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## Oral and craniofacial manifestations of mucopolysaccharidoses

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### Abstract

Mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders caused by the deficiency of lysosomal enzymes necessary for the degradation of glycosaminoglycans (GAGs). Non-degraded GAGs accumulate inside the lysosomes and compromise cell function in different tissues and organs. This accumulation causes progressive and multisystemic damage, leading to a wide spectrum of clinical manifestations, including oral and craniofacial manifestations. This work aims, therefore, to conduct a literature review that promotes specific knowledge regarding the oral and craniofacial manifestations of MPS. The results converged to a variability of alterations, among them facial dysmorphism, macroglossia, lingual protrusion, anterior open bite, dental caries, gingival inflammation, enamel hypoplasia, taurodontism, condylar hypoplasia and presence of dentigerous cysts. Preventive and interceptive actions in oral health are used as a means of improving oral hygiene and reducing oral problems. Finally, there is a need for improvement in comprehensive care for patients with MPS.

**Keywords:** Mucopolysaccharidoses, oral manifestations, craniofacial manifestations, oral health

### 1. Introduction

Lysosomal overload diseases (LOD) are a heterogeneous group of rare and progressive pathologies characterized by impairment of the lysosomal catabolic pathways necessary for essential cellular biological processes. Integrated in this group of metabolic disorders are mucopolysaccharidoses (MPS), resulting from deficiencies in lysosomal enzymes responsible for the degradation of glycosaminoglycans (GAGs) [1, 2].

MPS carriers are unable to produce or present any abnormality in these lysosomal hydrolases, interrupting the catabolism of GAGs, resulting in their accumulation within the lysosomes. This accumulation causes progressive damage and impairs cell function. In addition, when the cell no longer has space available, these GAGs are excreted in the urine, which is an important parameter for investigating MPS [2, 3].

In MPS, the affected physiological processes, in addition to the lysosomal deposit, are (a) changes in the pattern of plasma membrane receptors; (b) dysfunctional macrophage with accumulation of GAGs; (c) changes in the uptake of cytokines and growth factors; (d) changes in the recruitment of circulating cytokines and in the presentation of cytokines to recipients; (e) abnormal interactions of the extracellular matrix; and (f) altered cell adhesion [4].

In Portugal, MPS have a prevalence of 4.8/100,000 of born individuals. In 2017, the number of patients with lysosomal overload pathologies was 256 individuals, 32 of whom had MPS [1, 5].

Given the progressive clinical course of the disease, a multidisciplinary approach is needed to monitor these patients. Therefore, prevention and immediate intervention is essential to maintain health and improve quality of life. In addition, knowledge of oral and craniofacial manifestations present in patients with MPS is of crucial importance for the early diagnosis of the pathology. The purpose of this literature review is to promote specific knowledge of oral and craniofacial changes present in MPS, with a view to the planning and appropriate monitoring of these patients.

### 2. Materials and Methods

It is a qualitative study of literature review, appropriate for updating knowledge on the proposed theme, showing new ideas or scientific trends. Articles in the PubMed databases were surveyed, considering the period from 2009 to 2019.

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In addition, references prior to 2009 and/or indexed in other databases were consulted and used as a theoretical framework. The indexing terms used were “mucopolysaccharidoses and oral manifestations”, “mucopolysaccharidoses and craniofacial manifestations” and “mucopolysaccharidoses and oral health”. From there, the analysis of the theoretical foundation of the studies was continued. Finally, there was an assessment of the applied methodology, results obtained and discussion. To analyze the identified scientific production, specific qualitative and/or quantitative techniques of data treatment were not used, having analyzed each of the texts individually. Therefore, this

review was carried out through the analysis of 26 bibliographic references.

GAGs are long, unbranched polysaccharide chains, composed of repetitions of disaccharides, which are synthesized in the Golgi complex. Among the main functions, the attachment to the cytokines, the cell surface receptor and to specific proteins stands out, in addition to hyaluronic interactions. Except for hyaluronic acid, all GAGs are sulfated and linked with a protein nucleus - proteoglycan - which is the main component of the extracellular matrix. The specific individual units of monosaccharides define the GAG subtype, as shown in Table 1<sup>[4]</sup>.

**Table 1:** Subtypes of GAGs.

GAG	Composition
Heparan sulfate	Glucosamine and glucuronic or iduronic acid
Dermatan sulfate	N-acetylgalactosamine and iduronic acid
Chondroitin sulfate	N-acetylgalactosamine and glucuronic acid
Keratan sulfate	N-acetylglucosamine and galactose
Hyaluronic acid	N-acetylglucosamine and glucuronic acid

In a healthy cell, GAGs detach from the plasma membrane and enter the cell to be degraded in lysosomes. For the breakdown of GAGs, there is a series of enzymes that work in sequence until the removal of a sugar molecule at one end of the chain, such as iduronidase,  $\beta$ -galactosidase 1, arylsulfatase B and hyaluronidase. Enzymes play the role of digesting degradation products that are toxic to the cell. Monosaccharides and inorganic sulfate generated from this degradation are transported outside the lysosome<sup>[4]</sup>.

MPS are classified into seven large groups according to the

enzyme deficiency and accumulated GAGs, as shown in Table 2. The change in the degradation of GAGs is caused by mutations in the genes encoding lysosomal hydrolases. Most of these diseases are hereditary conditions with an autosomal recessive inheritance pattern, except for MPS II, which transmission is associated with the X chromosome. When born, MPS patients have a normal phenotype and no signs or symptoms, except for MPS VII whose common complication is hydrops fetalis - accumulation of interstitial fluid in the fetus<sup>[2, 4, 6]</sup>.

**Table 2:** Types of MPS, with corresponding enzyme deficiencies and accumulated GAGs.

Type	Syndrome	Enzyme deficiency	Accumulated GAGs
MPS I	Hurler-Scheie	$\alpha$ -L-iduronidase	Heparan sulfate Dermatan sulfate
MPS II	Hunter	Iduronate-2-sulfatase	Heparan sulfate Dermatan sulfate
MPS III	Sanfilippo A B C D E	Heparan-N-sulfatase $\alpha$ -N-acetylglucosaminidase Acetyl-CoA- $\alpha$ -glucosaminidase N-acetylglucosamine 6-sulfatase N-glucosamine-3-O-sulfatase	Heparan sulfate
MPS IV	Morquio A B	Galactose 6-sulfatase $\beta$ -galactosidase 1	Keratan sulfate Chondroitin 6-sulfate
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine 4-sulfatase (Arylsulfatase B)	Dermatan sulfate
MPS VII	Sly	$\beta$ -glucuronidase	Heparan sulfate Dermatan sulfate
MPS XI	Natowicz	Hyaluronidase	Hyaluronic acid

Due to the multisystemic nature of the disease, each type of MPS has specific traits in its clinical expression according to the progression of GAGs accumulation. In general, the clinical onset of the disease occurs in early childhood, however physical manifestations end up being common to most syndromes. Facial dysmorphism, macrocephaly, short stature, generalized dysostosis, joint dysplasias, skin thickening, cardiorespiratory impairment, hepatosplenomegaly, umbilical and inguinal hernias, corneal opacification, hearing impairments, delayed motor development and, in the most severe forms, cognitive impairment and neuropsychiatric disorders are frequent<sup>[2, 7]</sup>.

The heterogeneity of these manifestations and the similarity with the symptoms associated with other pathologies make the diagnosis difficult. Based on clinical suspicion, laboratory

tests should be performed. First, the quantitative analysis of GAGs in urine is used as a guide for the investigation of the disease. Thereafter, enzymatic assays are performed to confirm the diagnosis<sup>[2, 6, 8]</sup>. Prenatal diagnosis should be considered in cases of family history or gestational signs, being performed through the analysis of the enzyme deficiency in the amniotic fluid or by chorionic villus biopsy<sup>[2]</sup>.

There is no cure for these disorders, so early diagnosis is essential to provide adequate medical treatment, allowing the delay of the development of irreversible sequelae. Nowadays, enzyme replacement therapy (ERT) is considered the main form of treatment and consists of the replacement of the missing enzyme by a recombinant human enzyme, through intravenous infusions. These recombinant enzymes simulate

the biological effects of the missing one, being captured by the cells, and directed to lysosomes. In recent years, this therapy has improved the life expectancy of patients.

However, treatment varies according to the type of MPS, and other therapeutic methods are available, such as hematopoietic cell transplantation and gene therapy [6, 9, 11].

The oral and craniofacial manifestations described in individuals with MPS are varied and can have different degrees of severity depending on the type of the disease.

### 3. Craniofacial manifestations

Facial dysmorphism is common and consists of an anatomical malformation of the structures of the face. Some dysmorphic characteristics related to patients with MPS are the coarse face and thick lips, resulting from the thickening of the soft tissues of the face by the accumulation of GAGs. In addition, facial skeletal changes were found in conjunction with other physical manifestations due to multiple dysostosis. Facial asymmetry, high and prominent forehead, high palate, short mandibular ramus, and maxillary hypoplasia are characteristics frequently mentioned in the literature [10, 12, 17].

In patients with MPS, the impact on facial structures can also be associated with macroglossia and lingual protrusion. Abnormal tongue development can impair chewing and phonation, lead to opening of diastemas, in addition to breathing difficulties [10, 14, 15, 17, 19].

Regarding the radiological findings, it is possible to emphasize the changes related to the temporomandibular joint (TMJ). In general, the most frequent changes are condylar hypoplasia, increased coronoid processes, degenerative changes in the eminences and changes in the shape of the articular fossa [10, 13, 14, 16, 19, 22].

In a clinical study, using computed tomography and magnetic resonance imaging, Cavaleiro *et al.* [10] observed characteristics that were not clear in conventional radiographs, such as the morphological changes of the condylar processes with flattening and condylar erosion, in addition to the loss of joint height. They also found an intense proliferation of cartilage in the retrodiscal area between the condyle and the fossa and anterior disc displacement.

Symptoms of temporomandibular disorders (TMD) were observed in patients with MPS IVA and VI, such as ear pain, headaches associated with clicks and crackles in the opening, reduced condylar mobility, pain during excursions and pain on craniofacial muscle palpation [10, 21].

Imaging is also useful when assessing bone quality. Trabecular variation like osteoporosis and enlarged medullary spaces, cortical thinning and generalized bone rarefactions could be seen in patients with MPS types I, II, IV and VI [10, 13, 22].

Hypoplastic condyles and trabecular variation, together with macroglossia and tongue protrusion, are identified as the cause of severe dental malocclusions. The anterior open bite is one of the most recurrent findings, with a high incidence among patients with MPS [10, 12-17, 19, 21].

Kantaputra *et al.* [19] argue that the anterior open bite in patients with MPS VI results from a hypoplastic mandibular condyle. As an example, two patients who started ERT at an early age (before 3 years of age) did not develop anterior open bite. Likewise, Almeida-Barros *et al.* [21] found an anterior open bite in all patients with MPS VI who had hypoplastic condyles. For Torres *et al.* [14], condylar hypoplasia added to the open bite had implications on the chewing problems reported by the patients.

Among malocclusions, in patients with MPS, the most

frequent posterior crossbite [10, 14, 15], are class II with generalized diastemas [14] and class I with dental crowding [14, 18]. In addition, some deleterious oral habits were mentioned, such as mouth breathing and snoring [10, 13, 16].

Also, regarding radiological findings, manifestations such as delayed rhizogenesis and dental eruption, impaction of deciduous and permanent teeth, in addition to the presence of hyperplastic dental follicles compatible with dentigerous cysts were reported. In patients with MPS types I, IV, VI and VII, the posterior teeth are the most affected [10, 12, 14, 16, 19, 22]. In this follow-up, changes in the normal course of tooth eruption were also associated with chemotherapy and irradiation in patients under preparation for bone marrow transplantation [18].

### 3.1 Oral manifestations

Among the oral clinical changes observed in these patients, the problems associated with the high incidence of caries and periodontal disease were highlighted, marked by the need for dental treatment [12, 17, 20, 23].

A sample of 30 patients was examined by Ballikaya *et al.* [13]. Clinically, 90% of these patients had dental caries and 90.5% had gingival inflammation. The increase in dental caries in these patients was related to dry mouth and more acid pH of the saliva. In addition, the impact of mental impairment and joint and skeletal limitations on these individuals' manual dexterity contributed to poor dental hygiene [13].

Regarding vulnerability to dental caries, individuals with MPS are approximately three times more likely to develop caries than healthy individuals. The physical limitations and motor impairment of these patients lead to dependence concerning daily activities such as oral hygiene, performing them inappropriately or infrequently [23]. In contrast and reinforcing a causal relationship with the disease, patients with MPS with good hygiene and parental involvement also had dental caries [17].

Regarding periodontal evaluation, patients presented gingival inflammation and accumulation of dental calculus due to poor oral hygiene [12, 14, 16, 19]. In addition, significant gingival hyperplasias were observed in the areas of unerupted teeth [10]. Concerning dental morphology changes, anomalies in structure, number, size and shape were observed [10, 12, 14, 16, 18-22, 24, 25].

Structural changes in tooth enamel, both in primary and permanent dentition, were observed by Khan *et al.* [24] and Al-Jawad *et al.* [25] using synchrotron radiation and electron microscopy techniques. In patients with MPS I, abnormalities were observed during mineralization of the enamel matrix. The presence of a poorly calcified layer between the enamel and the dentin, at the amelodentary junction (ADJ), makes the structure in this region weak and susceptible to fractures. The enamel is hypoplastic and easily detachable from the underlying dentin. This lack of integration in ADJ is indicative of the lack of specific sulfatase to remove local GAGs from dentinal tubules [24, 25].

Significant differences in enamel texture distribution were seen in patients with MPS types II and IVA. In a healthy enamel, the crystals present in the cusp region are well aligned while in a deeper region the crystals are less ordered due to the change in configuration in the orientation of the prisms towards the ADJ. In individuals with MPS, the distribution is characterized by a constant gradation of the crystals over the entire thickness of the tooth [24, 25].

In clinical examinations, enamel hypoplasia was regularly observed in patients with MPS IV [14, 16, 18, 21, 22].

Among the shape anomalies, taurodontism was the most recurrent change [12, 13, 19, 22], being common in the first and second permanent molars in MPS VII [12, 19]. In addition, it showed a high prevalence in individuals with MPS VI, due to the accumulation of dermatan sulfate that affects growth factors. Another found modification was the presence of conoid teeth [10, 18].

In relation to number and size anomalies, the presence of supernumerary teeth, dental agenesis and microdontia have been reported [10, 19, 20, 22]. In patients with MPS I after hematopoietic stem cell transplantation, it was observed the development of these anomalies, that were related with the treatment [22].

Changes in pulp chambers and periapical tissues have been reported by Kantaputra *et al.* [12] and Wadenya *et al.* [18]. Among these changes are the broad root spaces, obliterated pulp chambers and interrupted root development.

As for otorhinolaryngological involvement, patients with MPS may have an accumulation of GAGs in the upper airways and neck. As a result, there is adenotonsillar hypertrophy that leads to airway obstruction and obstructive sleep apnea syndrome (OSAS), decreasing the life quality of these individuals [8, 10].

Sinus and lower tract infections are also common, secondary to an enlarged amygdala, adenoid and tongue [10, 17]. In addition, hearing loss is frequent due to otitis media with effusion [8] and earaches related to TMDs [10].

#### 4. Dental management of patients with mucopolysaccharidoses

Dental management of patients with MPS focuses on guidelines for health promotion and prevention of oral diseases. The following actions have been reported: dental evaluation and prophylaxis every six months, oral hygiene instructions, pit and fissure sealants, dietary advice, and topical fluoride application [14, 17, 18].

The emphasis must be on oral hygiene and on prevention of problems that require invasive procedures [10]. In this sense, it is essential to educate and motivate patients, but also parents and guardians, for good oral hygiene to reduce the incidence of caries and gingival inflammation [13, 16, 17]. When there are preventive failures, the treatment plan must be formulated based on the patient's complaints and his systemic condition [15].

In the curative treatment of oral and craniofacial changes, care is mainly symptomatic. Among interventional procedures are restorative treatment [10, 17, 20], endodontic treatment of teeth with irreversible pulpitis [20] and extraction of retained primary teeth [15]. Complex procedures that require sedation or general anesthesia can be at high risk due to the various cardiorespiratory problems [10, 13, 20].

It is recommended to evaluate mandibular movements to identify signs and symptoms of TMD in patients with MPS, especially with MPS VI who are most severely affected [21]. In addition, orthodontic treatments and prosthetic replacements aim, respectively, at adequate control of the eruption pathways and the restoration of occlusion with improved quality of life [14, 18].

In the dental treatment of patients with MPS, other factors were also considered, such as the individual's degree of mental deficiency and difficulty in clear communication, the presence of convulsive disorders that impair the care and the degree of joint stiffness, which hinder the performance of procedures and cause discomfort to the patient. In addition, the need for antimicrobial prophylaxis was stressed, as

patients with MPS are part of a group at high risk for bacterial endocarditis [20].

In airway obstructions and OSAS due to adenotonsillar hypertrophy, patients can benefit from adenotonsillectomy to which OSAS improves significantly. However, in some cases the obstruction may require endotracheal intubation. In cases of hearing loss due to otitis media by effusion, the treatment is the insertion of a ventilation tube [8].

#### 5. Discussion

According with the literature, studies on oral and craniofacial manifestations of MPS patients are still not widespread, being most of them clinical case reports. By proceeding to a systematic observation of the relationship between oral problems acquired by the accumulation of GAGs and the proper management of these patients, there are still gaps to be filled. With this aim, prospective cohort studies with a control group that are based on elucidating possible causal relationships between MPS and oral problems may be relevant [13], as well as multicenter clinical trials in groups of patients with MPS [26].

The little disclosure about these disorders can also discourage professionals in the treatment of these patients, in addition to decreasing the chances of an early diagnosis and correct referral. It is well known that the comprehensive care of patients with MPS is based on multidisciplinary, as well as the alignment of communication between the involved professionals. Torres *et al.* [14] warn of the lack of qualified professionals to care for these patients who require special care.

The starting point for health promotion in patients with MPS is early diagnosis. Family screening for the disease and treatment at a young age promotes a significant reduction in the accumulation of GAGs and, consequently, in the progression of morphological and neurological changes [14, 19]. Hematopoietic cell transplant therapy from the umbilical cord, for example, modified the course of the disease in a patient with MPS II, providing sufficient enzyme activity to alter the progression of symptoms and attenuating typical facial dysmorphism [14].

Knowledge of oral and craniofacial manifestations of MPS is also relevant in clinical practice, since when installed, they can serve as pathognomonic characteristics of the disease and allow referral to the pediatrician in advance [15, 19]. In addition, the oral assessment must be continued to detect any new health impairment [14].

This review allows to recognize the role of the dental doctor in identifying these changes for diagnosis purposes, but also in preventive oral actions and dental intervention that minimizes the severity of the established problem and avoids undesirable complications [13, 16]. In general, it was observed that oral management of a preventive nature has as priority the improvement of oral hygiene and non-invasive dental care such as dental prophylaxis, periodic evaluations, dietary advice, sealing of fissures and the topic application of fluoride [14, 17, 18].

These patients are more vulnerable to oral problems due to the limitations imposed by the disease, such as motor and cognitive difficulties [23]. From this point of view, the maintenance of oral hygiene for these patients is causally related to the education and awareness of parents or guardians. It is suggested that professionals demonstrate brushing techniques, reinforce the need to use fluoridated toothpaste, in addition to the use of dental floss to prevent caries and gum disease. The patient should also be

encouraged to use brushes suitable for his needs.

The importance of this preventive care is evident in data regarding the high levels of dental caries and periodontal disease reported in these patients [12, 17, 20, 23]. Dental care carried out as soon as possible can help to anticipate the onset or worsening of these problems, in addition to providing an environment for changing habits in oral health that can be perpetuated throughout the patient's life. In this perspective, Tatapudi *et al.* [17] suggested the development of new research addressing determinant causes of dental caries in patients with MPS having good oral hygiene.

When interventional treatment in oral and craniofacial manifestations becomes necessary, dental treatment strategy must consider the general health condition of the patient with MPS and attention must be focused on the cardiorespiratory, musculoskeletal, and neurological problems presented. In addition, the patient's complaints should be evaluated. Moreover, Yoon *et al.* [20] highlight the need for antibiotic prophylaxis in some procedures, to prevent endocarditis.

More complex dental treatments or more aggressive surgeries are not recommended, due to the need for sedation or general anesthesia, being a life risk for the patient, due to the difficulty of clearing the airways and cardiac involvement [10, 13, 18, 20].

The manifestations relevant to TMDs, such as headache and pain [10, 21], can affect many of these patients due to common TMJ changes. Thus, it is suggested that dental doctors are aware of these dysfunctions so that the referral to the TMD specialist is carried out. These professionals are prepared for advice on controlling symptoms and, therefore, improving the patient's quality of life.

## 6. Conclusions

The description of oral and craniofacial manifestations in patients with MPS is based on the increased specific knowledge about the disease. The results and discussions of this review corroborate the statement that recognizing these changes can help to make an early diagnosis and, therefore, prior referral to therapeutic resources and prevention of systemic worsening.

In the dental management of patients with MPS, preventive and interceptive actions in oral health aim to improve oral hygiene and reduce oral problems to avoid future complications.

The obtained data also allow to suggest new research of a prospective character, which systematize the causal relationships in oral health, or multicentric research in MPS. In addition, the importance of continuing education for health professionals and the need to improve care for patients with MPS is emphasized, considering the quality of life and comprehensiveness of their needs.

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