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Oral manifestations of mucopolysaccharidosis

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Abstract

Mucopolysaccharidosis (MPS) represent a heterogeneous group of rare, inherited metabolic disorders characterized by progressive multisystem involvement and substantial morbidity. Among the affected organ systems, the oral and craniofacial region is frequently involved and may provide early and valuable diagnostic clues, particularly in pediatric patients. Dental professionals therefore play a crucial role in the early recognition, diagnosis, and multidisciplinary management of individuals with MPS. Understanding the underlying mechanisms responsible for oral findings is essential for improving patient outcomes and tailoring dental care strategies. MPS constitutes a group of genetically inherited lysosomal storage disorders marked by deficiencies in specific enzymes critical for the catabolism of glycosaminoglycans (GAGs). The enzymatic insufficiency results in the progressive accumulation of GAGs within cellular and extracellular compartments across multiple tissues, manifesting in a diverse array of clinical phenotypes. Notably, individuals with MPS often present with pronounced oral and dental abnormalities, which can serve as significant indicators for early diagnosis and clinical management. This review investigates the pathophysiological mechanisms driving oral abnormalities in MPS, examining their diagnostic significance and potential for therapeutic intervention. Common findings include gingival hypertrophy, delayed tooth eruption, enamel hypoplasia, macroglossia, malocclusion, and craniofacial skeletal abnormalities, all of which may complicate oral hygiene and dental treatment. Additionally, radiographic features and challenges related to anesthesia and behavior management are discussed. By highlighting the diagnostic relevance of oral findings and the importance of early dental involvement within a multidisciplinary care framework, this review aims to raise awareness among dental practitioners and contribute to improved quality of life for patients with MPS.

Keywords: Mucopolysaccharidosis, glycosaminoglycan, dental findings, oral manifestations, dental management, pediatric dentistry

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1. Introduction

Mucopolysaccharidosis (MPS) encompasses a group of inherited lysosomal storage disorders arising from deficiencies in enzymes essential for the degradation of glycosaminoglycans (GAGs) (1). These GAGs (dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate) are complex macromolecules integral to connective tissue and contribute significantly to structural integrity and cellular function. In individuals with MPS, the absence or malfunction of specific lysosomal enzymes leads to the progressive pathological accumulation of GAGs in multiple tissues, resulting in multisystemic effects (1-3). Among these, oral and craniofacial abnormalities are prominent in most MPS subtypes and constitute key diagnostic features that often correlate with substantial morbidity, underscoring their clinical significance (4, 5).

The overall incidence of MPS is estimated to be approximately 1/25,000 live births (6). This chapter focuses on the oral manifestations associated with MPS, particularly their underlying pathophysiological mechanisms, clinical presentation, and implications for dental management within a multidisciplinary care framework. Oral findings will be systematically examined across the major MPS subtypes, highlighting the phenotypic diversity and unique clinical challenges these disorders present to dental practitioners.

2. The subtypes of MPS

MPS is categorized into distinct subtypes (I, II, III, IV, VI, VII, and IX) based on the specific lysosomal enzyme deficiency underlying each condition. Type II is linked to the X chromosome, whereas all other types are autosomal recessive disorders (7, 8).

- **MPS I (Hurler, Hurler-Scheie, and Scheie Syndromes):** Deficiency of alpha-L-iduronidase.
- **MPS II (Hunter Syndrome):** Deficiency in iduronate-2-sulfatase.
- **MPS III (Sanfilippo Syndrome):** Deficiency of enzymes involved in A: Heparan-N-sulfate degradation, B: α-N-acetylglucosaminidase, C: Acetyl-CoA-α-glucosaminidase, D: N-acetylglucosamine 6-Sulfatase, E: N-glucosamine-3-O-sulfatase.
- **MPS IV (Morquio Syndrome):** Deficiency of enzymes involved in A: galactose-6-sulfatase, B: beta-galactosidase.
- **MPS VI (Maroteaux-Lamy Syndrome):** Deficiency of enzymes involved in N-acetylgalactosamine 4-sulfate (Arylsulfatase B).
- **MPS VII (Sly Syndrome):** Deficiency of beta-glucuronidase.
- **MPS IX (Natowicz Syndrome):** Deficiency of hyaluronidase (7, 8).

These subtypes vary in severity, age of onset, and the extent of systemic involvement. Although clinical features may differ, oral manifestations are frequently present in mucopolysaccharidosis disorders (7).

3. Pathophysiology of oral manifestations

The oral manifestations of Mucopolysaccharidosis primarily result from excessive glycosaminoglycan deposition within the connective tissues, culminating in aberrant growth and morphogenesis of oral and dental structures (1, 2).

Persistent intracellular and extracellular accumulation of GAGs disrupts standard cellular processes, resulting in soft tissue hypertrophy, skeletal deformities, and compromised odontogenesis. This pathophysiological process is intrinsically linked to the specific enzymatic deficiency underlying each MPS subtype, where the inability to catabolize particular GAGs leads to progressive structural and functional impairments in craniofacial and dental tissues (3, 4).

GAG accumulation affects multiple structures in the oral cavity, including:

- **Periodontal Tissues:** Gingival hypertrophy due to connective tissue infiltration with GAGs (Fig. 1A, 1B)
- **Dental Pulp:** Enlargement and changes in the dental pulp morphology (Fig. 2).
- **Teeth:** Delayed eruption, abnormal morphology, and enamel hypoplasia (Fig. 1A, 1B, Fig. 2)
- **Maxilla and Mandible:** Skeletal changes, such as mandibular hypoplasia and maxillary underdevelopment. Radiographs may show a hypoplastic or thickened mandibular ramus, abnormal mandibular condyles, and the development of cysts and tumors (Fig. 2).
- **Tongue and Palate:** Macroglossia and high-arched palate development (Fig. 1A).
- **Delayed Tooth Eruption:** Teeth may exhibit delayed eruption, with retained primary teeth or impacted permanent teeth, reflecting the abnormal bone metabolism associated with MPS (Fig. 2).
- **Enlarged Dental Follicles:** Radiographs may show enlarged dental follicles, particularly around unerupted teeth (Fig. 2).
- **Thickened Lamina Dura:** There may be noticeable thickening of the lamina dura (Fig. 2).
- **Decreased Bone Density:** Bone in the jaws often appears radiolucent or less dense, reflecting systemic bone metabolism issues associated with the disease (Fig. 2).
- **Root Resorption and Malalignment:** Roots may undergo resorption prematurely, and teeth are often

misaligned, which can impact occlusion and necessitate orthodontic or surgical interventions (Fig. 2) (1-5).

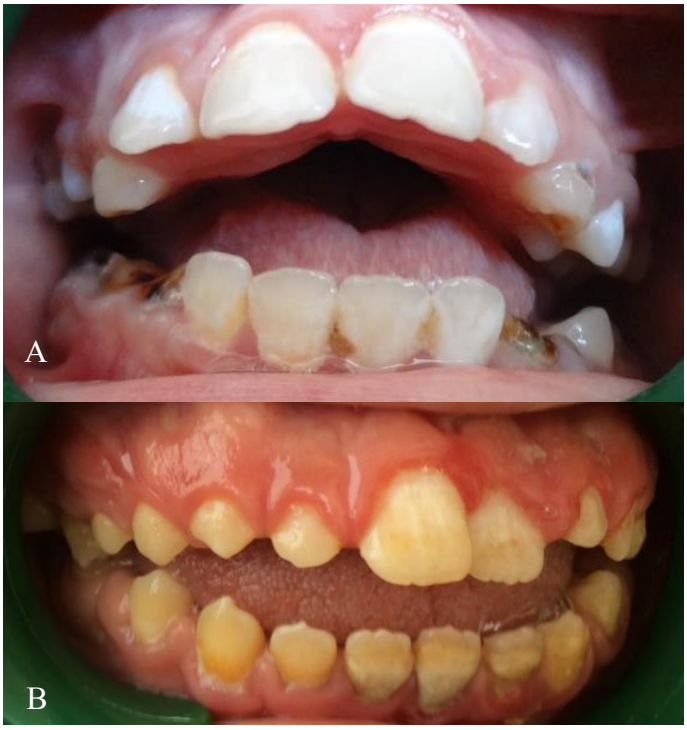

Figure 1. Intraoral findings of MPS. **(A)** Abnormal morphology and enamel hypoplasia, **(B)** Gingival hypertrophy and enamel hypoplasia.

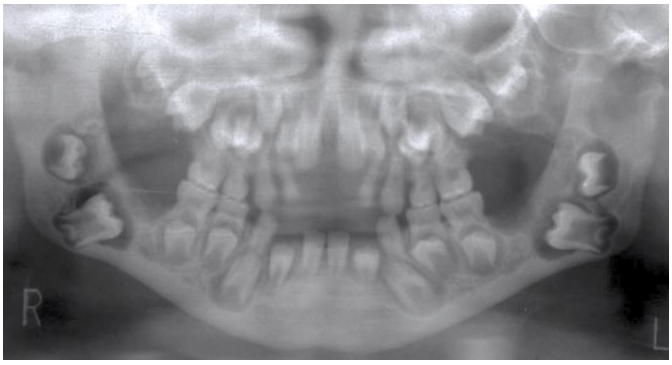

Figure 2. Radiographic findings of MPS.

4. Oral manifestations in specific mps subtypes

4.1. MPS I (Hurler, Hurler-Scheie, Scheie Syndromes)

Patients with MPS I often present with significant craniofacial and oral abnormalities. Gingival hypertrophy is a hallmark feature caused by the accumulation of GAGs in the gingival connective tissues. This leads to a "pebbled" appearance of the gingiva, often coupled with reduced oral hygiene capacity. Macroglossia is frequently observed and contributes to feeding difficulties and speech impairments. Dental anomalies, including delayed tooth eruption and hypoplastic enamel, as well as mandibular hypoplasia, are common, resulting in malocclusion and difficulties in mastication. A high palate is also a typical finding in MPS I patients (9).

4.2. MPS II (Hunter Syndrome)

Similar to MPS I, patients with MPS II exhibit gingival hypertrophy and macroglossia. Malocclusion due to mandibular underdevelopment and a high palate are often present. Delayed tooth eruption and abnormal tooth morphology, including large dental pulp chambers, are frequently observed in these patients. Patients with Hunter syndrome may also have an increased risk of periodontitis, possibly related to poor oral hygiene caused by limited mobility and difficulties associated with maintaining oral cleanliness due to soft tissue overgrowth (10).

4.3. MPS III (Sanfilippo Syndrome)

The oral manifestations of MPS III tend to be milder compared to other MPS subtypes. Gingival hypertrophy and delayed tooth eruption are present, but macroglossia is less pronounced. The skeletal changes affecting the jaw and palate are generally less severe. Cognitive decline in MPS III often makes cooperation with dental treatment more challenging, underscoring the importance of early diagnosis and proactive management (11).

4.4. MPS IV (Morquio Syndrome)

In Morquio syndrome, skeletal abnormalities are more pronounced than soft tissue manifestations. Patients often present with significant mandibular hypoplasia and severe malocclusion due to the underdevelopment of the maxilla and mandible. A high palate and malocclusion are also common. Unlike other MPS subtypes, gingival hypertrophy and macroglossia are not prominent features of MPS IV. These patients may also experience premature tooth loss, likely secondary to systemic skeletal abnormalities that affect bone density and support structures (12).

4.5. MPS VI (Maroteaux-Lamy Syndrome)

Patients with MPS VI commonly exhibit severe gingival hypertrophy, which can obscure teeth and complicate oral hygiene. Macroglossia, delayed tooth eruption, and abnormal tooth shape are frequently reported. Malocclusion, particularly due to mandibular hypoplasia, is another common finding in this syndrome. The progressive nature of these oral manifestations often necessitates early dental intervention to manage the complications (13).

4.6. MPS VII (Sly Syndrome)

The oral manifestations of MPS VII closely resemble those seen in MPS I and II, with significant gingival hypertrophy, macroglossia, and delayed tooth eruption. Malocclusion is also a common finding (14).

4.7. MPS IX (Natowicz Syndrome)

The oral manifestations of MPS IX are distinctive and include hypertrophic gingival tissues, malocclusion, and delayed tooth eruption. Patients may also exhibit increased susceptibility to dental caries due to compromised enamel and dentin integrity. Radiographically, the features may include thickened gingiva and irregular alveolar bone morphology, reflecting the broader skeletal and soft tissue involvement characteristic of this syndrome (15).

5. Clinical implications for dental management

The oral manifestations of MPS can significantly impact the quality of life for affected individuals, making effective dental management an essential component of care (1-5). Regular dental evaluations should be integrated into the comprehensive management plan for patients with MPS, focusing on preventing and managing oral complications (16-20).

Specific considerations include the following:

Oral Hygiene Maintenance: Gingival hypertrophy and malocclusion increase the risk of periodontal disease and dental caries. Patients may require tailored oral hygiene regimens, including professional cleaning, fluoride treatments, and antimicrobial mouth rinses.

Orthodontic Management: The skeletal abnormalities observed in patients with MPS often necessitate orthodontic treatment. However, the severity of jaw deformities and the progressive nature of the disease may complicate traditional orthodontic approaches.

Surgical Intervention: In cases of severe gingival hypertrophy or macroglossia, surgical intervention may be required to improve oral function, speech, and aesthetics. Collaboration with oral and maxillofacial surgeons is critical for addressing these complex cases.

Anesthesia Considerations: Macroglossia and craniofacial abnormalities can complicate airway management during dental procedures. Sedation and general anesthesia protocols should be carefully planned with the input of anesthesiologists familiar with the MPS.

Multidisciplinary Care: Given the multisystem involvement of MPS, dental care must be coordinated with other healthcare providers, including geneticists, pediatricians, and orthopedic specialists. Interdisciplinary collaboration is key to optimizing patient outcomes (16-20).

6. Conclusion

The oral manifestations of Mucopolysaccharidosis are diverse and often reflect the broader systemic involvement of the disease. Dentists and healthcare providers should be aware of the characteristic oral and craniofacial features associated with these disorders, as they play a critical role in diagnosis and patient management. Early detection and intervention can improve the quality of life for mucopolysaccharidosis patients, emphasizing the importance of interdisciplinary collaboration in their care. Further research on therapeutic approaches targeting oral complications of mucopolysaccharidosis is needed to optimize treatment outcomes.

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