Oropharyngeal Dysphagia in Mucopolysaccharidoses: Evidence from Videofluoroscopic Swallowing Study

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Abstract

Mucopolysaccharidoses (MPS) are rare inborn errors of metabolism, leading to the accumulation of glycosaminoglycans (GAG) in distinct tissues. We investigated oropharyngeal dysphagia using the videofluoroscopic swallowing study (VFSS) in patients with different MPS types. Since there is a lack of studies systematically evaluating this disorder in this population, the use of a standard technique should contribute to better evaluate individuals with MPS.. A cross-sectional and observational study enrolling patients followed by an outpatient service for lysosomal diseases at the Genetics Service of the Hospital de Clínicas de Porto Alegre (SGM/HCPA) was conducted. Patients underwent semi-structured interviews, clinical evaluation and VFSS. Nineteen patients were evaluated, including patients with MPS types I (16%), II (42%), IIIb (10%) and IVa (32%). Nearly all patients (95%) presented with oropharyngeal dysphagia in the VFSS. The most frequent findings were impaired chewing during oral phase (94%) and reduced laryngeal elevation in the pharyngeal phase (72%). Oropharyngeal dysphagia constituted a prevalent symptom in the studied cohort regardless of MPS type. Our data reinforces the notion that this disorder should be objectively assessed since it can significantly compromise the nutrition and the hydration of these patients as well as lead to tracheobronchial aspiration, thus resulting in aspiration pneumonia and even death.

Keywords

Inborn errors of metabolism, lysosomal disorders, swallowing disorder, videofluoroscopy, deglutition, deglutition disorders.

Introduction

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders induced by a lack of degradation of glycosaminoglycans (GAG), thus leading to an accumulation of GAG in various tissues and organs which underlies a myriad of clinical features [1–3]. The multisystemic cardinal signs and symptoms include bone dysplasia and joint stiffness, respiratory and cardiovascular commitment and, in some cases, severe neurological manifestation followed by poor cognitive performance. Eleven enzyme deficiencies have been described underlying seven different types of MPS (MPS I, II, IIIa, IIIb, IIIc, IIId, IVa, IVb, VI, VII, IX). The incidence of all MPS is estimated at 3.4 and 4.5 per 1000,000 live births [4].

It is recommended that the treatment of MPS should be based on a multidisciplinary care to minimize the associated complications, thus hampering the deterioration of the health-related quality of life in these patients [5]. For patients who received an early diagnosis, hematopoietic stem cell transplantation may bring clinical benefits. Currently, enzyme replacement therapy is available for patients with MPS I, II, IVa, VI and VII [6].

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Swallowing is a physiological process that involves cranial, motor, and parasympathetic nerves with the intention to transport the bolus from the mouth to the stomach. This process occurs through physiological phases (oral preparatory, oral proper, pharyngeal, and esophageal) that are interrelated. Oropharyngeal dysphagia constitutes any alterations that may occur in one or more phases of swallowing [7–8]. Of note, the anatomy of the craniofacial structure has a critical role in the biomechanics of swallowing. As patients with MPS may present with bone dysplasia, joint stiffens, spinal instability and spinal cord compression, oropharyngeal dysphagia –although poorly reported, is not uncommon in these patients.

A previous study pointed out alterations in stomatognathic system and functions are prevalent among individuals with MPS despite the enzyme replacement therapy is administered [9] and that patients with MPS II presented with a high frequency of dysphagia after otorhinolaryngologic videoendoscopic swallowing evaluation [10].

AIMS

To the best of our knowledge, the number of studies that systematically examined swallowing patterns in patients with MPS is limited. Notably, the assessment of swallowing is relying on clinical aspects and medical history, thus lacking a more objective evaluation as videofluoroscopic swallowing study (VFSS), which is a comprehensive test considered the gold standard for the evaluation of oropharyngeal dysphagia [11]. This study was conducted to evaluate the swallowing patterns using VFSS in patients with MPS from a reference center of medical care for patients with rare and metabolic diseases.

Methods

Participants

All individuals diagnosed with MPS (regardless of type) regularly followed up by the multidisciplinary team at the Genetics Service of the Hospital de Clínicas de Porto Alegre (SGM/HCPA) that fulfilled the study criteria were invited to participate. The study included candidates with a clinical and biochemical diagnosis of MPS, who, during clinical swallowing examination were identified as requiring a VFSS regardless of age or presence of neurological involvement. Candidates who used alternative nutrition routes (as gastrostomy, for example) were excluded from the study since the main indication for gastrotomy is dysphagia, thus inducing a selection bias. The candidates (or legal caregivers) who did not agree to participate in the study were also excluded.

Study Design

A cross-sectional and observational study was carried out from November 2016 to April 2018. All procedures were conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Research Ethics Committee of the HCPA under protocol #18-0115 and informed consent was obtained from all patients (or their parents, when legally obliged).

The study was divided into two phases. During the initial phase, when patients were recruited, the study goals and design were explained to the candidates and/or the caregivers. After obtaining the written consent, the participants were subjected to a semi-structured interview to evaluate the dietary intake and feeding-associated complaints, especially regarding swallowing (Supplemental material). In the second phase, the participants underwent VFSS to complete an objective evaluation of oropharyngeal dysphagia.

Video Fluoroscopic Swallowing Study (VFSS)

The VFSS was conducted as previously described by Suzuki et al. [12] and Arvedson et al. [13]. The evaluations were performed using X-ray equipment (model Precision RXi System®, GE Healthcare, Illinois, USA). Participants (and/or their caregivers) were instructed to fast for 3 h before the evaluation. During the assessment, the participants were offered food with distinct consistencies (thin or thick puree, mechanical soft and honey-like consistency drinks) as well as were also advised to use the cutlery and feeding utensils they were used to (such as spoons, bottles, straws, transition cups, etc.). Changes of utensils or bottle nipples could occur to increase the efficiency and safety of feeding [11,13–14].

All the evaluations considered the physical limitations and the feeding patterns of each participant. After preparation, the meals were mixed with barium sulfate (Bariogel® 100%, Cristalia, Brazil) and then administered in accordance with the age and the eating habits of each participant as well as therapeutic indication. Patients who were able to feed themselves were asked to reproduce the feeding behavior throughout the assessment. For those who were unable to feed themselves, parents or caregivers were asked to assist them.

During the evaluations, the patients remained seated and straight (children and adults) or semi-reclined (for babies). The participants who were wheelchair users were allowed to remain seated in their chairs since they are routinely fed in this position. All the evaluations were conducted by a radiology technician accompanied by a speech therapist using a lateral view of the participants.

All the evaluations were carried out in accordance with the safety criteria for radiation amount and the duration of the

exposure. The exposure to radiation did not exceed 150 seconds in pediatric patients and 300 seconds in adults [14–15].

Two speech therapists who had experience in oropharyngeal dysphagia and in VFSS and examined the results independently from each other. The results were then compared to achieve a consensus conclusion. The consensus ratings were subsequently used for analysis.

Statistical Analyses

Categorical variables are described by frequencies and percentages. The normality of quantitative variables was assessed using the Shapiro-Wilk test. Quantitative variables with symmetric distribution are described as mean and standard deviation; those variables with asymmetric distribution are shown as median accompanied by minimum and maximum values. Fisher's exact test was used to assess the association between categorical variables. The Kappa coefficient of agreement was used to assess the agreement between the perception of the participants/caregivers regarding the swallowing difficulties. SPSS Statistics® program (version 20.0 for Windows©, IBM, USA) was used in statistical analysis. A significance level of 5% was considered for the established comparisons.

Results

Demographic Data

Fifty-four candidates with MPS are accompanied in the lysosomal disease outpatient clinic at the SGM/HCPA. From those, 19 (35.2%) agreed to participate in the study.

The study cohort was predominantly composed by participants at the pediatric age (79%, n=15) and males (63%, n=12). Regarding the types of MPS, 16% (n=3) of the participants had the type I (Hurler disease), 42% (n=8) had type II (half with neuronopathic phenotype and half with attenuated phenotype), 10% (n=2) had type IIIb and 32% (n=6) had type IVa. The median age of the studied population was 10.9y (standard deviation (SD): 7.2; MIN=1.1; MAX=28).

Neurological impairment (cognitive decline), respiratory symptoms (asthma, bronchitis, pneumonia, or bronchiolitis) and bone dysplasia were found in 42% (n=8), 32% (n=6) and 74% (n=14) of the participants, respectively. By the time of the evaluation, 62% (n=12) of the participants were receiving enzyme replacement therapy for more than two years.

VFSS Analysis

Concerning the route of food intake, 89% (n=17) of the participants were exclusively fed by mouth and 11% of the sample were fed by mouth but also used nasogastric tubes.

The analysis of the semi-structured interview has shown that 58% (n=11) of the participants and/or their caregivers complained about swallowing difficulty. Of those, the vast majority (82%, n=9) related having the higher difficulty when mechanical soft consistency of food is offered. The most frequent complaints were difficulty in chewing, coughing, and choking.

Nearly all participants (95%, n=18) presented with oropharyngeal dysphagia in the VFSS, irrespective from the type of MPS (Table 1). Alterations in oral phase or pharyngeal phase was detected in 94% (n=17) of the participants, while 89% presented with alteration in both phases of swallowing. What regards the food consistencies, the vast majority reported more difficulties with soft mechanical foods (83%; n=15), followed by thick puree (67%; n=12) and thin puree (56%; n=10). Of note, 94% (n=17) of the participants displayed oropharyngeal dysphagia when having thickened drinks (Table 2).

The most frequent alteration in the oral phase was impaired chewing, which was detected in 83% (n=15) of the sample. Other alterations were difficulty in ejecting the bolus from the oropharynx (72%, n=13), posterior oral escape (44%, n=8), and increased duration of the oral phase (22%, n=4).

In the pharyngeal phase, the most frequent alteration was reduction in the laryngeal elevation (72%, n=13), followed by delay in triggering the pharyngeal phase of swallowing (44%, n=8), laryngeal penetration (33%, n=6) and tracheal aspiration (22%, n=4). Remarkably, all events of aspiration were silent ones (Table 3).

The impact of neurological impairment on oropharyngeal dysphagia was also examined. Surprisingly, 10 patients out of 11 (91%) without reported neurological impairment presented with oropharyngeal dysphagia. In this subgroup, all participants presented with altered pharyngeal phase and 90% (n=9) of them displayed alteration in both phases of swallowing (oral and pharyngeal).

The VFSS showed alteration in both oral and pharyngeal phases in all patients who presented with respiratory symptoms.

The comparison of data obtained from the VFSS with that originated from the semi-structured interview revealed that eight participants denied any difficulty in swallowing regardless of the consistency of the food. Almost all participants (87%, n=7) had oropharyngeal dysphagia in the VFSS.

Table 1. Prevalence of oropharyngeal dysphagia in patients with MPS.

	MPS type				*p value*
	I	**II**	**III**	**IV**	
Oropharyngeal dysphagia *(95%)*	3 (100%)	8 (100%)	2 (100%)	5 (83%)	0.579

Table 2. Influence of the food consistency on the oropharyngeal dysphagia in patients with MPS.

	MPS type				*p value*
Food consistency	**I**	**II**	**III**	**IV**	
Thick puree (n=10, 56%)	1 (33%)	5 (62%)	2 (100%)	2 (40%)	0.606
Thin puree (n=12, 67%)	2 (67%)	5 (62%)	2 (100%)	3 (60%)	0.999
Mechanical soft (n=15, 83%)	2 (67%)	7 (87%)	2 (100%)	4 (80%)	0.828
Liquid (thin/thick) (n=7, 94%)	3 (100%)	8 (100%)	2 (100%)	4 (80%)	0.556

Table 3. Changes in oropharyngeal dysphagia in patients with MPS undergoing video fluoroscopic swallowing study (VFSS).

	MPS type				*p value*
Findings in the VFSS	**I**	**II**	**III**	**IV**	
Changes in oral phase (n=17; 94%)	3 (100%)	8 (100%)	2 (100%)	4 (80%)	0.556
Chewing difficulty (n=15, 83%)	3 (100%)	7 (87%)	2 (100%)	3 (60%)	0.578
Increased oral phase duration (n=4, 22%)	1 (33%)	2 (25%)	1 (50%)	-	0.431
Posterior oral escape (n=8, 44%)	-	4 (50%)	1 (50%)	3 (60%)	0.415
Difficulty in ejecting the bolus into the oropharyngeal region (n=13, 72%)	2 (67%)	6 (75%)	2 (100%)	3 (60%)	0.999
Changes in pharyngeal phase (n=17, 94%)	2 (67%)	8 (100%)	2 (100%)	5 (100%)	0.278
Delay in triggering the pharyngeal phase (n=8, 44%)	-	4 (50%)	2 (100%)	2 (40%)	0.218
Reduced laryngeal elevation (n=13, 72%)	2 (67%)	6 (75%)	2 (100%)	3 (60%)	0.999
Laryngeal penetration (n= 6, 33%)	-	3 (37%)	2 (100%)	1 (20%)	0.180
Tracheal aspiration (n=4, 22%)	1 (33%)	2 (25%)	1 (50%)	-	0.431

The influence of the food consistency on the oropharyngeal dysphagia in patients and alterations in oropharyngeal dysphagia in patients with MPS undergoing VFSS was detailed in Table 2.

Discussion

The main finding of the present study was the high prevalence of oropharyngeal dysphagia due to altered oral and pharyngeal phases of swallowing in patients with MPS regardless of its type. Our findings are in line with previous studies which examined the occurrence of dysphasia using otorhinolaryngologic fiberoptic endoscopic evaluation of swallowing in individuals with MPS [9–10,16]. In the present work, dysphagia was systematically evaluated the patients using the VFSS, a gold standard technique for detecting disturbances in the swallowing stages. Additionally, this study also detected the presence of oropharyngeal dysphagia in patients without neurological impairment and a discrepancy between the perception of oropharyngeal dysphagia (by the patients and/or the caregivers) and its prevalence in accordance with the VFSS, which has not been previously described in the literature.

Difficulty in chewing was the most frequent change of the oral phase of swallowing. This finding is in line with previous studies from Turra and Schwartz [9] which detected a prevalence of oral phase alterations of 95.3% in MPS patients (including MPS type VI). The authors attributed such high prevalence to changes in the stomatognathic systems since patients presented with alteration in dental arch, lips, tongue, cheeks, jaw, and hard palate.

Although tracheal aspiration was the least frequent alteration of the laryngeal phase described here, the participants enrolled in the study also presented with other alterations in pharyngeal phase (such as reduced laryngeal elevation, delay in triggering the pharyngeal phase of swallowing and laryngeal penetration) that

are directly related to an increased chance to tracheal aspiration. The elevation and the anteriorization of the hyolaryngeal complex, for example, has been associated with an adequate upper esophageal sphincter opening, which is critical for the efficiency of swallowing and maintenance of the airflow [17–18]. Since we found that patients with MPS may display a reduced laryngeal elevation, it could be proposed that these individuals have an inadequate upper esophageal sphincter opening, thus hampering the pharyngoesophageal transit and consequently increasing the risk of tracheal aspiration. The limited time to radiation exposure may also have contributed to the low frequency of tracheal aspiration reported here. In fact, due to fatigue, some participants may have reduced compliance to the evaluation [19].

Even though there were no significant statistical differences, there is a trend toward a reduced frequency of the complaints about swallowing obtained in the analyses of the semi-structured interview compared to the frequency of alterations found in the VFSS. These findings may indicate that there is a lack of perception of the swallowing disorders, thus contributing to lower rates of diagnosis. Collectively, these findings suggest that patients with MPS should have an annually routine instrumental dysphagia and respiratory health assessment.

A high prevalence of oropharyngeal dysphagia was detected when patients had mechanical soft foods. These results were in line with those reported in the interview by the participants or their caregivers. Turra and colleagues [9] have already described that the oral anatomical alteration in patients with MPS may underlie disturbances in the mastication function.

Notably, the VFSS detected oropharyngeal dysphagia in patients with cognitive impairment and in patients without developmental delay. These results are practice-changing since there was an assumption that only patients with neurological manifestations of the disease would present with oropharyngeal dysphagia. Furthermore, these findings reinforce the notion that some MPS-induced orofacial dysmorphic features may influence a higher prevalence of oropharyngeal dysphagia.

Although the restricted number of patients may be pointed out as a limitation of the present study, the inclusion of MPS patients without neurological involvement brought a new light to necessity of systematically investigating oropharyngeal dysphagia in these patients. Finally, another relevant point was the short albeit recommended exposure to the radiation which may have influenced the quantification of the tracheal aspiration prevalence.

Conclusion

The present study reported a high prevalence of oropharyngeal dysphagia in patients with MPS regardless of its type. Additionally, we have also demonstrated that the occurrence of oropharyngeal dysphagia is not limited to the patients with neurological impairments. Since alterations in swallowing can critically influence the nutrition (hampering the absorption of the adequate nutrients amounts) and respiratory function (by leading to accumulation of secretion in the airways) of patients with MPS, an evaluation of swallowing abilities should be included in the follow-up of patients diagnosed with MPS even if they have attenuated phenotypes. To date, this is the first study that used the VFSS in patients with MPS.

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Declaration of Conflict of Interests

The authors declare no conflict of interest.

Supplementary Material

The following online material is available for this article:

Supplementary - Semi-structured interview before the video fluoroscopic swallowing study (VFSS).

References

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. *The online metabolic and molecular bases of inherited disease*. New York: McGraw Hill; 2019:3421-3452. doi:10.1036/ommbid.165.
2. Giugliani R, Federhen A, Rojas MVM, et al. Mucopolysaccharidosis I, II, and VI: brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33(4):589-604. doi:10.1590/s1415–47572010005000093.
3. Fitzgerald J, Verveniotis SJ. Morquio's syndrome. A case report and review of clinical findings. *NY State Dent J*. 1998;64(8):48-50.
4. Federhen A, Pasqualim G, Freitas TF, et al. Estimated birth prevalence of mucopolysaccharidoses in Brazil. *Am J Med Genet A*. 2020;182(3):469-483. doi:10.1002/ajmg.a.61456.
5. Giugliani R, Federhen A, Rojas MVM, et al. Terapia de reposição enzimática para as mucopolissacaridoses I, II e VI: recomendações de um grupo de especialistas brasileiros. *Rev Assoc Med Bras*. 2010;56(3):257-277. doi:10.1590/S0104–42302010000300009.

6. Solano M, Fainboim A, Politei J, et al. Enzyme replacement therapy interruption in patients with Mucopolysaccharidoses: recommendations for distinct scenarios in Latin America. *Mol Genet Metab Rep*. 2020;23:100572. doi:10.1016/j.ymgmr.2020.100572.

7. Goyal RK, Mashimo H. Physiology of oral, pharyngeal, and esophageal motility. GI Motility online. https://www.nature.com/gimo/contents/pt1/full/gimo1.html. Published May 16, 2006. Accessed April 16, 2022.

8. Carbo AI, Brown M, Nakrour N. Fluoroscopic swallowing examination: radiologic findings and analysis of their causes and pathophysiologic mechanisms. *Radiographics*. 2021;41(6):1733-1749. doi:10.1148/rg.2021210051.

9. Turra GS, Schwartz IV. Evaluation of orofacial motricity in patients with mucopolysaccharidosis: a cross-sectional study. *J Pediatr*. 2009;85(3):254-260. doi:10.2223/jped.1899.

10. Ferreira ACRG, Oliveira AC, Veiga LLP, Santana LD, Barbosa PB, Guedes ZCF. Interferência da disfagia orofaríngea no consumo alimentar de indivíduos com mucopolissacaridose II. *Revista CEFAC*. 2012;14(6):1184-1196. doi:10.1590/S1516–18462012005000073.

11. Costa MMB. Videofluoroscopy: the gold standard exam for studying swallowing and its dysfunction. *Arq Gastroenterologia*. 2010;47(4):327-328. doi:10.1590/S0004–28032010000400001.

12. Suzuki HS, Nasi A, Ajzen S, Bilton T, Sanches EP. Clinical and radiological study of swallowing in patients with deglutition disorders, classified into two age groups: adults and older people. *Arq Gastroenterol*. 2006;43(3):201-205. doi:10.1590/s0004–28032006000300009.

13. Arvedson JC, Lefton-Greif MA. *Pediatric videofluoroscopic swallow studies: a professional manual with caregiver guidelines*. San Antonio: Communication Skill Builders/Psychological Corporation; 1998.

14. American Speech-Language-Hearing Association. Guidelines for speech-language pathologists providing swallowing and feeding services in schools. https://www.asha.org/policy. Published 2007. Accessed April 16, 2022.

15. Weir KA, McMahon SM, Long G, et al. Radiation doses to children during modified barium swallow studies. *Pediatr Radiol*. 2007;37(3):283-290. doi:10.1007/s00247–006–0397–6.

16. Ferreira ACRG, Guedes ZCF. Prospective studies of swallowing in Mucopolysaccharidosis II (Hunter syndrome) before and after enzyme treatment. *Rev Soc Bras Fonoaudiol*. 2011;16(2):221-225. doi:10.1590/S1516–80342011000200018.

17. Cook IJ, Dodds WJ, Dantas RO, et al. Opening mechanisms of the human upper esophageal sphincter. *Am J Physiol*. 1989;257(5):G748-G759. doi:10.1152/ajpgi.1989.257.5.G748.

18. Singh S, Hamdy S. The upper oesophageal sphincter. *Neurogastroenterol Motil*. 2005;17(1):3-12. doi:10.1111/j.1365–2982.2005.00662.x.

19. Taniguchi MH, Moyer RS. Assessment of risk factors for pneumonia in dysphagic children: significance of videofluoroscopic swallowing evaluation. *Dev Med Child Neurol*. 1994;36(6):495-502. doi:10.1111/j.1469-8749.1994.tb11879.x.