Sleep and Breathing (2019) 23:1315–1321
https://doi.org/10.1007/s11325-019-01900-9

ORIGINAL ARTICLE

Obstructive sleep apnea and craniofacial appearance in MPS type I-Hurler children after hematopoietic stem cell transplantation

Till Koehne[1] · Sarah Müller-Stöver[2] · Anja Köhn[2] · Katharina Stumpfe[2] · Susanne Lezius[3] · Carmen Schmid[1] · Zoltan Lukacs[4] · Bärbel Kahl-Nieke[1] · Nicole Muschol[2]

Received: 30 March 2019 / Revised: 5 July 2019 / Accepted: 11 July 2019 / Published online: 22 July 2019

Abstract

Objectives Mucopolysaccharidosis type I (MPS I) is an inherited lysosomal storage disorder characterized by severe multisystemic organ manifestations including obstructive sleep apnea syndrome (OSAS). Hematopoietic stem cell transplantation (HSCT) is the treatment of choice in severe MPS I (MPS IH, Hurler syndrome). However, the effect of HSCT on OSAS in MPS IH still remains unclear. The purpose of this study was to analyze respiratory patterns during sleep following HSCT in MPS IH children and to relate these findings to craniofacial abnormalities.

Methods Overnight polysomnographies of nine MPS IH children (mean age: 8.2 years) previously treated with HSCT were retrospectively analyzed. Magnetic resonance images of the head were assessed with regard to soft and hard tissue abnormalities of the upper respiratory tract.

Results The mean apnea hypopnea index (AHI) was 5.3 events/h (range, 0.3–12.2), and the majority of apnea/hypopneas were obstructive. Whereas two patients had severe OSAS (AHI > 10) and two moderate OSAS (5 > AHI < 10), five patients had no evidence of OSAS (AHI < 2.0). Donor cell chimerism was significantly lower in MPS IH patients with OSAS as compared to patients without OSAS ($p < 0.001$). The upper airway space and the maxilla were significantly smaller and the adenoids larger in MPS IH patients with OSAS as compared to those of non-OSAS patients.

Conclusion OSAS was only observed in MPS IH patients with graft failure or low donor cell chimerism. Conversely, successful HSCT seems to ameliorate adenoid hyperplasia and maxillary constriction in MPS IH patients and thereby minimizes the risk of OSAS at least at younger ages.

Keywords Mucopolysaccharidosis · Polysomnography · Craniofacial · MRI · Airway

Introduction

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive disease caused by the absence or reduced acitivity of alpha-L-iduronidase [1], a lysomal enzyme necessary for the degradation of the glycosaminoglycans (GAGs) dermatan and heparan sulfate. The lysosomal accumulation of undigested GAGs results in a progressive neurological, musculoskeletal, and cardiorespiratory disorder. Based on the wide spectrum of clinical severity and the variable time of onset, there is a severe phenotype (Hurler syndrome, MPS IH) and attenuated forms of the disease (Hurler-Scheie or Scheie syndrome, MPS IH/S, MPS IS) [2]. Hematopoietic stem cell transplantation (HSCT) has tremendously improved morbidity and mortality of patients with the severe MPS IH phenotype [3]. However, the clinical response to HSCT is variable in

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11325-019-01900-9) contains supplementary material, which is available to authorized users.

✉ Till Koehne
tkoehne@uke.de

[1] Department of Orthodontics, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

[2] Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[3] Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4] Newborn Screening and Metabolic Diagnostics Unit, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

different organs and some features—such as musculoskeletal manifestations—show little improvement [4].

Obstructive sleep apnea (OSAS) is commonly observed in MPS IH and approximately affects 75% of patients [5]. The high prevalence has been attributed to enlargement of the tongue, adenoids, and tonsils; storage depositions in the larynx and trachea; and craniofacial dysplasia [6, 7]. However, there is a significant gap in knowledge concerning the role of HSCT in modifying OSAS in MPS IH. The only study analyzing the effect of HSCT on OSAS using polysomnography did not show a positive long-term outcome [8]. In contrast, a study based on sleep oximetry revealed a sustained improvement in nocturnal hypoxia following HSCT [9]. Little is also known about craniofacial risk factors for OSAS in MPS IH patients after HSCT.

The aims of this study were firstly to analyze respiratory patterns during sleep in young MPS IH patients using polysomnography and to correlate these findings to the patients' chimerism as a measure of the long-term "success" of HSCT [10], and secondly, to identify craniofacial risk factors for OSAS among MPS IH patients treated with HSCT.

Materials and methods

Subjects

A retrospective case series review was performed in MPS patients treated at the University Medical Center Hamburg-Eppendorf between 2012 and 2015. Nine patients met the inclusion criteria: (1) confirmed diagnosis of MPS IH (Hurler type), (2) age younger than 18 years, (3) post HSCT, and (4) overnight polysomnography available. Individuals who required respiratory support or supplemental oxygen were excluded. Laboratory parameters including chimerism were included if done within 4 months of the sleep study.

Enzyme, GAG, and chimerism analyses

For testing of glycosaminglycans (GAG), the spectrophotometric assay using dimethylene blue (DMB) in the basic pH range has been employed as described previously [11]. Age-dependent reference ranges have been used. For the assessment of α-iduronidase activity, a fluorometric method using a methylumbellifyeryl-substrate was used. Leukocytes were isolated using a dextran gradient and washed with demineralized water. Prior to the assay, the leukocyte pellet was sonicated for 30 s. The reaction was stopped with a glycine/carbonate buffer, and results were calculated relative to a 4-methylumbelliferone standard curve. Donor cell engraftment was measured by chimerism analysis using variable number tandem repeat techniques as described previously [12].

Polysomnography

All patients underwent overnight polysomnography (Alice 5, Heinen+Löwenstein, Germany). Physiological signals recorded included electrocardiogram, electrooculogram, electroencephalogram, and tibial and submental electromyogram. Respiratory efforts were monitored using abdominal and thoracic piezoelectric effort belts (Pro-Tech, WA, USA). Oronasal airflow was measured by nasal pressure measurements. Oxyhemoglobin saturation was measured by pulse oximetry and transcutaneous CO2 monitoring. The patients were recorded with an infrared camera (Axis communication, Sweden) and an ambient microphone (Pro-Tech, WA, USA). Two patients were monitored for respiratory efforts, oronasal airflow, and oxyhemoglobin saturation only. Sleep architecture was staged according to the standard criteria of Rechtschaffen and Kales [13]. Arousals and respiratory events were defined as recommended by previous reports in children [14] and current guidelines [15].

Magnetic resonance imaging

Magnetic resonance images (MRI) of the full head were available from all subjects of the study cohort except one individual. MRI was performed as a standard of care and used as far as it was done within 2 years of the sleep study (median time interval: 9 months). The thickening of the upper airways and of the adenoids (AD) was assessed on axial cross-sections through the posterior nasal spine (PNS) and the clivus (CL) at the spheno-occipital synchondrosis. Maxillary and mandibular morphology was determined by measurements of six bony landmarks [16, 17] (Fig. 1): anterior nasal spine (ANS), nasomaxillary suture (NMS), pterygomaxillary fissure (PTM), condylion (COND), gonion (GO), and pogonion (POG). Craniofacial distances were calculated using EXCEL (Microsoft Corporation, Redmond, WA, USA) and ImageJ (National Institute of Health, Bethesda, MD, USA).

Statistical analysis

Comparisons between children with or without OSAS were performed using Student's *t* test for continuous measures (anthropometric, serum measurement, and MRI data) or Fisher's exact test for chimerism levels, which were dichotomized into full chimerism (≥ 99%) and mixed/low chimerism (< 99%). Gender differences were tested using Fisher's exact test. *P* values less than 0.05 were regarded as significant. All statistical analyses were made with EXCEL (Microsoft Corporation, Redmond, WA, USA) and/or Prism 6 (GraphPad Software Inc., San Diego, CA, USA).

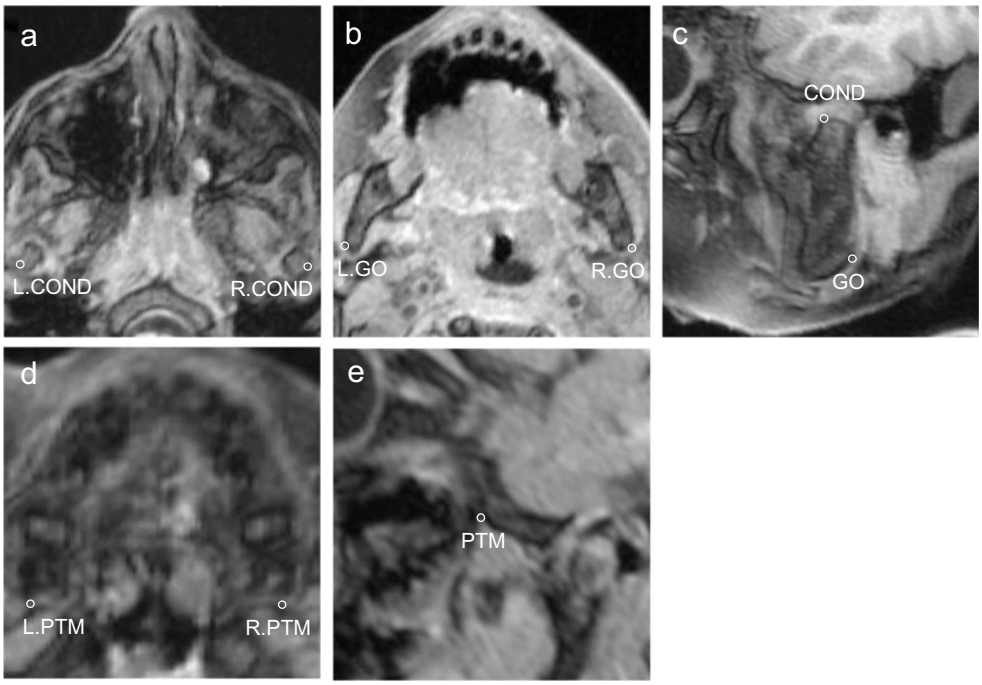

Fig. 1 Location of bony landmarks on MRI scans. **a**–**e** Identification of the condylon (COND), gonion (GO), and pterygomaxillary fissure (PTM) on axial (**a**, **b** and **d**) and sagittal (**c** and **e**) MRI scans

Results

Patients characteristics

Patient age ranged from 4 to 12 years of age (Table 1). Three subjects were males and six females. All patients were treated with HSCT within the first 26 months of life except one patient (6 years and 2 months). The time between HSCT and polysomnography ranged from 3 to 10 years (median, 5 years). Six patients had a history of ENT surgeries including adenoidectomy and tonsillectomy (Table S1).

Polysomnographic characteristics

The mean sleep time was 510.9 ± 100.1 min (Table 2). The sleep architecture was normal. The mean arousal index was 18.1 ± 3.3 arousals/h of total sleep time (TST), which was above the reference range for children [18]. The mean AHI was 5.3 ± 5.2 events/h (range, 0–12.2). The majority of apnea events were obstructive, and the obstructive apnea index was 3.7 ± 4.4 (0–10.2). The mean central apnea index was 0.8 ± 0.4 (range, 0.3–1.5), which was slightly above the reference range. The mean oxygen saturation nadir was 85.8 ± 10.4 (range, 68–96). There were two outliers who had an oxygen

Table 1 Clinical characteristics

No.	Sex	Age at PSG (year)	Age at HCST (year)	Time between HSCT and PSG (year)	Genotype 1. Allele (cDNA)	1. Allele (protein)	1. Allele (cDNA)	1. Allele (protein)
1	M	9	1.4	8.1	c.208C>T	p.Q70X	c.1205G>A	p.W402X
2	F	12	1.8	10.3	c.979G>C	p.A327P	n.i.	n.i.
3	F	5	1.5	4.7	c.606c>A	p.Y202X	c.979G>C	p.A327P
4	F	4	1.2	3.3	c.208C>T	p.Q70X	c.1413C>G	p.Y471X
5	F	8	1.5	3.5	c.1205G>A	p.W402X	c.1205G>A	p.W402X
6	M	10	1.0	9.4	c.1205G>A	p.W402X	c.1205G>A	p.W402X
7	F	9	6.2	2.8				
8	F	5	2.2	3.3	c.208C>T	p.Q70X	c.1205G>A	p.W402X
9	M	6	1.4	4.6	c.208C>T	p.Q70X	c.208C>T	p.Q70X

saturation nadir of only 69 and 68 (Table S2). The mean desaturation index was 8.2 ± 7.6 event/h (range, 0.3–20.5), which was higher than normal [19]. Five patients were diagnosed as having no OSAS (AHI < 2.0), whereas two patients had moderate (AHI = 5–10) and two patient had severe OSAS (AHI > 10) [19].

Relations of OSAS to HSCT characteristics

Demographic and HSCT characteristics were compared between patients with OSAS and without OSAS (Table 3). Age and BMI were not statistically different between the two groups and also not of relevant difference. The proportion of females was higher in the group without OSAS as compared to patients with OSAS. The age at HSCT and the time since HSCT were not statistically different between the two groups. Importantly, donor chimerism (as a measure of successful HSCT) was significantly lower in patients with OSAS as compared to those of patients without OSAS. In fact, four out of five patients without OSAS had full donor chimerism (≥ 99.9%) and one had high mixed chimerism (79%). In contrast, donor chimerism ranged from 0% (i.e., graft failure) to 59% in the MPS IH patients with OSAS. Whereas mean levels of alpha-L-iduronidase in leukocytes were not significantly different between the two groups, excretion of glycosaminoglycans in urine was significantly higher in the subjects with OSAS as compared to those without.

Relation of OSAS to facial characteristics

Craniofacial anomalies are considered to be a risk factor for OSAS in MPS IH. Facial features were less coarse in MPS IH subjects without OSAS, and especially, the midfacial hypoplasia was less striking. In contrast, our patient with OSAS showed all typical facial stigmata of MPS IH including a small upturned nose and sagging cheeks (data not shown). To further analyze the craniofacial phenotype, MRI images of the head were analyzed with regard to the upper respiratory tract and the jaw bones (Fig. 2 and Table 4). The upper airway, as indicated by the distance between the posterior nasal spine (PNS) and the adenoid tissue, was significantly smaller in MPS IH patients with OSAS as compared to those without OSAS. The adenoid tissue was 33% thicker in patients with OSAS. The sagittal position of the maxilla, as indicated by the distance between the PNS and the clivus, as well as the total length of the maxilla, was not different between the two groups. Importantly, the height and width of the maxilla were significantly smaller in patients with OSAS as compared to those of patients without OSAS. The morphology of the mandible was not different between the two groups.

Table 2 Mean polysomnographic parameters

Variables	Mean ± SD
Sleep architecture	
TST [min]	510.9 ± 100.1
REM [% of TST]	14.4 ± 6.9
Stage I [% of TST]	3.0 ± 2.5
Stage II [% of TST]	61.9 ± 7.3
Stage III and IV [% of TST]	19.1 ± 8.8
Arousal index [*n*/h]	18.1 ± 3.3
Respiratory events and PLMS	
Apnoe-Hypnoe index [*n*/h TST]	5.3 ± 5.2
Central apnea index [*n*/h TST]	0.8 ± 0.4
Obstructive apnea index [*n*/h TST]	3.7 ± 4.4
Mixed apnea index [*n*/h TST]	0.2 ± 0.3
Obstructive hypnea index [*n*/h TST]	0.6 ± 0.8
SpO2 Nadir [%]	85.8 ± 10.4
Desaturation index [events/h]	8.2 ± 7.6

Discussion

The results of this study indicate that successful HSCT may minimizes the risk of OSAS in MPS IH children. Conversely, MPS IH children with transplant failure or low mixed donor chimerism develop OSAS at an early age due to adenoid hypertrophy and maxillary hypoplasia resulting in narrowing of the upper airway.

One important finding of our study is the clear difference between the chimerism levels of MPS IH patients with OSAS and those without OSAS. In fact, OSAS was not observed in subjects with full or high mixed donor chimerism, whereas OSAS was evident in all subjects with transplant failure or low mixed donor chimerism. Our results therefore suggest that low donor chimerism is a strong predictor for OSAS development at least in young MPS IH patients. To our knowledge, there is only one other study, which analyzed polysomnographic characteristics in MPS IH patients following HSCT [8]. However, these authors did not report an association between AHI and donor cell chimerism. In contrast, they found a positive correlation between AHI and elapsed time since HSCT. In this study OSAS was evident in patients exceeding more than 10 years from HSCT. We had only one patient in our study, who was followed up more than 10 years post HSCT, and this patient had a low AHI (0.3) and full chimerism (≥ 99.9%). It is clear that no conclusion can be drawn from this single case, and we agree with the authors that patients with long-term follow up since HSCT should be closely monitored for OSAS. Nevertheless, our results indicate that successful HSCT can at least postpone the onset of OSAS in MPS IH children. This is in line with a sleep oximetry study of 61 MPS IH patients after HSCT [9]. The authors reported a lower rate of sleep disordered breathing in MPS IH patients treated

Table 3 Comparison of MPS IH patients with and without OSAS

Variables	No OSAS ($n = 5$)	OSAS ($n = 4$)	p value
Patient characteristics	Mean ± SD	Mean ± SD	
Age [year]	7.8 ± 3.2	7.7 ± 2.4	n.s.[a]
Sex [no. of male/no. of female]	1/4	2/2	n.s.[b]
BMI [kg/m^2]	18.0 ± 2.2	17.1 ± 1.0	n.s. [a]
HSCT			
Age at HSCT [year]	1.2 ± 0.6	2.7 ± 2.4	n.s.[a]
Time since HSCT [year]	6.0 ± 3.1	5.0 ± 3.0	n.s.[a]
Chimerism [%]	99.9 (79.2–99.9)*	35.75 (0–59.3)*	
Full donor chimerism	4	0	0.048[b]
Mixed/no donor chimerism	1	4	
Alpha-L-iduronidase in leucocytes [nMol/h × mg]	3.2 ± 2.6	1.8 ± 2.2	n.s.[a]
Glycosaminoglycan in urine [mg/mmol Krea]	20.6 ± 6.4	49.0 ± 18.2	0.016[a]

n.s. not significant

*Shown as median (range)

[a] Student's *t* tests

[b] Fisher's exact test

with HSCT as compared to those treated with enzyme replacement therapy. Interestingly, they also reported an association between sleep disordered breathing, high urinary excretion of glycosaminoglycanes (GAG), and low iduronidase enzyme activity. This association was less clear in our study. Although mean GAG excretion levels were higher in our patients with OSAS as compared to those without OSAS, we did not observe a lower leucocyte alpha-L-iduronidase activity in MPS IH patients with OSAS as reported previously [9]. In this regard, it is important that polysomnography is still the gold standard in diagnosing OSAS and that the only other study using polysomnography did also not observe a clear correlation between metabolic parameters and OSAS development [8]. Taken together, our results suggest that donor chimerism levels have the highest predictive value for OSAS among the laboratory markers used to follow up HSCT in MPS IH patients.

Another important aspect of this study was the craniofacial phenotype of the patients. In fact, there was a striking difference in facial appearance of patients with and without OSAS. The facies of MPS IH patients without OSAS was clearly less coarse and facial stigmata such as the small upturned nose and full cheeks were less pronounced. It is well known that HSCT improves the coarse facies of patients with MPS IH [20–22], but these findings have not been related to OSAS so far. In this regard, our analyses of head MRIs revealed several interesting findings. Firstly, the adenoid tissues were thicker and the upper airway was smaller in MPS IH subjects with OSAS as compared to those of patients without OSAS. Adenoid hypertrophy has been reported in several studies [6, 7, 23]. Accordingly, adenoidectomy/adenotomy is common in MPS IH individuals and has also been performed in 66% of our patients. In fact, we had only one individual without a previous adenoidectomy in our non-OSAS group and this patient

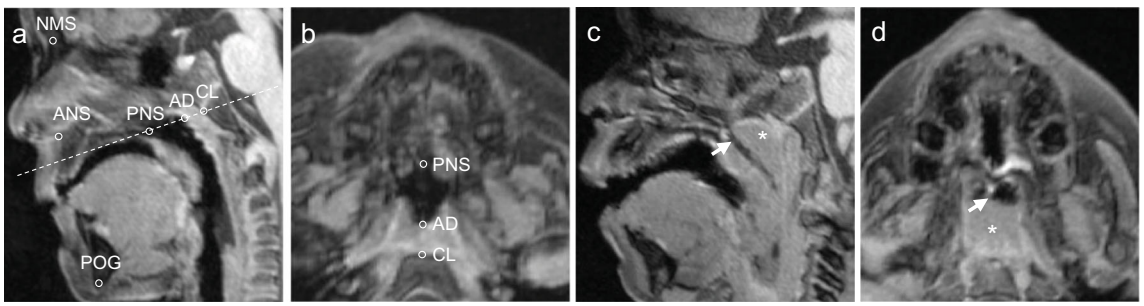

Fig. 2 MRI imaging of MPS IH patients with and without OSAS. (**a**, **b**) Sagittal (**a**) and axial (**b**) MRI images of a 5-year-old MPS IH patient with low AHI (0.3). The white dashed line in **a** indicates the orientation of the axial cross-section (**b**) through the posterior nasal spine (PNS) and the anterior surface of the clivus (CL) at the spheno-occipital synchondrosis. (NMS = nasomaxillary suture, ANS = anterior nasal spine, AD = anterior surface of the adenoid) (**c**, **d**) MRI images of a 5-year-old MPS IH patient with high AHI (12.2). Note the narrow upper airway (white arrows) and the enlarged adenoids (white asterisks)

Table 4 Comparison of young MPS IH patients with and without OSAS

Variables	No OSAS ($n = 4$) Mean ± SD	OSAS ($n = 4$) Mean ± SD	p value (t test)
Upper airway			
Airway space (PNS-AD) [cm]	1.6 ± 0.2	1.0 ± 0.4	0.040
Adenoid thickness (AD-CL) [cm]	1.2 ± 0.2	1.8 ± 0.2	0.008
Maxilla-Clivus (PNS-CL) [cm]	2.8 ± 0.3	2.9 ± 0.2	n.s.
Maxillary dimensions			
Maxilla height (PTM-ANS) [cm]	4.0 ± 0.3	3.4 ± 0.1	0.017
Maxilla length (ANS-PNS) [cm]	4.4 ± 0.6	4.2 ± 0.4	n.s.
Maxilla width (L.PTM-R.PTM) [cm]	4.6 ± 0.2	4.2 ± 0.1	0.014
Mandibular dimensions			
Mandibular length (POG-COND) [cm]	9.6 ± 0.9	9.4 ± 0.6	n.s.
Mandibular height (GO-COND) [cm]	3.5 ± 0.4	3.6 ± 0.5	n.s.
Mandibular width (L.GO-R.GO) [cm]	8.5 ± 1.2	8.5 ± 0.2	n.s.

n.s. not significant

had the most thickened adenoid tissues in this group. In contrast, adenoid hypertrophy was observed in our patients with OSAS irrespective whether these previously had an adenoidectomy. This indicates that adenoidectomy protects from OSAS only in those patients with successful HSCT. A second craniofacial finding in our MPS IH patients with OSAS was the hypoplasia of the maxillary skeleton. The maxilla was smaller in width and height in patients with OSAS as compared to those without. However, it remains unclear, whether this is rather the cause or the effect of OSAS in MPS IH. In fact, it is known that HSCT has only a mild musculoskeletal effect in MPS IH patients [4, 24]. Moreover, mouth breathing and inferior tongue position in patients with adenoid hypertrophy can clearly affect the growth of the maxilla [25]. Maxillary hypoplasia in MPS IH patients is most likely rather the effect than the cause of OSAS. Nevertheless, maxillary expansion with orthodontic appliances is an effective treatment in children with OSAS [26, 27] and could also be considered in MPS IH patients.

Our study has several limitations. Due to the retrospective design, we cannot exclude a selection bias. Although overnight polysomnography was recommended in all patients during our annual follow-up, we had several patients that declined to participate. However, the prevalence of OSAS was rather low in our patient cohort as compared to those of other studies [8, 28], which suggest that this selection bias did not favor more severe OSAS cases. Another limitation of our craniofacial assessment was the intubation of the patients during MRI scanning. This limited our craniofacial measurements to the upper respiratory tract, although laryngeal and tracheal anomalies can also contribute to OSAS in MPS IH patients. Finally, another limitation of this study is clearly the small cohort size especially for older ages. It would was also be valuable to have more MPS IH individuals with several PSGs after HSCT to show a change or trend in OSAS severity. In fact, we had only two individuals with multiple PSGs. Although also these two cases suggest that HSCT decreases the risk of OSAS only in those MPS patients with high chimerism levels, it is clear that there is a need for larger studies.

Nevertheless, this is only the second study reporting polysomnographic characteristics in MPS IH patients following HSCT and the first study, which relates these findings to the craniofacial appearance. With regard to the diagnosis of OSAS our results indicate that OSAS is more likely to occur in MPS IH patients with transplant failure and low mixed donor chimerism. With regard to treatment, our results highlight the value of adenoidectomy in MPS IH patients and suggest that maxillary expansion could be a valuable approach in MPS IH patients with OSAS and maxillary constriction. Most importantly, we believe that polysomnography should be included in the annual follow-up of every MPS IH patient, since undiagnosed OSAS can severely affect overall development of MPS IH patients.

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 and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. McKusick VA, Howell RR, Hussels IE, Neufeld EF, Stevenson RE (1972) Allelism, non-allelism, and genetic compounds among the mucopolysaccharidoses. Lancet 1(7758):993–996

2. Muenzer J, Fisher A (2004) Advances in the treatment of mucopolysaccharidosis type I. N Engl J Med 350(19):1932–1934. https://doi.org/10.1056/NEJMp048084
3. Moore D, Connock MJ, Wraith E, Lavery C (2008) The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. Orphanet J Rare Dis 3:24. https://doi.org/10.1186/1750-1172-3-24
4. Schmidt M, Breyer S, Lobel U, Yarar S, Stucker R, Ullrich K, Muller I, Muschol N (2016) Musculoskeletal manifestations in mucopolysaccharidosis type I (Hurler syndrome) following hematopoietic stem cell transplantation. Orphanet J Rare Dis 11(1):93. https://doi.org/10.1186/s13023-016-0470-7
5. Pal AR, Brown N, Jones SA, Bigger BW, Bruce IA (2015) Obstructive sleep apnea in MPS: a systematic review of pretreatment and posttreatment prevalence and severity. JIEMS:1–10. https://doi.org/10.1177/2326409815616392
6. Simmons MA, Bruce IA, Penney S, Wraith E, Rothera MP (2005) Otorhinolaryngological manifestations of the mucopolysaccharidoses. Int J Pediatr Otorhinolaryngol 69(5):589–595. https://doi.org/10.1016/j.ijporl.2005.01.017
7. Muhlebach MS, Shaffer CB, Georges L, Abode K, Muenzer J (2013) Bronchoscopy and airway management in patients with mucopolysaccharidoses (MPS). Pediatr Pulmonol 48(6):601–607. https://doi.org/10.1002/ppul.22629
8. Moreau J, Brassier A, Amaddeo A, Neven B, Caillaud C, Chabli A, Fernandez-Bolanos M, Olmo J, Valayannopoulos V, Fauroux B (2015) Obstructive sleep apnea syndrome after hematopoietic stem cell transplantation in children with mucopolysaccharidosis type I. Mol Genet Metab 116(4):275–280. https://doi.org/10.1016/j.ymgme.2015.10.004
9. Pal AR, Langereis EJ, Saif MA, Mercer J, Church HJ, Tylee KL, Wynn RF, Wijburg FA, Jones SA, Bruce IA, Bigger BW (2015) Sleep disordered breathing in mucopolysaccharidosis I: a multivariate analysis of patient, therapeutic and metabolic correlators modifying long term clinical outcome. Orphanet J Rare Dis 10:42. https://doi.org/10.1186/s13023-015-0255-4
10. Khan F, Agarwal A, Agrawal S (2004) Significance of chimerism in hematopoietic stem cell transplantation: new variations on an old theme. Bone Marrow Transplant 34(1):1–12. https://doi.org/10.1038/sj.bmt.1704525
11. Lukacs Z (2008) Mucopolysaccharides. In: Blau N, Duran M, Gibson KM (eds) Laboratory guide to the methods in biochemical genetics. Springer, Berlin, pp 287–324
12. Clark JR, Scott SD, Jack AL, Lee H, Mason J, Carter GI, Pearce L, Jackson T, Clouston H, Sproul A, Keen L, Molloy K, Folarin N, Whitby L, Snowden JA, Reilly JT, Barnett D, United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working G (2015) Monitoring of chimerism following allogeneic haematopoietic stem cell transplantation (HSCT): technical recommendations for the use of short tandem repeat (STR) based techniques, on behalf of the United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working Group. Br J Haematol 168(1):26–37. https://doi.org/10.1111/bjh.13073
13. Rechtschaffen A, Kales A (1968) A manual of standardized terminology: techniques and scoring systems for sleep stages of human subjects. UCLA Brain Information Services/Brain Research Institute, Los Angeles
14. Mograss MA, Ducharme FM, Brouillette RT (1994) Movement/arousals. Description, classification, and relationship to sleep apnea in children. Am J Respir Crit Care Med 150(6 Pt 1):1690–1696. https://doi.org/10.1164/ajrccm.150.6.7952634
15. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM, American Academy of Sleep M (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 8(5):597–619. https://doi.org/10.5664/jcsm.2172
16. Savara BS, Tracy WE (1967) Norms of size and annual increments for five anatomical measures of the mandible in boys from three to sixteen years of age. Arch Oral Biol 12(4):469–486
17. Savara BS, Singh IJ (1968) Norms of size and annual increments of seven anatomical measures of maxillae in boys from three to sixteen years of age. Angle Orthod 38(2):104–120. https://doi.org/10.1043/0003-3219(1968)038<0104:NOSAAI>2.0.CO;2
18. Beck SE, Marcus CL (2009) Pediatric polysomnography. Sleep Med Clin 4(3):393–406. https://doi.org/10.1016/j.jsmc.2009.04.007
19. Verhulst SL, Schrauwen N, Haentjens D, Van Gaal L, De Backer WA, Desager KN (2007) Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. Pediatr Pulmonol 42(2):159–167. https://doi.org/10.1002/ppul.20551
20. Fonseca FR, de Santana Sarmento DJ, Vasconcelos Medeiros PF, Diniz DN, dos Santos MT (2014) Patients with mucopolysaccharidosis have tendencies towards vertical facial growth. J Oral Maxillofac Surg 72(12):2539–2546. https://doi.org/10.1016/j.joms.2014.07.006
21. Kantaputra PN, Kayserili H, Guven Y, Kantaputra W, Balci MC, Tanpaiboon P, Tananuvat N, Uttarilli A, Dalal A (2014) Clinical manifestations of 17 patients affected with mucopolysaccharidosis type VI and eight novel ARSB mutations. Am J Med Genet A 164A(6):1443–1453. https://doi.org/10.1002/ajmg.a.36489
22. Keith O, Scully C, Weidmann GM (1990) Orofacial features of Scheie (Hurler-Scheie) syndrome (alpha-L-iduronidase deficiency). Oral Surg Oral Med Oral Pathol 70(1):70–74
23. Santamaria F, Andreucci MV, Parenti G, Polverino M, Viggiano D, Montella S, Cesaro A, Ciccarelli R, Capaldo B, Andria G (2007) Upper airway obstructive disease in mucopolysaccharidoses: polysomnography, computed tomography and nasal endoscopy findings. J Inherit Metab Dis 30(5):743–749. https://doi.org/10.1007/s10545-007-0555-5
24. Aldenhoven M, Wynn RF, Orchard PJ, O'Meara A, Veys P, Fischer A, Valayannopoulos V, Neven B, Rovelli A, Prasad VK, Tolar J, Allewelt H, Jones SA, Parini R, Renard M, Bordon V, Wulffraat NM, de Koning TJ, Shapiro EG, Kurtzberg J, Boelens JJ (2015) Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood 125(13):2164–2172. https://doi.org/10.1182/blood-2014-11-608075
25. Woodside DG, Linder-Aronson S, Lundstrom A, McWilliam J (1991) Mandibular and maxillary growth after changed mode of breathing. Am J Orthod Dentofac Orthop 100(1):1–18. https://doi.org/10.1016/0889-5406(91)70044-W
26. Villa MP, Malagola C, Pagani J, Montesano M, Rizzoli A, Guilleminault C, Ronchetti R (2007) Rapid maxillary expansion in children with obstructive sleep apnea syndrome: 12-month follow-up. Sleep Med 8(2):128–134. https://doi.org/10.1016/j.sleep.2006.06.009
27. Cistulli PA, Palmisano RG, Poole MD (1998) Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. Sleep 21(8):831–835
28. Lin HY, Chen MR, Lin CC, Chen CP, Lin DS, Chuang CK, Niu DM, Chang JH, Lee HC, Lin SP (2010) Polysomnographic characteristics in patients with mucopolysaccharidoses. Pediatr Pulmonol 45(12):1205–1212. https://doi.org/10.1002/ppul.21309