

# Oral manifestation and dental treatment of pediatric patient with beta-mannosidosis: A case report

SAGE Open Medical Case Reports  
Volume 9: 1–7  
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DOI: 10.1177/2050313X211065796  
journals.sagepub.com/home/sco



Mohammad A Alshoraim<sup>1</sup> and Dania E Al Agili<sup>2</sup> 

## Abstract

$\beta$ -mannosidosis is a rare autosomal recessive lysosomal storage disease of glycoprotein catabolism caused by a deficiency of  $\beta$ -mannosidase. Clinical presentation includes intellectual deficits, hearing loss, and recurrent respiratory infections. This report describes the dental treatment and follow-up dental care of a child with  $\beta$ -mannosidosis. The patient presented to the dental clinic at the age of 6 years with a localized swelling of his lower posterior teeth. Sickle cell disease and physical and mental developmental delays were noted. Clinical examination revealed a flattened nasal bridge, large head, short neck, open bite, gingival overgrowth, macroglossia, enlarged pulp chambers, and poor oral hygiene. Surgical treatment under general anesthesia included extractions, pulp therapy, and restorations. Four years later, the child returned with generalized gingival inflammation and new carious lesions. Periodontal and restorative treatment was provided, and a preventive dental regimen was established. Mannosidosis cases require complex dental procedures, consultations, and prompt follow-up.

## Keywords

$\beta$ -mannosidosis,  $\beta$ -mannosidase, lysosomal storage diseases, pediatric dentistry, dental care for disabled, Saudi Arabia

Date received: 29 July 2021; accepted: 19 November 2021

## Introduction

$\beta$ -mannosidosis is a rare lysosomal storage disease (LSD) with an estimated incidence of 0.1 per 100,000.<sup>1,2</sup> It is an autosomal recessive condition characterized by a deficiency in the activity of the lysosomal enzyme  $\beta$ -mannosidase, and is often seen in consanguineous families.<sup>3,4</sup> It is caused by mutations in the MANBA gene (609489), which codes for  $\beta$ -mannosidase. Dysfunction in this enzyme results in the accumulation of mannose- $\beta$ -1-4-*N*-acetylglucosamine, which causes cytotoxicity. To date, 23 cases have been reported in the literature since it was first described in humans in 1986.<sup>5</sup> LSDs are usually progressive, and treatment is often supportive, though disease progression can be slowed occasionally.<sup>5,6</sup>

The clinical presentation of  $\beta$ -mannosidosis is heterogeneous. Intellectual disability is the most widely reported symptom; however, the extent of this disability varies between patients. Magnetic resonance imaging (MRI) scans reveal cortical and subcortical atrophy<sup>3-5,7-12</sup> and neurological symptoms include demyelinating neuropathy, spinocerebellar ataxia, hydrocephalus, and recurrent seizures.<sup>3,7,13,14</sup> Some patients exhibit behavioral problems, including hyperactivity and “aggressiveness.”<sup>4,5,8</sup> Hearing loss, flattening of the nasal

bridge, macroglossia, and brachycephaly have all been observed in patients with  $\beta$ -mannosidosis.<sup>5,7,8,13</sup> Rarer symptoms include recurrent respiratory infections and angiokeratoma corporis diffusum.<sup>5</sup> Diagnosis of  $\beta$ -mannosidosis is usually confirmed with lysosomal enzyme activity tests and whole-exome sequencing (WES).<sup>2,4,7,11-13,15</sup>

Patients with LSD are at high risk of having inadequate oral hygiene, caries, and poor gingival health.<sup>16</sup> Impairment in the development of multiple tissues including teeth, bone, and cartilage as a result of accumulation of glucuronic acid-containing glycosaminoglycans (GAGs) is reported in mucopolysaccharidoses (MPS), which are part of the LSD family.<sup>17,18</sup> Patients with mucopolysaccharidosis type VI, typically have

<sup>1</sup>Department of Pediatric Dentistry, East Jeddah General Hospital, Jeddah, Saudi Arabia

<sup>2</sup>Department of Dental Public Health, Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia

## Corresponding Author:

Dania E Al Agili, Department of Dental Public Health, Faculty of Dentistry, King Abdulaziz University, P.O. Box 80200, Jeddah 21589, Saudi Arabia.

Email: dalagili@yahoo.com





**Figure 1.** Extra-oral photographs of the patient. (a &c): extra-oral frontal views show prominent forehead, short neck, rounded eyebrows, and incompetent lips. (b&d) extra-oral lateral views show flattened nasal bridge, macrocephaly, and large ears.

malformed roots, macroglossia, large dental follicles, maxillary hypoplasia, mandibular prognathism, anterior open bite, and hypoplastic mandibular condyles.<sup>17</sup> The oral and dental manifestations of  $\beta$ -mannosidosis have not been reported in the literature. In this article, we describe the dental treatments and follow-up care of a child with  $\beta$ -mannosidosis who presented to the dental clinic at the age of 6 years with a localized swelling of his lower posterior teeth.

### Case description

The patient, a male child, presented to the dental clinic for the first time at the age of 6 years complaining of severe intra-oral pain in the lower left quadrant. The child was born to second-degree consanguineous parents. He was diagnosed with sickle cell disease (SCD) at the age of 6 months. Physical and mental developmental delays were noticed along with problems with vision and hearing, suggestive of an LSD. Results of lysosomal enzyme activity tests were characteristic of  $\beta$ -mannosidosis. At the age of 5 years, WES had confirmed the diagnosis. The patient received blood transfusions regularly for SCD. Around the same time, the patient had a splenectomy, tonsillectomy, and insertion of a tympanotube. During this time, he was under Oспен, Ferimap-XT, Exjade, and vitamin D supplements.

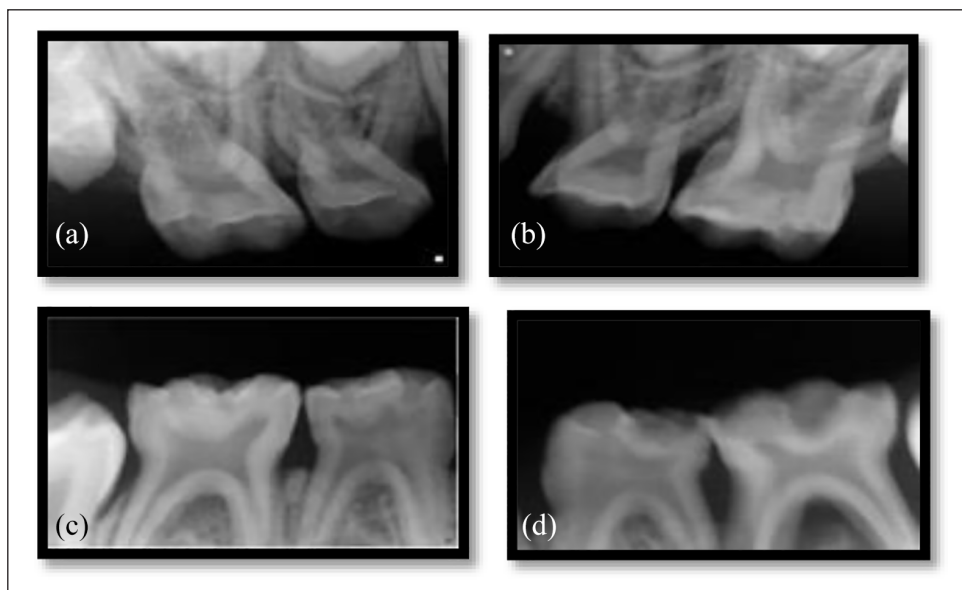
Past dental history included topical fluoride application, plaque removal, and oral hygiene instructions. The behavior of the child was classified as “lacking cooperative ability” according to Wright and Kupietzky’s<sup>19</sup> classification. Flattened nasal bridge, macrocephaly, prominent forehead, short neck,

large ears, and rounded eyebrows were observed (Figure 1). The patient was below the fifth percentile for height and weight according to the National Center for Health Statistics (NCHS) growth charts.<sup>20</sup> He had significant plaque accumulation, multiple carious teeth, and a dental abscess related to the lower left primary molars. In addition, the patient had an anterior open bite, gingival overgrowth, macroglossia, malocclusion, widely spaced teeth, and incompetent lips (Figure 2). Oral radiographs showed enlarged pulp chambers (Figure 3).

The basic behavior guidance technique, tell-show-do, was used in the initial dental examination visit. However, due to poor cooperation and low hemoglobin level (8.3 g/dL), it was decided that the restorative treatment would be best completed in one visit under general anesthesia (GA). The patient was admitted 1 day before the surgery and received an intravenous transfusion of 180 ml of packed red blood cells, in addition to his normal oral medications. After a pre-operative assessment, induction of GA via oral intubation was performed. The upper right second primary molar and lower right first primary molar had reversible pulpitis; therefore, mineral trioxide aggregate (MTA) pulpotomies were performed and the teeth were restored with stainless steel crowns (SSCs). Composite resin restorations and fissure sealants were placed in restorable teeth and extractions were performed on the lower left primary molars. The patient was discharged when he became fully alert and stable. He returned 1 week later for his postoperative follow-up (Figure 4). At the 6-month follow-up visit, the restorations were intact, soft tissues were healthy, and no caries were detected.



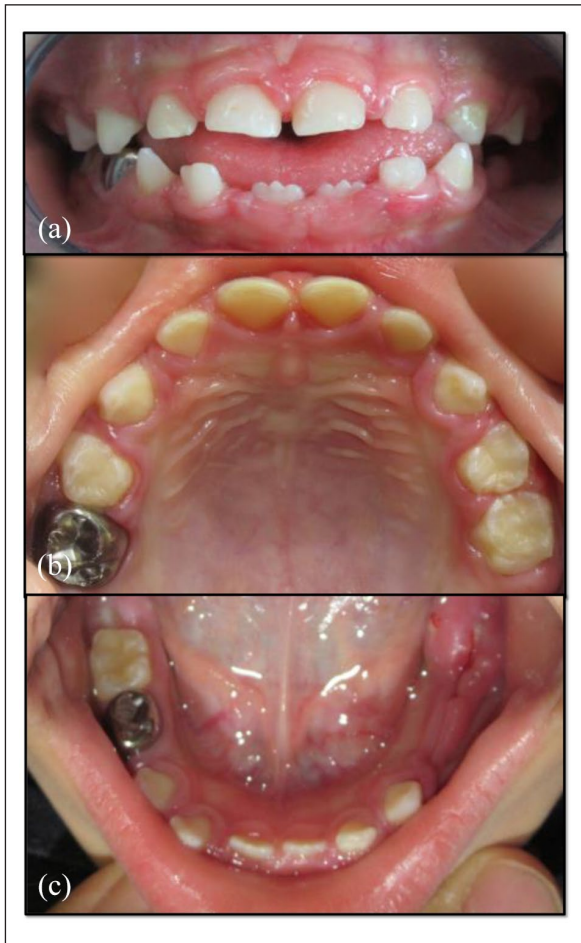
**Figure 2.** Pre-dental treatment intra-oral photographs. (a) and (b) Right and left frontal views show gingival overgrowth, macroglossia, widely spaced teeth, malocclusion, and anterior open bite. (c) Maxillary occlusal view shows generalized marginal gingivitis around widely spaced primary dentition. (d) Mandibular occlusal view shows dentoalveolar abscess related to lower primary molars and multiple carious lesions in primary molars.



**Figure 3.** Peri-apical radiographs of all quadrants showing enlarged pulp chambers of all primary molars. (a & b) Upper right and upper left posterior periapical radiographs, respectively. (c) lower right periapical radiograph shows proximal caries related to lower right first primary molar. (d) lower left periapical radiograph shows dento-alveolar abscess related to lower left primary molars.

Because the patient's family moved to another city, the patient did not return for annual or later recall visits. At the age of 10 years, the patient returned complaining of gingival swelling. His medical condition was stable, and his medications were unchanged, except for the addition of an angiotensin-converting enzyme inhibitor (ACEi) due to a new finding of hypertension. Oral examination revealed high plaque index, multiple new carious lesions, and drug-induced gingival

overgrowth (DIGO). To resolve the DIGO, ACEi was changed to another antihypertensive drug following a consultation with his cardiologist. The dental management included oral scaling, root planing, and polishing to remove plaque and calculus. Improvements in patient's behavior enabled restoring his carious lesions under local anesthesia, as opposed to GA, in the subsequent visits. An SSC was placed on the upper left first primary molar and composite restorations of all first



**Figure 4.** Intra-oral photographs of postdental treatment. (a) Frontal view shows improvement of gingival health and erupting of permanent anterior central incisors. (b) Maxillary occlusal view shows stainless steel crown on upper right second primary molar. (c) Mandibular occlusal view shows stainless steel crown on lower right first primary molar, partial healing of extraction sockets, and initiation of eruption of lower permanent first molars.

permanent molars were performed under cotton-roll isolation and high suction aspiration. Oral rinsing by 0.12% chlorhexidine gluconate solution twice daily for 30s after toothbrushing was prescribed for 2 weeks. A cephalometric radiograph was obtained, and analysis showed a convex profile with bimaxillary protrusion, upper and lower teeth protrusion and proclination, class II skeletal with steep mandibular plane, and retruded chin. Figures 5–7 show the panoramic, periapical, and cephalometric radiographs of the patient at the age of 10 years. A written informed consent was obtained from the parent of the patient for publication. An ethical approval was not required for publishing the case report.

## Discussion

To the best of our knowledge, this is the first case report that describes the dental treatments and follow-up care in a pediatric patient with  $\beta$ -mannosidosis. Because  $\beta$ -mannosidosis is

progressive, more symptoms are expected as patient's age.<sup>3,7</sup> In a reported case of  $\beta$ -mannosidosis, spastic tetraparesis and cerebellar ataxia, present at the age of 12 years, progressed to tetraplegia, dysphagia, and dysarthria by the age of 26.<sup>21</sup> In addition, the clinical presentation of  $\beta$ -mannosidosis varies between cases. Our patient's sister displayed less severe clinical manifestations, despite having a lower  $\beta$ -mannosidase enzyme activity. This heterogeneous manifestation is also described in a case report of  $\beta$ -mannosidosis in a male patient and his younger sister. The sister, who died at the age of 20 years, exhibited severe facial dysmorphism, mental retardation, hearing impairment, and recurrent infections, while her brother exhibited only mild manifestations despite having an absolutely deficient level of  $\beta$ -mannosidase activity.<sup>8</sup> The literature reports no correlation between the levels of  $\beta$ -mannosidase activity and the severity of the condition; however, the expression of another lysosomal enzyme, glycosidase chitobiase, may explain the variation in severity. It partially compensates for the lack of  $\beta$ -mannosidase activity by participating in the degradation of *N*-linked oligosaccharides. The location of the MANBA gene mutation may also contribute to the spectrum of presentation.<sup>22</sup>

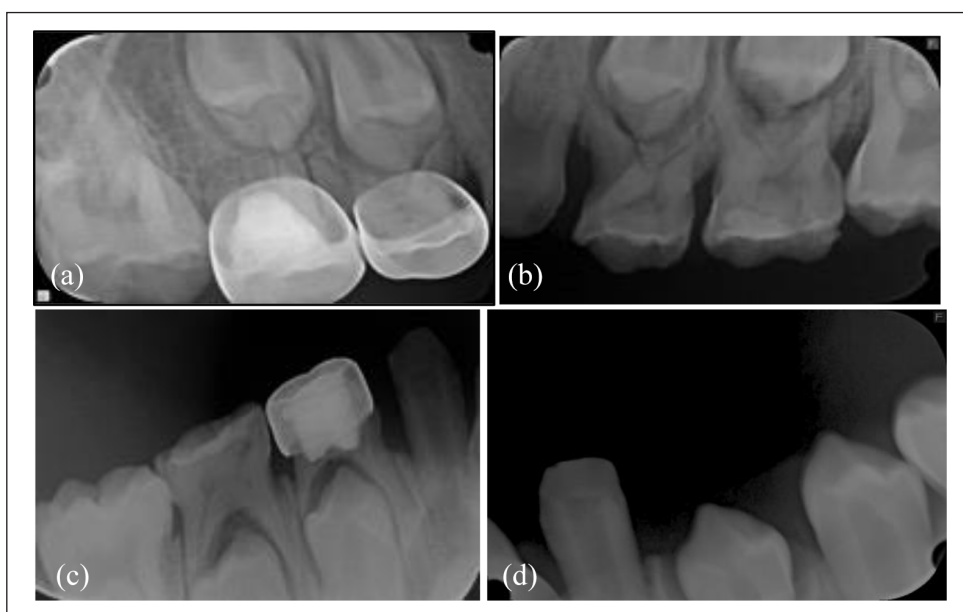
The complex medical condition, the extent of dental work, and the young age of our patient required pharmacological behavior management, such as the use of GA, to restore his oral health at the age of 6. At the age of 10, when the patient returned for a checkup visit, there was a clear improvement in behavior, which enabled us to complete the needed dental treatment in the clinic over subsequent dental visits. This decline in dental behavior management problems may reflect a previously established dentist–patient relationship and normal psychological development.<sup>23,24</sup>

Malocclusion, anterior open bite, and incompetent lips are oral features commonly found in other LSD patients,<sup>17</sup> and macroglossia and gingival hyperplasia were previously reported in a  $\beta$ -mannosidosis case.<sup>8</sup> Macroglossia increases the risk of airway obstruction and can interfere with the mechanical removal of plaque.<sup>25</sup> Several reports in the literature showed that tongue reduction in patients with Beckwith–Wiedemann, Down's syndrome, or cystic hygroma improved airway, open bite, oral hygiene, swallowing, and articulation.<sup>26,27</sup> Anterior open bite in patients with MPS VI is thought to be a consequence of hypoplastic mandibular condyles, which results from excessive accumulation of GAGs. Although several reports in the literature showed that enzymatic treatment of MPS patients at an early age inhibited the accumulation of mucopolysaccharides, and hence the development of an open bite,<sup>17</sup> the results were inconclusive.<sup>18</sup> In our case, orthodontic treatment is a worthwhile option and will be considered when all permanent teeth have fully erupted to restore oral health function, improve esthetics, and facilitate better oral hygiene practice.

LSD patients have up to five times poorer oral health compared to healthy patients.<sup>16</sup> The array of orodental features, in addition to cognitive and physical impairments, makes it difficult for these patients to practice proper oral hygiene and



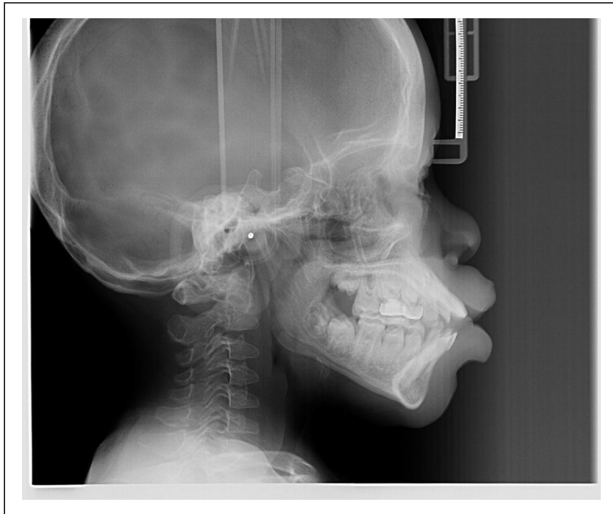
**Figure 5.** Panoramic radiograph of the patient in the last follow-up visit, at the age of 10 years. He is in mixed dentition phase with normal development of teeth. Failure of exfoliation of upper primary lateral incisors is noticed regardless of eruption of permanent lateral incisors.



**Figure 6.** Peri-apical radiographs of the patient in the last follow-up visit, age 10 years. All the radiographs shows diminished pulp chamber size of all remaining primary molars compared to intra-oral radiographs at age 6 years and shows physiological root resorption of primary molars due to eruption of premolars. (a) Upper right posterior periapical radiograph shows intact stainless steel crowns (SSCs) of the two primary molars. (b) Upper left posterior periapical radiograph, shows sound primary molars. (c) lower right periapical radiograph shows intact pulp therapy and SSC related to lower right first primary molar. (d) lower left periapical radiographs shows eruption of the two premolars.

increase their risk for developing oral disease. The increased size of pulp chambers and root canal spaces, commonly seen in LSD patients,<sup>17</sup> increases the risk of pathological or accidental pulp exposure, even in the restoration of early carious lesions. Careful access opening is important, since excessive hemorrhage from teeth pulp may be mistaken for a perforation.<sup>28</sup> Obturating materials used for pulpectomy in primary teeth, such as calcium hydroxide and iodoform paste, should

be recommended over zinc oxide eugenol (ZOE). Delayed resorption, if extruded from the apex, and delayed natural exfoliation of the tooth are among the concerns reported with the use of traditional ZOE.<sup>29</sup> Dentists should be aware of all of the orodental manifestations and the possible complications that may arise before they initiate dental treatment. Important findings that have implications on dental treatment are behavioral problems and orofacial dysmorphism.



**Figure 7.** A cephalometric radiograph of the patient at the age of 10 years showing a convex profile with bimaxillary protrusion, upper and lower teeth protrusion and proclination, class II skeletal with steep mandibular plane, and retruded chin.

Our study provides an educational and in-depth understanding of the oral and dental manifestations and dental management of patients with  $\beta$ -mannosidosis. However, as with most case reports, our study has limitations. Lack of generalizability, difficulty in establishing a causal relationship, and possibly over-interpretation are among those limitations.<sup>30</sup>

## Conclusion

$\beta$ -mannosidosis is a rare LSD with heterogeneous manifestations. Patients with  $\beta$ -mannosidosis have distinctive orofacial features and a range of behavioral problems such as hyperactivity, impulsivity, or aggressiveness, which require special care. A comprehensive oral care plan that includes regular conservative dental therapy is essential to prevent oral diseases, and hence avoid complex dental treatment. Motivating patients and caregivers to practice preventive oral care at home and to attend follow-up dental appointments is equally important.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

## ORCID iD

Dania E Al Agili  <https://orcid.org/0000-0002-0214-5479>

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