and/or turbinectomy) or neurosurgery were recorded. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the Ethical Committee of Necker university hospital (CPP Ile de France II).

2.2. Metabolic parameters

Measurement of urinary GAG was performed at diagnosis and for the monitoring of disease progression, by two dimensional electrophoresis with qualitative (heparan and dermatan sulfate accumulation) and quantitative measurement (in mg/mmol of creatinine) as previously described [13].The activity of alpha IDUA was measured on leukocytes isolated from peripheral blood based on catabolism of the fluorescent substrate 4-methylumbelliferyl-alpha-L-iduronide (4 MU) as previously described [10]. Enzyme activity was expressed as micromole/g prot/h (or in % compared to normal range).

2.3. Developmental quotient

Psychomotor evaluation was performed before HSCT and regularly after HSCT with standardized psychological tests according to patient age: developmental quotient (DQ) by Brunet-Lezine test, intellectual quotient (IQ) by the WPPSI-R (Wechsler Preschool and Primary Scale of Intelligence); WISC III (Wechsler Intelligence Scale for Children). Another test was used in one case: NEMI (New Intelligence Metrical Scale). These tests were realized by a well-trained neuropsychologist with experience in testing children with MPS I.

2.4. Polysomnography

All the PSG were performed in the sleep laboratory of Necker hospital. The patients were accompanied by one parent throughout the night. No sedation or sleep deprivation was used.

The following standardized measurements were simultaneously recorded during the study: electroencephalogram (C_3A_2, C_4A_1, O_1A_2, and O_2A_1), right and left electrooculogram, submental, anterior tibialis electromyogram, electrocardiography, nasal flow through a nasal pressure transducer, pulse oximetry by a pulse oximeter (SpO_2), oximeter pulse wave form, thoracic and abdominal respiratory inductance plethysmography, digital synchronized infrared video monitoring (Cidelec, St Gemme sur Loire, France), and transcutaneous carbon dioxide pressure (PtcCO2, SenTec Digital Monitor, software version SMB SW-V06.10; MPB SW-V04.03).

Scoring of sleep stage and respiratory events were performed according to the actualized 2012 scoring rules of the American Academy of Sleep Medicine [3]. The percentage of time in each sleep stage was calculated as a percentage of the total sleep time. The following definitions for respiratory events were used for scoring purposes [3]. Obstructive apnea (OA) was defined as the absence of nasal airflow, with continued chest wall and abdominal movements for at least two breaths. Central apnea (CA) was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 s or of shorter duration and associated with an arousal and/or a 3% oxygen desaturation; central apnea occurring after gross body movements or after sighs was not considered as a pathological finding. Mixed apnea was defined as an apnea that usually begins as central and ends as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 50% with a corresponding decrease in SpO_2 of at least 3% and/or an arousal. The apnea–hypopnea index (AHI) and obstructive AHI (OAHI) were calculated as the sum of apnea and hypopnea and obstructive apnea and hypopnea events per hour of total sleep time, respectively. An OAHI < 1.5/h and CAI < 5/h were considered as normal. An OAHI > 1.5–5/h, >5–10/h, and >10/h were defined mild, moderate and severe OSAS, respectively.

Mean, minimal SpO_2 values, and the percentage of total sleep time spent with SpO_2 < 90% were calculated. The oxygen desaturation index (ODI) was defined as the number of SpO_2 drops of at least 3% per hour of total sleep time. Mean, maximal values of $PtcCO_2$ and the percentage of total sleep time spent with a $PtcCO_2$ > 50 mm Hg were calculated. All PSG were scored by a single author to minimize bias due to interobserver variability.

2.5. Statistical analysis

All the data are presented as median [25%–75% interquartiles] or mean values. Comparisons between 2 groups were performed using the Student's t-test. Correlations were performed with the Pearson test. The differences were considered to be statistically significant when P was <0.05.

3. Results

3.1. Characteristics of the patients

Thirteen patients with MPS I were evaluated (7 males and 6 females). The characteristics of the patients, including their genotype, type of HSCT and markers of metabolic clearance are resumed in Table 1. The median age of the patients was 9 years [2.5 to 17.1 years]. Median age at HSCT was 17 months [14–19 months]. Three patients