Dental Findings and Management in a Mucopolysaccharidosis Type IIIB Patient

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ABSTRACT

Mucopolysaccharidosis type IIIB (MPS IIIB) is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme a-N-acetylglucosaminidase. Affected subjects present developmental delay, attention deficit disorder, uncontrollable hyperactivity, and aggressive behavior, followed by progressive dementia and death in late adolescence. The purpose of this paper is to report the dental findings and treatment in a child with MPS IIIB. His primary molars and permanent mandibular incisors presented obliterated pulp chambers and root canals, which may be a clinical manifestation of this disorder. (J Dent Child 2012;79(3): 176-80)

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Mucopolysaccharidosis type III (**MPS III**), also known as Sanfilippo syndrome, is an autosomal recessive disorder caused by a deficiency in 1 of the 4 enzymes involved in the lysosomal degradation of heparan sulfate glycosaminoglycan. MPS III is the most frequently occurring type of the mucopolysaccharidoses.[1,2] A prevalence of 0.28 to 4.16 per 100,000 has been reported, the latter in the Netherlands.[1, 3] However, other researchers put it at 1.89 cases per 100,000 live Dutch births.[4]

Four different subtypes of MPS III are recognized, each due to the deficiency of a different enzyme: Type A - heparan N-sulfatase deficiency, Type B - alpha-N-acetylglucosaminidase deficiency, Type C - acetyl CoA: alpha-glucosaminide acetyltransferase deficiency, and Type D - N-acetylglucosamine 6-sulfatase deficiency.[5] In northern Europe, type A is the most common form of MPS III, whereas in Brazil, southern Europe, and Turkey, type B was found to be more prevalent.[2,6-8]

MPS IIIB is caused by a deficiency of the lysosomal enzyme α-N-acetylglucosaminidase (NAG), which catalyzes the removal of terminal α-N-acetylglucosamine residues from heparan sulfate. In the absence of NAG, the partially degraded heparan sulfate accumulates in the tissues and is excreted in the urine.[9] Affected subjects present with developmental delay, attention deficit disorder, uncontrollable hyperactivity, and aggressive behavior, followed by progressive dementia and death in the late adolescence, with pneumonia being its primary cause.[9]

Over 100 different mutations underlying MPS IIIB have been identified, including deletions, insertions, point mutations, and splicing site mutations.[10-13] The extensive allelic heterogeneity reflects the wide spectrum of clinical phenotypes reported in MPS IIIB patients.[3]

Although several types of therapies have been attempted for this disease, no effective treatment exists. As this disorder is characterized by severe intellectual disability with behavioral problems and only mild somatic disease,

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the main focus of treatment is the central nervous system. Several potential therapeutic approaches have been suggested, including enzyme replacement therapy, hematopoietic stem cell transplantion, gene therapy, substrate deprivation therapy, and enzyme enhancement therapy.[14,15]

Descriptions of the dental findings in MPS III patients are rare in the literature, and the only paper available dates back to the late 1970s.[16] The purpose of this paper is to report the dental findings and dental treatment of a child with MPS IIIB.

CASE REPORT

A 12-year-old boy diagnosed with MPS IIIB was brought to the Center for Dental Care for Special Needs Patients at the School of Dentistry, University of São Paulo at Ribeirao Preto, Brazil. He was the third child of healthy nonconsanguineous parents and was born at term after an uneventful pregnancy. His development was normal until 5 years of age, after which time a slow decline in development was observed. At 10 years of age, he stopped swallowing, requiring the use of a gastrostomy feeding tube. He was 100% tube-fed. The patient has frequent seizures which are well-controlled with carbamazepine 200 mg, topiramate 25 mg, and ranitidine 150 mg. His last seizure was at 9 years of age. All medications have to be ground, dissolved in water, and administered through the gastric tube.

Physical examination revealed the characteristic facies and presentation of mucopolysaccahridoses, including severe intellectual disability, short stature, scaphocephaly with moderate enlargement of the head, coarse facial features, sunken nasal bridge, hypertelorism, protruding philtrum, dark eyelashes, dry and coarse hair, and hypertrichosis (Figure 1A). Flexion deformities of the upper and lower extremities were evident, with minimal spade-shaped hand deformity (Figure 1B). Umbilical hernia, hepatomegaly, and splenomegaly were also found.

The intraoral examination at 12 years of age revealed over-retention of primary teeth and altered timing and sequence of tooth eruption, as the permanent first molars had not yet erupted. No unusual color, size, or shape of the teeth were seen. Poor oral hygiene was evident with heavy dental plaque and calculus deposits, generalized gingivitis, and multiple carious lesions (Figure 1C). Presence of heavy calculus was probably due to his poor oral hygiene and gastrostomy feeding.

Radiographic examination revealed complete obliteration of the pulp chambers and root canals of the primary molars, initial canal obliteration of the permanent mandibular incisors, possible dentigerous cysts associated with the permanent mandibular canines, agenesis of the mandibular right third molar germ and carious lesions in the primary molars (Figure 2A-B).

Full-mouth dental rehabilitation in one appointment under general anesthesia was considered but his parents refused to consent. Consequently, treatment using local anesthesia in a dental office setting was planned. The mother was instructed on caries and periodontal disease prevention, diet counseling to reduce sucrose intake, and tooth-brushing and flossing techniques. Rubber cup/pumice prophylaxis and topical applications of 1.23% acidulated phosphate fluoride

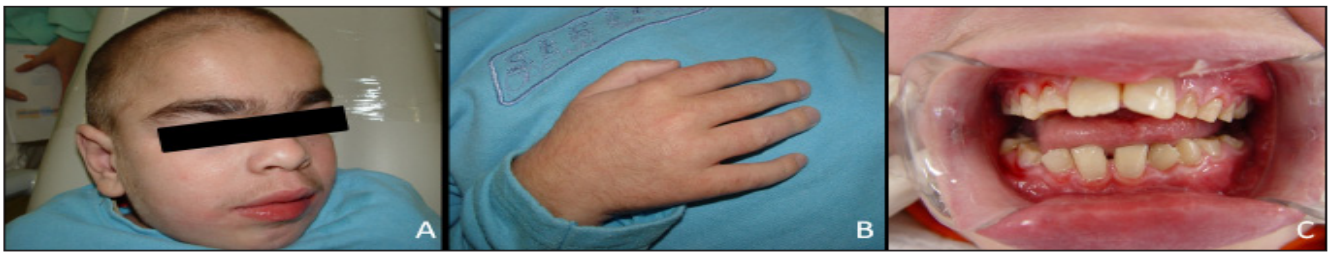

Figure 1. Clinical features of MPS III in a 12-year-old child: (a) facial characteristics (b) flexion deformities of the upper extremities, with minimal spade-shaped hand deformity; (c) intraoral view showing overretention of primary teeth, generalized gingivitis, white spot lesions, multiple carious lesions, and a composite restoration on the maxillary left central incisor, which had a coronal fracture due to trauma.

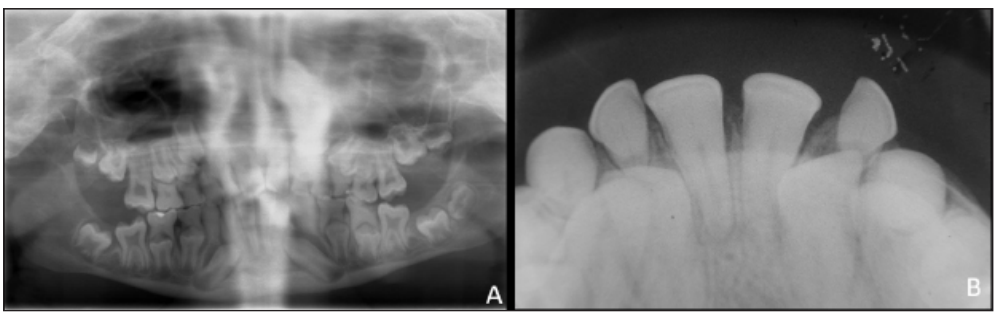

Figure 2. (a) Panoramic radiograph showing obliterated pulp chambers and root canals of the primary teeth at 12 years of age. Radiographic image is suggestive of a dentigerous cyst associated with the crowns of the permanent mandibular canines, agenesis of the mandibular right third molar germ and carious lesions in the primary molars. (b) Occlusal view of the permanent anterior teeth showing evidence of initial obliteration.

gel were done. Calculus was removed with hand scaling. As the patient used fluoride-containing dentifrice, supplemental fluoride was not prescribed. Because the patient was not capable of spitting out the dentifrice after tooth-brushing, instructions were given to use a small amount and remove the excess after brushing with a gauze.

The restorative/surgical procedures were performed at The Center's dental clinic. Because of the patient's severe spasticity, mild physical immobilization was done by his mother and restraint straps were used for safety during dental treatment (Figure 3A). Due to his difficulty to swallow and spit, high-power saliva ejectors were used during treatment, with the patient seated in an upright position to avoid choking.

The central fissure of the occlusal surface of the primary maxillary right second molar and palatal groove of the permanent maxillary left central incisor were sealed with a resin-based pit and fissure sealant (Fluroshield, Dentsply Caulk, Milford, Del., USA). Photoactivated composite resin (Z350, 3M ESPE, St. Paul, Minn., USA) restorations were placed on the primary mandibular right and left second molars, permanent maxillary left first molar, and maxillary right central incisor (Figure 3B).

The primary mandibular left first molar was extracted because of the advanced stage of physiological root resorption and advanced stage of root formation of the permanent successor. The tooth was sent for histopathological analysis, which revealed an extensive deposition of secondary dentin in the coronal pulp chamber and root canals, confirming the radiographic evidence of pulp obliteration. The pulp tissue exhibited some calcifications, few chronic inflammatory cells, and several enlarged blood vessels (Figure 4A-B).

After completion of the treatment, follow-up visits were scheduled on a 3-month basis because of the parents' difficulty to perform oral hygiene at home given the patient's uncooperative behavior, physical limitations, and intellectual disability. These appointments were aimed at evaluating plaque control, and checking for carious lesions, and periodontal disease. Radiographs were taken to closely monitor the progression of physiological exfoliation of the primary teeth and eruption of the permanent success, which is important in a patient with over-retention of primary teeth, altered timing and sequence of tooth eruption, and a suspected dentigerous cyst. During the follow-up period,

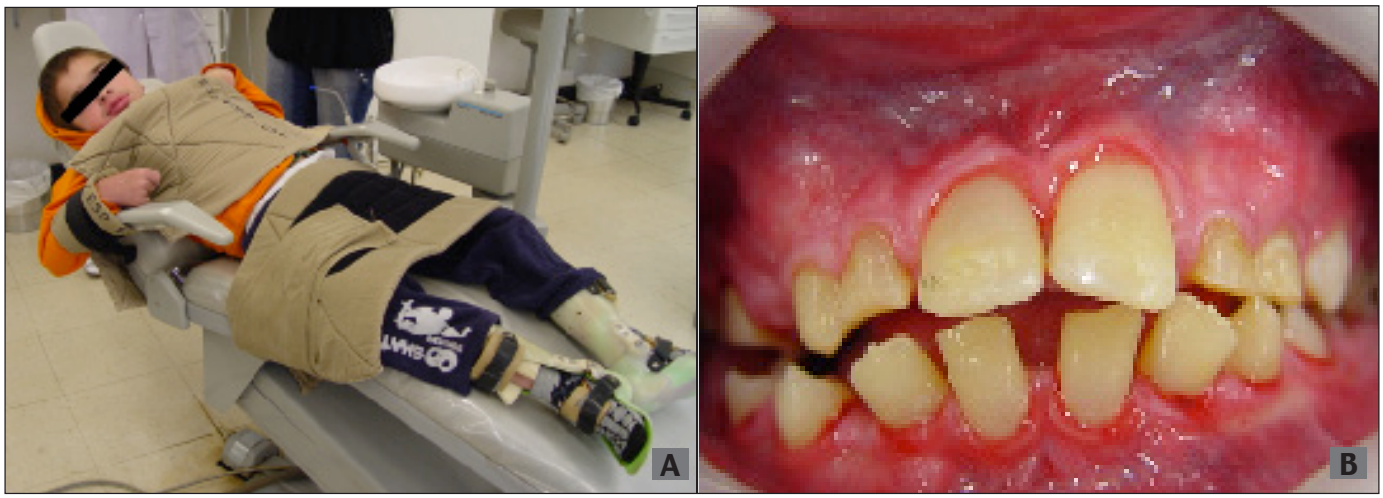

Figure 3. (A) Patient positioned for dental treatment. (B) Oral condition.

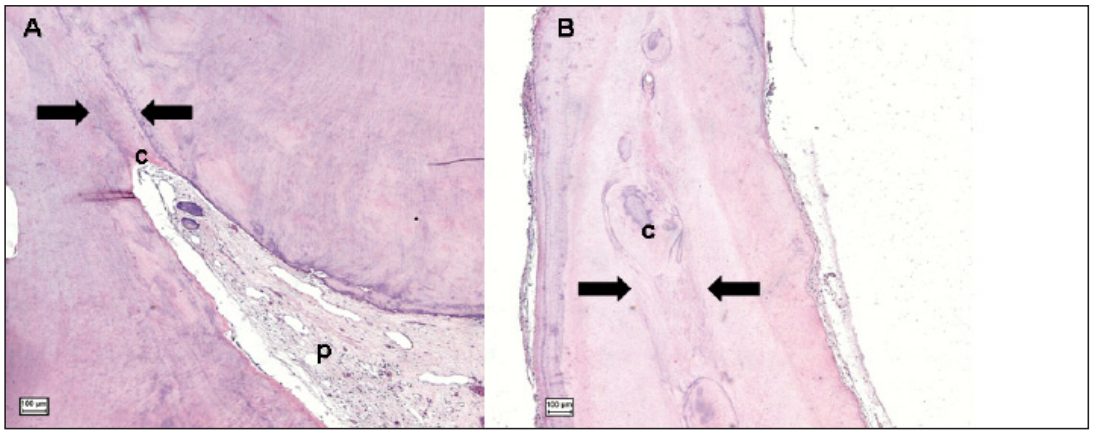

Figure 4. Photomicrograph of a primary molar section: (A) coronal portion; (B) radicular portion. P=pulp partially filled with secondary dentin (arrow); C=obliterated root canal.

which lasted 3 years, the primary teeth were extracted as physiological root resorption advanced.

The patient is currently 15 years old. The most recent panoramic radiographic (Figure 5) revealed almost complete obliteration of the root canals of the permanent mandibular incisors and development of the mandibular right third molar and maxillary right and left fourth molars. The radiolucent image associated with the crowns of the permanent mandibular canines have disappeared, indicating that it was probably a hyperplastic dental follicle, as the radiographic differentiation between a dentigerous cyst and a normal dental follicle is based on size. In addition to that, dentigerous cysts have a tendency to expand rapidly, which was not observed in the followup radiographs.[17,18] There was not sufficient space in the dental arch for eruption of the permanent canines due to malpositioning of the mandibular incisors. Orthodontic correction or surgical repositioning of the teeth, however, are not viable due to the patient's health and mental status. Although new carious lesions did not develop during the follow-up period, heavy dental plaque and calculus deposits were observed at all recall visits.

DISCUSSION

The clinical course of MPS III can be divided into 3 phases. In the first phase, which usually starts between 1 and 4 years of age, developmental delay becomes apparent after an initial normal development during the first 2 years of life. The second phase generally starts around 3 to 4 years of age and is characterized by severe behavioral problems and progressive mental deterioration, ultimately leading to severe dementia. In the final stage, behavioral problems slowly disappear, but motor retardation with swallowing difficulties and spasticity emerge. Patients usually die at the end of the second or beginning of the third decade of life, although survival into the fourth decade has been reported.[1] The patient in case is currently in the last stage of MPS III and has presented with the characteristic features of each stage of the condition.

Behavioral problems usually include restless, destructive, erratic, anxious, and sometimes aggressive behavior. Most patients are very difficult to manage at home,[19] especially because of their uncooperative behavior, physical strength, and physical restlessness.[19,20] Our patient was neither aggressive nor uncooperative, but it was difficult to control his physical restlessness. He had muscular hypertonicity and impaired deglutition, necessitating physical immobilization for safety and high-power saliva ejectors for choking prevention.

The patient has responded poorly to a behavioral approach to treatment, which is not surprising in this syndrome.[21] Antipsychotic drugs appear to be the most effective intervention; however, at present, no evidence-based choice can be made on the best pharmacological therapy for the treatment of the behavioral problems in MPS III patients.[1] In the present case, the patient only takes anticonvulsant drugs.

Sleep disturbances are also very frequent among MPS III patients, with reported prevalence of up to 90%.[19,22] Sleep disturbances consist of settling difficulties, early waking, and frequent nocturnal waking. Some patients even show a complete reversal of their day/night rhythm.[1] Management of sleeping problems is very challenging. If medication for sleep disturbances is necessary, melatonin appears to be the best choice, as it is effective in approximately 75% of the cases. If melatonin therapy fails, benzodiazepines may be tried.[23] In spite of using benzodiazepines, our patient still had problems sleeping at night. Many times, however, he came to the clinic sleeping or slept during the whole session. Nevertheless, physical immobilization was still used for the safety of the patient and the dental team.

Facial dimorphisms, although frequently mild and easily missed, are detected in most MPS III patients. They typically have mild coarse facial features, sometimes prominent broad eyebrows with medial flaring and synophrys. Eyelashes are dark and the hair is usually dry and coarse, with hypertrichosis in most patients. The mandibular lip is often everted and thick, while the maxillary lip is upturned with a protruding philtrum. Helices of the ears show variable thickening, and the nose tip may appear fleshy.[19] Patients have a dolichocephalic skull shape with a short forehead. Growth is affected in approximately half of the patients older than 12 years. Macrocephaly is regularly found in children, while older patients have a normal head circumference.[10] Most of these facial dimorphisms were observed in our patient.

Studies reporting dental findings in MPS III patients are rare. Webman et al.[16] described the case of an 8-year-old patient who had a normal dentition for his age, lacked tooth spacing and presented no changes in tooth color, shape, and size. The radiographic examination showed obliterated pulp chambers and root canals of the primary and permanent incisors, which was also observed in our case. Periapical radiolucencies were occasionally noted in their patient.

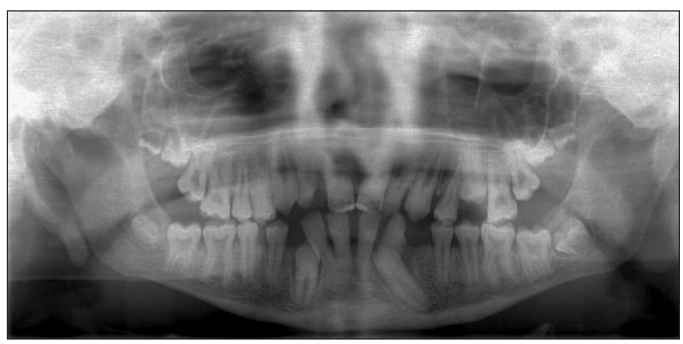

Figure 5. Panoramic radiograph at 15 years of age showing obliterated pulp chambers and root canals of the permanent mandibular central incisors and development of the mandibular right third molar and maxillary right and left fourth molars.

In the present case, unlike the one reported by Webman et al.,[16] tooth eruption was delayed. Microscopically, the extracted tooth in this case had a normal morphology, except for the deposition of secondary dentin in the pulp chamber and root canals. Knowing the oral manifestations of MPS III may allow dental professionals, especially pediatric dentists, to play an important role in establishing an early diagnosis of this devastating progressive disorder and, thus, help improve patients' quality of life. However, more research is needed to determine whether the dental manifestations seen in our case are indeed a common feature of this condition.

REFERENCES

1. Valstar MJ, Ruijter GJ, van Diggelen OP, Poorthuis BJ, Wijburg FA. Sanfilippo syndrome: A mini-review. J Inherit Metab Dis 2008;31:240-52.
2. Baehner F, Schmiedeskamp C, Krummenauer F, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 2005; 28:1011-7.
3. Van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). Clin Genet 1981;20:152-60.
4. Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999;105:151-6.
5. Johns Hopkins University. OMIM database. Mucopolysaccharidosis type IIIA. OMIM no. 252900. Available at: "http://omim.org/entry/252900". Accessed on September 20, 2011.
6. Coelho JC, Wajner M, Burin MG, Vargas CR, Giugliani R. Selective screening of 10,000 high-risk Brazilian patients for the detection of inborn errors of metabolism. Eur J Pediatr 1997;156:650-4.
7. Emre S, Terzioğlu M, Coşkun T, et al. Biochemical and molecular analysis of mucopolysaccharidoses in Turkey. Turk J Pediatr 2002;44:13-7.
8. Michelakakis H, Dimitriou E, Tsagaraki S, Giouroukos S, Schulpis K, Bartsocas CS. Lysosomal storage diseases in Greece. Genet Couns 1995;6:43-7.
9. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York, NY: McGraw-Hill; 2001:3421-52.
10. Tessitore A, Villani GR, Di Domenico C, Filocamo M, Gatti R, Di Natale P. Molecular defects in the alpha-N-acetylglucosaminidase gene in Italian Sanfilippo type B patients. Hum Genet 2000;107:568-76.
11. Lee-Chen GJ, Lin SP, Lin SZ, et al. Identification and characterization of mutations underlying Sanfilippo syndrome type B (mucopolysaccharidosis type IIIB). J Med Genet 2002;39:E3.
12. Beesley C, Moraitou M, Winchester B, Schulpis K, Dimitriou E, Michelakakis H. Sanfilippo B syndrome: Molecular defects in Greek patients. Clin Genet 2004;65:143-9.
13. Beesley CE, Jackson M, Young EP, Vellodi A, Winchester BG. Molecular defects in Sanfilippo syndrome type B (mucopolysaccharidosis IIIB). J Inherit Metab Dis 2005;28:759-67.
14. Muenzer J, Wraith JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006;8:465-73.
15. Husain AM, Escolar ML, Kurtzberg J. Neurophysiologic assessment of mucopolysaccharidosis III. Clin Neurophysiol 2006;117:2059-63.
16. Webman MS, Hirsch SA, Webman H, Stanley HR. Obliterated pulp cavities in the Sanfilippo syndrome (mucopolysaccharidosis III). Oral Surg Oral Med Oral Pathol 1977;43:734-8.
17. Tamgadge A, Tamgadge S, Bhatt D, Bhalerao S, Pereira T, Padhye M. Bilateral dentigerous cyst in a non-syndromic patient: Report of an unusual case with review of the literature. J Oral Maxillofac Pathol 2011;15:91-5.
18. Sun CX, Ririe C, Henkin JM. Hyperplastic dental follicle: Review of literature and report of two cases in one family. Chin J Res 2010;13:71-5.
19. Ruijter GJ, Valstar MJ, Van de Kamp JM, et al. Clinical and genetic spectrum of Sanfilippo type C (MPS IIIC) disease in The Netherlands. Mol Genet Metab 2008;93:104-11.
20. Bax MC, Colville GA. Behavior in mucopolysaccharide disorders. Arch Dis Child 1995;73:77-81.
21. Cleary MA, Wraith JE. Management of mucopolysaccharidosis type III. Arch Dis Child 1993;69: 403-6.
22. Nidiffer FD, Kelly TE. Developmental and degenerative patterns associated with cognitive, behavioral and motor difficulties in the Sanfilippo syndrome: An epidemiological study. J Ment Defic Res 1983; 27:185-203.
23. Hopwood JJ, Morris CP. The mucopolysaccharidoses: Diagnosis, molecular genetics and treatment. Mol Biol Med 1990;7:381-404.