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Obstructive Sleep Apnea in MPS: A Systematic Review of Pretreatment and Posttreatment Prevalence and Severity

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Abstract

The mucopolysaccharidoses (MPSs) are a group of inherited, metabolic disorders characterized by progressive multisystem accumulation of partially degraded glycosaminoglycans. This manifests with multilevel airway obstruction, presenting with obstructive sleep apnea (OSA). We systematically reviewed the literature to determine the severity and prevalence of OSA in MPS based on polysomnography analysis. Fifteen studies with 294 participants met the inclusion criteria for review. The pretreatment prevalence of OSA in MPS was 81% with a mean apnea–hypopnea index (AHI) of 10.4. Patients with MPS I are most significantly affected, with 75% suffering with moderate to severe OSA (mean AHI, 16.6). Enzyme replacement therapy (ERT) results in an almost significant reduction in OSA in MPS I ($P = .06$), while adenotonsillar surgery significantly improves AHI ($P = .002$). Obstructive sleep apnea least affects MPS III. There is a lack of long-term post-ERT and hematopoietic stem cell transplant data relating to OSA outcomes in this population, with further prospective studies required to determine the ongoing response to treatment.

Keywords

adenotonsillectomy, airway obstruction, continuous positive airways pressure, lysosomal storage diseases, mucopolysaccharidosis, obstructive sleep apnea, polysomnography, sleep disordered breathing

Background

Mucopolysaccharide diseases are a heterogeneous group of rare, inherited lysosomal storage disorders with a combined incidence of 1 in 22 000,[1] characterized by 11 distinct deficiencies of lysosomal hydrolase enzymes in 7 forms of mucopolysaccharidosis (MPS; I to VII, Table 1). Failure of enzymatic pathways to proceed normally causes lysosomal dysfunction with failure of catabolism and accumulation of partially degraded glycosaminoglycan (GAG) resulting in altered cellular function. GAGs are a diverse group of polysaccharides composed of highly sulfated alternating uronic acid and animo sugar residues with critical cell surface and connective tissue roles. Pathogenic storage of GAGs in MPS manifests with multisystem disease, commonly presenting with cardiorespiratory, musculoskeletal, visceral, and neurocognitive disease, with preferential organ involvement seen in specific types. Current therapeutic strategies include hematopoietic stem cell transplant (HSCT) for the severe Hurler phenotype of MPS I, and enzyme replacement therapy (ERT) in attenuated cases of MPS I and MPS II, IVA, and VI.[2-4]

Involvement of the respiratory system from an early age is a well-recognized feature of MPS I, II, IV, and VI, while

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Table 1. MPS Types and Clinical and Airway Manifestations.

Type	Name	Deficient Enzyme	Gene	Stored GAG	Primary Clinical Features	Airway Manifestations
MPS I	Hurler	α-L-iduronidase	*IDUA*	HS, DS	Progressive neurocognitive degeneration; cardiorespiratory involvement; musculoskeletal: dysostosis multiplex; hepatosplenomegaly and umbilical hernia; corneal clouding	Coarse facial features with limited mouth opening; macroglossia; adenotonsillar hypertrophy; laryngeal mucosal deposits; tracheal GAG deposits
	Hurler-Scheie			HS, DS	Moderate phenotype	
	Scheie			HS, DS	Mild phenotype without CNS involvement	
MPS II	Hunter	Iduronate-2-sulfatase	*IDS*	HS, DS	X-linked; attenuated to severe phenotypes; manifestations as in MPS I	As MPS I
MPS IIIA	Sanfilippo	N-sulfoglucosamine sulfohydrolase	*SGSH*	HS	Progressive neurocognitive degeneration	Minimal involvement
MPS IIIB	Sanfilippo	N-alpha-acetylglucosaminidase	*NAGLU*	HS	As IIIA	As IIIA
MPS IIIC	Sanfilippo	Heparan acetyl-CoA: alpha-glucosaminide N-acetyltransferase	*HGSNAT*	HS	As IIIA	As IIIA
MPS IIID	Sanfilippo	N-acetylglucosamine-6-sulfatase	*GNS*	HS	As IIIA	As IIIA
MPS IVA	Morquio syndrome A	Galactosamine-6-sulfatase	*GALNS*	KS, CS	Normal intelligence; skeletal dysplasia and joint instability, cervical myelopathy	Tortuous trachea due to mismatch between tracheal growth and cervicothoracic vertebral growth; adenotonsillar hypertrophy
MPS IVB	Morquio syndrome B	β-D-galactosidase	*GLB1*	KS	As IVA	As IVA
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase	*ARSB*	DS	Normal intelligence; cardiorespiratory involvement Musculoskeletal: dysostosis multiplex; hepatosplenomegaly; corneal clouding	Diffuse airway narrowing orofacial skeletal involvement; macroglossia; adenotonsillar hypertrophy.
MPS VII	Sly	β-glucuronidase	*GUSB*	DS, HS	Rare; variable phenotype; hydrops fetalis; similar to MPS I	As MPS I
MPS IX	Natowicz	Hyaluronidase	*HYAL1*	Hyaluronan	Rare; musculoskeletal with periarticular masses	Coarse facial features

Abbreviations: CS, chondroitin sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; MPS, mucopolysaccharidosis; GAG, glycosaminoglycan.

Table 2. Search Terms for Systematic Review (MeSH Headings).

Topic	Search terms
Population	"mucopolysaccharidosis" OR "mucopolysaccharidos*" OR "MPS" including types I-VII and syndrome names ("Hurler", "Hurler-Scheie", "Scheie", "Hunter", "San Fillipo", "Morquio", "Morateaux-Lamy", "Sly")
Outcome	"obstructive sleep apnoea", "obstruction, "sleep apnoea", "sleep", "apnoea", "apnea", "airway", "airway obstruction", "snoring", "sleep disordered breathing", "polysomnogram", "polysomnography", "sleep study"
Intervention	"enzyme replacement therapy", "ERT", "laronidase", "idursulfase", "N-acetylgalactosamine-4-sulfatase", "elosufase alfa" "Hematopoietic stem cell therapy" OR "Haematopoietic stem cell transplantation" OR "Haemopoietic stem cell transplantation" OR "Hematopoietic stem cell transplantation" OR "Hematopoietic cell transplantation" OR "Hematopoietic stem cell therapy" OR HSCT, "bone marrow transplant", "cord blood stem cell transplantation" "positive pressure respiration", "continuous positive airway pressure", "CPAP" "adenotonsillectomy", "adenoidectomy", "tonsillectomy"

individuals with MPS III are rarely affected. Airway obstruction in MPS is often progressive and may involve multiple levels within the airway. A common manifestation of upper airway disease in MPS is with sleep disordered breathing (SDB), describing a spectrum of conditions ranging from primary snoring, through upper airways resistance syndrome to obstructive sleep apnea (OSA[5,6]). This is a consequence of increased upper airway resistance due to the multilevel craniofacial, oropharyngeal, and laryngotracheal involvement seen in MPS.[7-9] At the most severe end of this spectrum, OSA is defined by the American Thoracic Society as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns." This manifests as arousals, sleep fragmentation, and transient nocturnal hypoxaemia.[10]

Intervention for OSA in MPS is complicated by the multilevel nature of obstruction and associated musculoskeletal and cardiorespiratory comorbid disease contributing to increased anesthetic risk and significant morbidity and mortality. Failure to recognize and treat OSA has neurobehavioral and physiological consequences, including failure to thrive, cognitive and developmental delay and, in severe cases, cardiorespiratory sequelae.[11,12] Therapy for OSA in MPS is aimed at either disease modification, with ERT or HSCT, or local airway intervention. Surgical intervention most commonly takes the form of adenotonsillectomy but may include microlaryngeal surgery, tracheostomy, or Montgomery t-tube insertion in severe cases. Nocturnal intervention involves support with continuous positive airways pressure (CPAP[13,14]).

The existing literature describing the incidence of OSA in MPS is based on cross-sectional analysis of small cohorts, using variable outcomes, primarily performed prior to initiation of treatment.[5,6,15] As a result, no definitive conclusions may be drawn regarding the impact of disease in each MPS type.[16] Accurate identification of the prevalence and severity of OSA in MPS would allow recognition of at risk groups and improved management of these complex patients with targeted screening and informed clinical decision making. We aim to provide a systematic review and meta-analysis of the current literature quantifying OSA in this population, combining the outcomes of all studies investigating this topic and assessing the role of therapeutic intervention on outcomes in MPS.

Objectives

The objective of this study was to determine the prevalence and severity of OSA among the types of MPS prior to treatment and to assess the efficacy of treatment on the severity of OSA following ERT, HSCT, or surgery.

Methods and Protocol

Literature Review and Search Strategy

A comprehensive 3-step search strategy was utilized in this review. An initial search of MEDLINE (Ovid), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL was undertaken in March 2015 using search terms stated (Table 2), followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified key words and index terms was then undertaken across all included databases. Finally, the reference lists of all identified reports and articles were searched for additional studies. Articles published in the English language between 1974 and March 2015 were considered for inclusion in this review.

Eligibility of Studies

The quantitative component of the review considered both experimental and epidemiological study designs, including randomized controlled trials, nonrandomized controlled trials, prospective and retrospective cohort studies, case control studies, and analytical cross-sectional studies for inclusion. Individual case reports of a patient were excluded. Two of the authors (ARP and NB) independently screened the titles and abstracts produced by the search against the eligibility criteria, identifying full reports that met the inclusion criteria.

Titles, abstracts, and citations of 369 studies identified through electronic searching were independently reviewed by the lead author to assess potential relevance for full review based on criteria for population, intervention, and study design.

Table 3. Cross-Sectional and Retrospective Studies Investigating OSA in MPS.[a]

Author	Year	Study Design	Total n	MPS Types	*N* per group	Median age (yrs)	Pre or post-ERT
[1]Moreira*	2014	Retrospective	45	I	17	5.8 (all)	Pre
				II	16		
				VI	12		
[2]Kasapkara*	2013	Cross-sectional	19	I	4	7 (all)	Post
				II	4		
				VI	11		
[3]Gonuldas $^{+}$	2014	Cross-sectional	42	I	4	10 (all, mean)	No record
				II	5		
				III	8		
				IV	7		
				VI	18		
[4]Santamaria $^{+}$	2007	Cross-sectional	11	I	2 (S)	22.8	Pre
				II	3	6.9	
				IIIb	1	18.6	
				IV	4	19.1	
				VI	1	2.9	
[5]Nashed*	2009	Retrospective	14	I	8 (4H, 4HS)	5.2 (all)	Pre in 11 and post in 3
				II	3		
				IV	2		
				VI	1		
[6]Lin*	2010	Cross-sectional	24	I	3	15.8	Pre
				II	15	9.8	
				III	1	9.9	
				IV	1	2	
				VI	4	6.6	
[7]Wooten	2013	Cross-sectional	30	II	30 (18 Att, 12 Sev)	9	Pre
[8]John^{+}	2011	Prospective cross-sectional	27	VI	27	8.0 (mean)	Pre

Abbreviations: MPS, MPS, mucopolysaccharidosis; OSA, obstructive sleep apnea.
[a]Apnea–hypopnea index based on *3% SpO_2 drop or $^{+}$4% SpO_2 drop; phenotype: H, Hurler; HS, Hurler Scheie; S, Scheie; Att, Attenuated; Sev, Severe.

Table 4. Studies Investigating ERT in MPS Measuring OSA as an Outcome

Author	Year	Study design	Total n	MPS types	*N* per group	Median age (yrs)	Pre or post-ERT
[9]Kakkis*	2001	Prospective observational 1 year f/u	10	I	1H, 8 HS, 1 S	11.5	Pre and post (52 wks)
[10]Sifuentes*	2007	Observational f/u from Kakkis, 2001	5	I	5 HS	18	Post (6 yrs)
[11]Wraith^{+}	2004	Randomized control trial	45	I	1H, 37 HS, 7 S	15.6	Pre and post (26wks)
[12]Clark^{+}	2009	Open-label extension from Wraith, 2004	39	I	39 (Att)	16	Post (3.5 yr)
[13]Wraith^{+}	2007	Prospective open-label	20	I	16H, 4 HS	2.9	Post (52 wks)
[14]Muenzer^{+}	2007	Randomized control trial	7	II	7	14	Pre and post (24 wks)
[15]Lin	2010	Retrospective review. same patients as in (6)	4	VI	4	8.3	Pre and post (2 years)

Abbreviations: MPS, MPS, mucopolysaccharidosis; OSA, obstructive sleep apnea; ERT, enzyme replacement therapy.
Apnea–hypopnea index based on *2% SpO_2 drop or $^{+}$3% SpO_2 drop; Phenotype: H, Hurler; HS, Hurler Scheie; S, Scheie; Att, Attenuated; Sev, Severe.

Types of Participants

We aimed to study 2 groups of patients:

Pretreatment enzyme naive patients with MPS I to VII and
Posttreatment (ERT or HSCT) patients with MPS

From these groups, we identified the following interventions:

ERT,
HSCT,
adenotonsillectomy, and
CPAP

Primary Outcomes

Prevalence and severity of OSA measured by multichannel polysomnography (PSG) based on apnea–hypopnea index (AHI).

AHI was based on the number of obstructive events per hour of sleep time. An apneic event was defined as a cessation in airflow for 10 seconds duration associated with a measured drop in oxygen saturation (Spo_2). A hypopnea event was defined as a 50% reduction in airflow. Studies varied in the required Spo_2 drop required for an event to occur (between 2 and 4% Spo_2), and this variation is identified with asterisks in Tables 3 and 4.

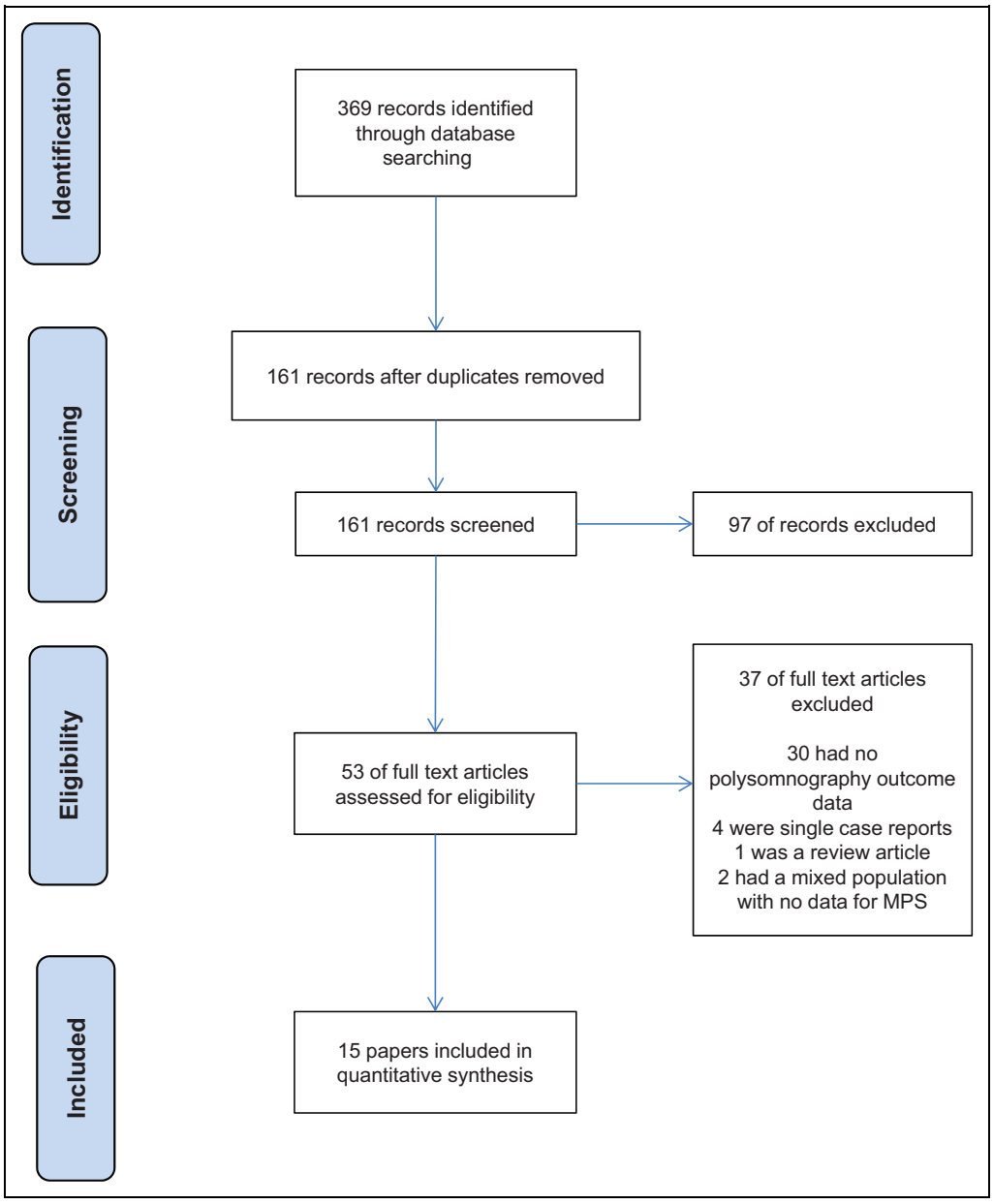

Figure 1. PRISMA flow chart of search flow for systematic review.

In children, an AHI <1.5/hour is deemed normal with an AHI of 1.5 to 5/h, 5 to 10/h, and >10/h defined as mild, moderate, and severe OSA, respectively. In adults, an AHI <5/hour was defined as normal, mild as 5 to 15/hour, moderate as 15 to 30/h, and severe as greater than 30/hour.

Study Selection

Fifty-three full text articles examining OSA, SDB, or upper airway obstruction in all 11 forms of MPS were assessed (Prisma flow chart; Figure 1). Randomized controlled trials and case series assessing the role of ERT or HSCT as an intervention in patients with MPS using OSA as an outcome measure were considered. Studies assessing OSA prior to and following adenotonsillar surgery were assessed for change in OSA post-intervention. Thirty-seven articles were excluded, for reasons described in Figure 1. The primary reason for exclusion was that PSG had not been performed to assess OSA or there had been a failure to report PSG data. After inclusion and exclusion criteria were applied, 15 studies were included in the data analysis.

Assessment of Metabias

An assessment of possible bias among the identified studies was undertaken. Publication bias was undertaken by screening of the clinical trial register at the International Clinical Trials

Registry platform of the World Health Organization for registered trials using sleep apnea as an outcome in MPS.

Data Extraction and Analysis

Data were extracted from studies using data extraction sheets designed in Excel, including study design, demographics, PSG criteria, and OSA outcomes based on AHI. Both continuous AHI values as well as categorized OSA severity data based on the above-described criteria were recorded and presented individually. Data in table or graphic form were used. We combined data for the same continuous variables measured with identical metrics. Pre- and posttreatment paired data were analyzed using Student *t* test for parametric, and Wilcoxon-matched pairs signed ranked test for nonparametric data.

Results

Included Studies

Tables 3 and 4 present the details of the selected articles. Fifteen studies were included in the analysis. Eight were cross-sectional or retrospective studies of patients, 7 prior to ERT[6,15,17-21] with 1 post ERT.[22] Six prospective trials of ERT intervention measuring OSA were available, including two multicenter, double-blind, randomized, placebo-controlled, phase III trials of ERT in MPS I and II, respectively. Two studies were long-term follow-up or open-label studies of initial cohorts contained in previous publications included in our search.[23-28] One publication retrospectively reviewed pre- and post-ERT outcomes in MPS VI.[29]

Participants

A total of 294 participants with MPS (median age 9.8 years) were recruited to the included publications, including 212 from 8 cross-sectional reviews and 82 individuals from 7 trials of therapeutic ERT intervention. A total of 113 MPS I, 83 MPS II, 10 MPS III, 14 MPS IV, and 74 MPS VI individuals were assessed. All but 2 studies (Santamaria et al[15] and Sifuentes et al[28]) assessed a predominantly pediatric population, based on median age. No studies reported OSA outcomes using PSG or AHI in post-HSCT cohorts.

Prevalence of OSA

The pretreatment prevalence (n = 210) of OSA (AHI > 1.5) in publications presenting individual AHI or severity data was 81% (170/210). Studies presenting data categorized by severity and pooled data by MPS type are presented in Figure 2. Based on pretreatment data, MPS I has the highest prevalence of OSA (83%), with 75% of patients suffering with moderate to severe OSA. While MPS VI has a similar proportion of patients with severe OSA (52%), a higher percentage of patients have either no or mild OSA in comparison to MPS I (MPS VI, 38% vs MPS I, 18%). Patients with MPS III are least affected by airway obstruction, while only 23% of patients with MPS IV suffer with moderate to severe obstruction.

Severity of OSA

Figure 3 presents numerical AHI values pooled among 13 of the studies analyzed, based on MPS group and therapy. In studies for which summary data for all MPS types was given, the mean AHI was 10.4/h. Analyzed by MPS type, the AHI values confirm the findings of Figure 2, with severe OSA most marked in MPS I (mean AHI: 16.06/h), followed by MPS VI (12.1/h) and II (10.0/h). Patients with MPS IV suffer with moderate OSA (6.3/h), while patients with MPS III have close to normal values (2.9/h).

Role of ERT

Analysis of AHI values in 5 studies presenting both pre- and post-ERT data in MPS I demonstrates an improvement in median AHI (pre-ERT 17.1; post-ERT 12.2; Figure 3). However, due to the limited data available and variance, this improvement just failed to reach statistical significance ($P = .06$). A single study presents data for ERT in MPS II, and while the median values appear to demonstrate deterioration in AHI values as presented in Figure 3, this occurs due to the variability in values for individual patients and limited presentation of raw data. The text of the article reports 4 of 5 patients with an abnormal AHI at baseline had at least a 50% reduction after 12 months of ERT. One study examined PSG in MPS VI pre and 2 years postcommencement of ERT but presented respiratory disturbance index (RDI), including central apneas. The authors witnessed an improvement in RDI in all patients and a dramatic improvement in a single individual (RDI pre-ERT 54.9/h, post-ERT 11.1/h), although a modest decrease in the remainder proved nonsignificant on statistical analysis in the group as a whole. No post-ERT data are currently available in MPS IV as elosulfase alfa has only recently been licensed and phase III trials did not measure OSA as an outcome.[30]

Role of HSCT in MPS I

Quantitative data in a single post-HSCT MPS I patient were recorded and, as such, no conclusions were drawn.[6]

Intervention

One study assessed the role of surgical intervention in 25 patients undergoing adenoidectomy (n = 13) or adenotonsillectomy (n = 12) in a mixed group of patients with MPS.[18] Pre- and postoperative PSG was performed and demonstrated a significant improvement in AHI (mean, range; preoperative AHI 10.4, 1.6-32.7; postoperative AHI 2.0, 0.5-7.5; $P = .002$). Nashed et al[6] measured OSA following CPAP in 4 patients with MPS I and 2 patients with MPS II. The 2 patients with MPS II did not tolerate nocturnal ventilatory support, while a significant improvement was seen in the 4 patients with MPS I treated successfully with CPAP (mean AHI; pre-CPAP:

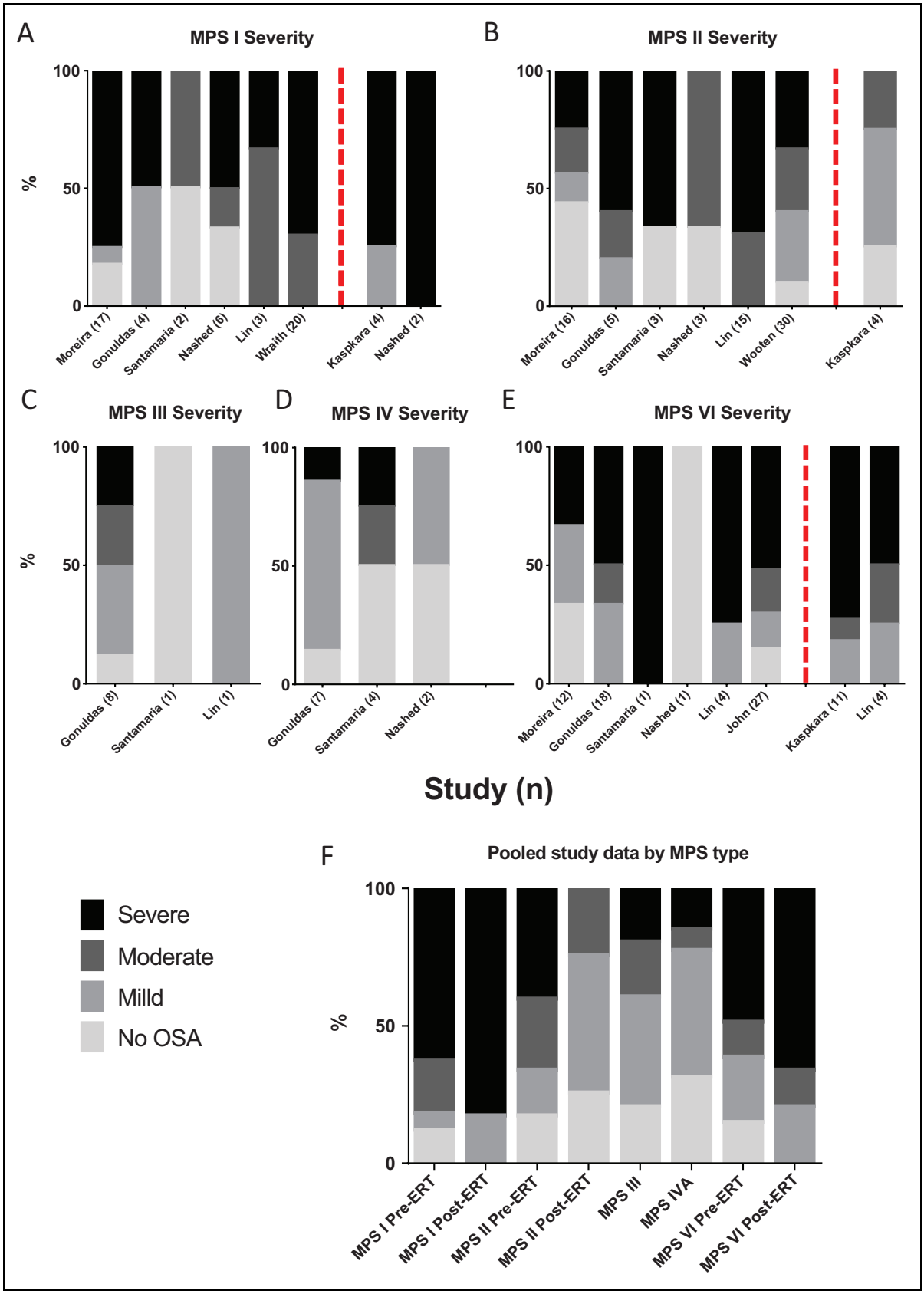

Figure 2. Severity of OSA in MPS based on systematic review. Stacked bar charts demonstrating proportion of patients (%) with severe, moderate, mild, and no OSA by MPS type (A) MPS I, (B) II, (C) III, (D) IV, and (E) VI from each study grouped prior to treatment and following ERT (bars to right of red dotted line). Severity of OSA based on AHI. (F) Pooled data from all studies are presented. Normal: AHI < 1.5; mild: AHI 1.5 to 5; moderate: AHI 5 to 10; severe: AHI > 10. N represents number of patients reported per study. OSA indicates obstructive sleep apnea; MPS, mucopolysaccharidosis; AHI, apnea–hypopnea index.

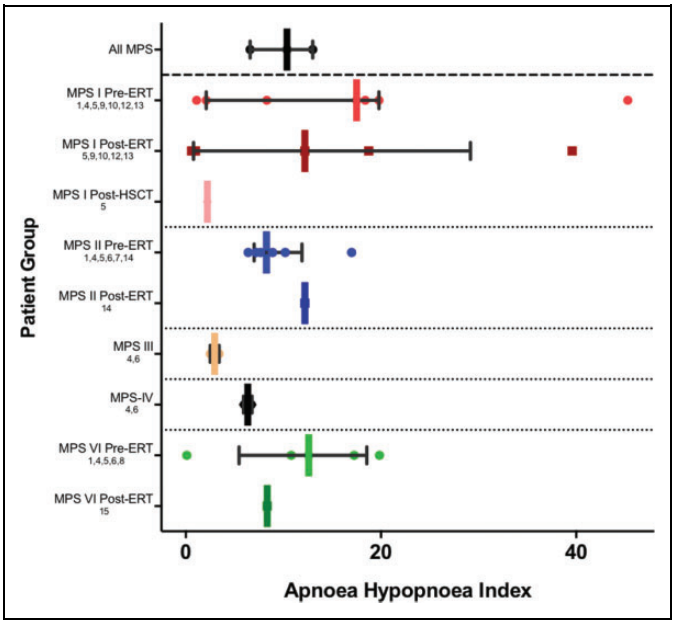

Figure 3. Median AHI based on studies presenting quantitative data presented by MPS patient group. Data points from each individual pre- and posttreatment studies are plotted, with solid bars representing median AHI for MPS type. Error bars represent interquartile range. Study reference to study numbers in Table 3 and 4 in superscript. AHI indicates apnea–hypopnea index; MPS, mucopolysaccharidosis.

28.0, post-CPAP: 3.3; $P = .01$). However, 2 patients also underwent intervening adenotonsillectomy. The individual patient in their cohort treated with HSCT underwent adenotonsillectomy between baseline and posttreatment studies with an improvement from moderate (6.6/h) to mild (2.2/h) OSA.

Bias

No trials of ERT were identified from the clinical trials register whose results have been unpublished, excluding possible publication bias. A number of studies provided abbreviated or summarized outcomes for OSA and analyzed subgroup data, raising the possibility of outcome reporting bias. To minimize this bias, data from these subgroups were excluded in our analysis. In a number of the cross-sectional studies, only patients with symptoms of snoring were enrolled for PSG, suggesting selection bias.

Discussion

OSA is well recognized in MPS and is known to contribute to cardiorespiratory and neurocognitive morbidity. We summarize and analyze the available literature on the prevalence and severity of OSA in this disease. Due to the low incidence of MPS, studies are often limited to small and often retrospective cohorts, with heterogeneous samples including variable numbers of MPS types with differing profiles. This limits assessment of patterns of OSA in the population as a whole.

By combining data from 15 studies, we are able to present data on 294 individuals. Our analysis demonstrates a prevalence of OSA among untreated patients with MPS of 81%, in keeping with registry data[31] and findings from studies measuring SDB using other parameters.[5,32] This is approximately 40 times the prevalence in the general pediatric population.[33] Such high prevalence occurs because of a number of changes seen within the airway in MPS.

Infiltrative involvement of the soft tissue within the upper aerodigestive tract, including the tongue, adenoids, tonsils, and laryngeal mucosa, is presumed to occur due to GAG deposition and is most commonly seen in MPS I and II. In MPS IV, a predominantly musculoskeletal phenotype results in changes limiting midfacial development, temporomandibular joint function, and abnormalities of the cervicothoracic vertebra. This impinges on the orofacial airway and leads to tracheal tortuosity secondary to a discrepancy in tracheal and spinal growth. MPS VI presents with a combination of the above infiltrative and skeletal changes. Restrictive lung defects further compromise respiratory reserve. Given these changes and high rate of prevalence, it is essential that an assessment for OSA and consideration of intervention is made in all patients with MPS.

Review of the current literature demonstrates significant variance in severity and uncertainty to which MPS group is most affected by OSA.[5,17] Following our analysis of pretreatment cohorts, MPS I presents with the highest prevalence and most severe OSA. When documented in individual studies, the majority of the MPS I cohorts studied were predominantly composed of the attenuated Hurler-Scheie phenotype. Thus, patients with the severe Hurler phenotype would be predicted to suffer with more severe disease. MPS VI followed by MPS II are the subsequent types most affected by OSA. Common to these forms is the fact they all store Dermatan sulfate (DS). Hence, it may be hypothesized that primary DS storage in the soft tissue of the pharynx and larynx is responsible for the airway specific changes in MPS I, II, and VI, which manifest with airway obstruction. While MPS I and II also store heparan sulfate MPS III, which stores heparan sulfate alone, is seen to have the lowest prevalence and severity of OSA. Keratan sulfate storage in MPS IV is seen to present with an intermediate airway phenotype, predominantly affecting the cartilaginous trachea. These findings are in keeping with our recent findings that increasing levels of pathological urinary DS substrate (normalized against levels of nonaccumulated chondroitin sulfate (CS) substrate—DS: CS ratio), a measure of decreasing metabolic correction, positively correlate with increasing severity of SDB as measured with sleep oximetry[34] and provide a potential avenue for further research into the etiology of airway disease in MPS.

A significant gap in the current literature concerns the role of metabolic treatment in modifying OSA in MPS. Untreated, MPS I presents with the greatest degree of upper airway obstruction. However, despite over 50% of patients with MPS I presenting with the severe phenotype and thus being candidates for HSCT, no quantitative PSG data exist to demonstrate outcomes following this intervention. Our group has recently published on long-term post-HSCT outcomes for SDB in 41 patients with MPS I.[34] We observe a significant and sustained

improvement in nocturnal hypoxia. While based on sleep oximetry rather than PSG, we demonstrate a correlation between improved airway obstruction, urinary substrate reduction, and delivered enzyme (leukocyte iduronidase) post-HSCT. We found good concordance between oximetry and abbreviated PSG in those who underwent both investigations. A recent multicenter analysis of post-HSCT outcomes in 217 patients with Hurler syndrome identified continuing nocturnal hypoxia in a small proportion of this population, with a requirement for CPAP in 8 individuals. Both factors were found, by multivariate analysis, to relate to delivered enzyme levels posttransplant, with progressive age also identified as a predictor for hypoxia. No quantitative respiratory data were presented by this study.[35]

Limited data in a small number of patients are available for the role of ERT in improving OSA in MPS I, II, IV, and VI. The only studies to present baseline and posttreatment data are the prospective phase II/III and open-label studies of ERT undertaken prior to its widespread clinical introduction. While well designed, these studies present pooled rather than individual patient data for OSA. These examine a wide range of outcomes, with OSA often a secondary measure, and the majority having a relatively short follow-up duration (26-52 weeks). The longest follow-up duration of 6 years was reported in only 5 patients.[28] As such, it is unclear whether the airway disease traditionally seen in childhood, in the era prior to ERT, is simply delayed and manifests in adulthood.

A number of potential confounding factors limit the conclusions we may draw from our analysis of the included studies. As shown in Tables 3 and 4, variable age at assessment and treatment initiation potentially bias the severity of disease manifestations in the studied cohorts. Among the ERT trials, a diagnosis of MPS was often made prior to the era of ERT, contributing to a delay between diagnosis and treatment. In a number of cases in the MPS I literature, treatment of the severe Hurler phenotype (a cohort who would currently be better managed with HSCT) is undertaken with ERT.[24] Furthermore, patients often undergo surgical intervention, in the form of adenotonsillectomy, prior to diagnosis or between baseline and posttreatment PSG studies. As a result, although ERT is clearly of clinical benefit and our analysis certainly demonstrates improvement, conclusive evidence of the role of ERT and HSCT in definitively resolving OSA in the long term is limited and requires further investigation, given the influence of the above factors.

Due to the on-going burden of disease following ERT and the continuing risks and difficulties of airway intervention in this population,[36] such posttreatment data would provide normative parameters to guide clinicians as to the potential benefit that may be achieved with surgery or CPAP. Certainly, the single study to examine OSA pre- and postadenotonsillectomy demonstrated significant improvement and in those patients in whom the anesthetic risks are deemed acceptable, such intervention would be recommended as first-line treatment. In individuals judged unfit for surgery, or who progress despite adenotonsillectomy, consideration should be given to CPAP. However, evidence of successful outcome for this intervention is currently available in only 4 patients.

Strengths of the current literature include the methodical use of multichannel PSG and adherence to current diagnostic criteria for OSA. Additionally, studies are available from multiple geographic locations, providing information on international prevalence. However, several limitations are apparent in the literature. The majority of the studies were evaluated as level 4 evidence. Significant heterogeneity is seen among patient groups studied in terms of age at investigation and diagnosis and extent of disease progression. The AHI values obtained, even for identical forms of MPS, show considerable variability. This emphasizes the clinical heterogeneity seen in MPS but limits the statistical conclusions that may be drawn. There are a number of possible explanations for such a wide deviation in measured OSA, including technical aspects of PSG acquisition and analysis. PSG is an objective investigation with well-defined measures and criteria. Additional sources of potential variation include selection bias of patients based on history and symptomology, previous surgical interventions, and genetic variations in patient populations between regions.

Conclusion

This study systematically analyses the available data from all current studies investigating OSA in MPS I to VI. The current literature confirms the high prevalence of OSA in this population, with the majority of untreated patients presenting with moderate to severe OSA. Analysis of relevant studies demonstrates that patients with MPS I are most susceptible to severe OSA, followed by MPS VI, II, IV, and III, respectively. There is a significant paucity of evidence available on the long-term outcomes of OSA in patients following ERT and especially HSCT. Future research should examine the response of OSA to such interventions and the continuing need and derived benefit following surgery or CPAP in the MPS population.

Author's Note

ARP conceived the study, performed the literature search, data collection, data and statistical analysis, and drafted the manuscript and figures. NB contributed to study methodology and search strategy. BWB, SAJ, and IAB aided in study conception. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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