Hunter's syndrome and oral manifestations: a review

Angela Templeton Downs, DDS Tim Crisp, DMD Gerald Ferretti, DDS, MS

Abstract

Review of the literature on Hunter's syndrome and oral manifestations in pediatric dental patients including the primary and secondary systemic manifestations are presented. Numerous oral manifestations are presented as well. Based on the cases presented in the reviewed studies, little information is available on oral considerations and treatment of these children. Early restoration of the oral cavity is important prior to treatment of the disease itself. (Pediatr Dent 17:98–100, 1995)

Hunter's syndrome is an X-linked recessive mucopolysaccharide disorder caused by a defect in the metabolism of glycosaminoglycans, which results from a deficiency of the enzyme iduronate sulfatase. There is an accumulation of dermatan and heparan sulfates in various tissues. Mild and severe forms exist that are a result of mutagenic alleles. Hunter's syndrome clinically resembles other mucopolysaccharide disorders such as Hurler's, San Filippo's, Morquio's, and Schere's syndromes, which are autosomal recessive. Hunter's syndrome is the exception being transmitted as an X-linked recessive disorder.[1–6]

Primary systemic manifestations of Hunter's syndrome are:

1. Macrocephaly
2. Moderate to severe developmental delay
3. Dysmorphic facies
4. Skeletal abnormalities
5. Joint contractures
6. Hepatosplenomegaly
7. Cardiac valvular disease
8. Hirsutism
9. Hyperkinesis
10. Rough and uncoordinated behavior.

Secondary systemic manifestations are frequent otitis media and hearing insufficiencies.[1–3, 6–9]

Oral manifestations include short and broad mandible; localized, radiolucent lesions of the jaws; flattened temporomandibular joints; macroglossic tongue; conical, peg-shaped teeth with generalized wide spacing; highly arched palate with flattened alveolar ridges; and hyperplastic gingiva.[1, 2, 6, 7, 10, 11]

We review the literature considering systemic and oral manifestations of children diagnosed with Hunter's syndrome. We review a mode of treatment for these patients as well.

Literature review

Charles Hunter[6] noted a rare disease in children as early as 1915. On 8- and 10-year-old brothers, he reported findings such as a slowed learning process, throat trouble, tonsil and adenoid operations, dull hearing, inguinal hernias, short stature, curiously shaped heads, large faces, puffy eyes, saddle nose, thick lips, open mouths, large tongues, abducted arms, thick wrists, and a very clumsy and stiff gait. These children also suffer from increasingly frequent and severe respiratory infections[1, 2, 6] that generally increase with age.

This syndrome is found in fewer than 20 cases per million births, making the disease the rarest form of the mucopolysaccharide disorders as reported by Dorfman.[1] Carrier females generally are asymptomatic, though they often show decreased levels of iduronate sulfatase in serum. Clinical manifestations of Hunter's syndrome in females are exceedingly rare with only a few cases reported.[1, 12] Clarke et al.[12] reported the syndrome in a karyotypically normal girl. Neufeld et al.[13] reported two girls with clinical manifestations of mucopolysaccharidosis type II and enzyme deficiencies as well as a normal karyotype. There may be no family history of mucopolysaccharide disorders when a child is diagnosed with one. Successive births or numerous children may result in a family having more than one child with the syndrome before the first one has any physical signs or has been diagnosed. Despite genetic counseling, many people continue to have children affected by this type of disorder.

There are two forms of Hunter's syndrome. Type A is the most severe form with a life expectancy of 14–15 years and a much earlier onset. Type B is a much milder form with a life expectancy of 30–50 years[1, 2] and physical features similar to, but not as severe as those of Type A. Yatziv et al.[14] suggested that the presence or absence of severe mental retardation and the longevity of the affected individuals be distinguishing factors in order to help clinically determine the difference between these two forms. Young et al.[15] established that patients with Hunter's syndrome did clearly fall into one of two groups according to the presence or absence of intellectual deterioration. They also reported the

more severely affected patients showed a higher incidence of behavioral disorders.

Dorfman[1] has reported Hunter's syndrome to be characterized by the accumulation of dermatan and heparan sulfate in various tissues and can be diagnosed if there is found to be more dermatan than heparan in tissues; while in Hurler's syndrome, heparan is more abundant. Other diagnostic characteristics include the patient's physical features; dysostosis; dermatan or heparan in urine; enzyme studies showing iduronate sulfatase deficiency in serum, white blood cells, or cultured fibroblasts.[1, 2]

Hunter[6] reported what have become the classical features of the syndrome bearing his name. The many primary systemic manifestations of Hunter's syndrome include macrocephaly, with the skull thickened and deformed, and the cranial base and orbital roofs become thick and dense with the sagittal and lamboidal sutures closing prematurely. Very prominent frontal bossing and temporal bulges, as well as changes in the skull can be present. As the children grow, they exhibit moderate to severe developmental delay with hyperkinesis along with rough and uncoordinated behavior.[1, 2, 6, 7, 14, 15] Gardner[7] reported that these children show resistance to discipline and are stubborn and fearless, and become so difficult to manage that they are generally institutionalized. Their ability to speak and walk decreases with age. He also noted that they have progressive difficulty in eating solid food and that weight loss is common.

Hunter[6] and Dorfman[1] reported problems with tonsils and adenoids leading to frequent and severe respiratory infections. Morehead and Parsons[16] have reported tracheobronchomalacia/major airway collapse.

Skeletal abnormalities include an enlarged chest with flaring ribs and short stature. The abnormal extremities show broad, claw-like short fingers. These children exhibit hepatosplenomegaly due to the accumulation of dermatan and heparan, which also causes cardiac valvular disease resulting in distortion of the heart valves and thickening of the coronary arteries. Hirsutism is noted and usually increases after age 2.[1–3, 6]

Secondary systemic manifestations include frequent otitis media resulting in hearing insufficiencies and progressive deafness.[1–3, 6]

Death usually occurs due to cardiac or respiratory arrest.[1–3, 6, 14] Morehead and Parsons[16] reported tracheobronchomalacia to be a part of respiratory complications. Liu[17] and Gardner[7] have reported that the mandible of the Hunter's syndrome patient is usually short and broad with a wide intergonial distance; and the distance around the arch is larger, resulting in increased interdental spacing. Gardner[7] has noted that the rami are often short and narrow.

The localized lesions of the jaws often resemble dentigerous cysts and are usually bilateral areas of bony destruction.[7, 11, 17, 18] Liu[17] reported that these lesions usually are associated with unerupted first permanent molars. Liu[17] and Gardner[7] reported that based on other studies that these enlarged dental follicles represented pools of chondroitin sulfate B (dermatan sulfate). Gardner[7] and Stewart et al.[10] noted that these lesions contain dense, fibrous connective tissues and large amounts of acid mucopolysaccharides. These areas of destruction also tend to worsen with age. The gingival tissues are hyperplastic, hypertrophic, and enlarged, while the tongue is thickened and macroglossic.[1, 2, 6, 7, 10] The goal would be to extract any cystically involved teeth, restore any carious teeth, and maintain oral health. Antibiotics should be given as a prophylatic measure due to the heart conditions associated with Hunter's syndrome.

The temporomandibular joint often shows a flattening of the articular surface, while the condyle may be flattened or reduced in size accompanied by a large coronoid process with hypomotility.[7]

The teeth are small and shortened. There is generalized wide interdental spacing.[2, 6, 7, 10, 17] The teeth can be peg-shaped and conical and often hypoplastic. Anterior open-bites have been noted due to the enlarged protruding tongues.[7, 17] There is delayed root formation, and the molars are often further posterior with a distoangular tipping.[7] The palate is highly arched in many patients with prominent palatal rugae. There are deep grooves in the midsagittal plane and the alveolar ridges are flattened.[7] The gingival tissues are hyperplastic, hypertrophic, and enlarged, while the tongue is thickened and macroglossic.[1, 2, 6, 7, 10]

Hunter's syndrome is diagnosed by a presence of the classical features reported by Hunter,[6] Gorlin,[2] and Dorfman.[1] Clinical examinations, skeletal surveys, urine and serum iduronate sulfatase analysis, psychomotor tests, and genetic evaluations all have been used in confirming Hunter's syndrome.[1, 2, 4, 5]

Bone marrow transplant (BMT) has been considered a possible mode of treatment in patients with mucopolysaccharidosis because this is a stem cell disorder.[19] Warkentin et al.[20] reported that a BMT could serve as a permanent source of normal cells capable of producing the deficient enzyme. This would permit the affected cells to degrade accumulated glycosaminoglycans and prevent further deposition.

In BMT, lethal doses of chemotherapy and total body radiation are used to completely destroy all bone marrow elements — both malignant and normal cell lines — thereby eliminating the inborn error of metabolism. A healthy donor's cells are used to repopulate the marrow with normal cells. This procedure is not retroactive but can prevent progression.[19]

Recommendation for BMT depends on age, compatibility of donor, degree of cardiac and brain involvement, and parental consent. The prognosis is difficult to determine because of limited transplant experience with Hunter's syndrome patients. We hope

the future will provide more information and results in this area.

The most common reasons for treatment failure are infection, host rejection of the transplanted organ, and graft-versus-host disease. Oral complications include oral infection and mucositis. The most common cause of morbidity and mortality during and after the transplantation procedure is infection. It is therefore very important to remove any possible source of oral infection prior to transplantation and to maintain oral health.[19, 20]

Warkentin et al.[20] have pointed out that post-BMT evaluations reveal notable but limited clinical improvement. Longer followup is necessary in order to document clinical improvement and sustain biochemical correction. They point out that an extensive re-evaluation is needed for one-year post-BMT.

Conclusion

Hunter's syndrome is a very serious disease affecting children. Since few studies have been done on these children relating to bone marrow transplantation and oral health, much more information is needed. For the children undergoing bone marrow transplantation, restoring and maintaining health of the oral cavity is very important. Much more information is needed on the success-failure rate of bone marrow transplantation in these children.

Dr. Downs is assistant professor in pediatric dentistry, University of Kentucky; Dr. Crisp is a pediatric dentist in Lexington; Dr. Ferretti, is professor and director at Kentucky Clinic Dentistry, University of Kentucky, Lexington.

We thank Mollie Young, Dr. Ted Raybould, and Dr. Doug Damm.

1. Dorfman A: Mucopolysaccharidoses. Nelson Textbook of Pediatrics, 11th ed. Vaughan VC III, McKay RJ Jr, Behrman RE, Eds. Philadelphia: WB Saunders Co, 1979, pp 1845–48.
2. Gorlin RJ, Cohen MM Jr, Levin LS: Mucopolysaccharidosis II. Syndromes of the Head and Neck, 3rd ed. New York: Oxford University Press, 1990, pp 106–8.
3. LeRoy JG, Crocker AC: Clinical definition of the Hurler-Hunter phenotypes — a review of 50 patients. Amer J Dis Child 112: 518–30, 1966.
4. Young ID, Harper PS: Long-term complications in Hunter's syndrome. Clin Genet 16:125–32, 1979.
5. Young ID, Harper PS, Archer IM, Newcombe RG: A clinical and genetic study of Hunter's syndrome: I. Heterogeneity. J Med Genet 19:401–7, 1982.
6. Hunter C: A rare disease in two brothers. Proc R Soc Med 10:104–16, 1917.
7. Gardner DG: The oral manifestations of Hurler's syndrome. Oral Surg 32:46–57,1971.
8. Young ID, Harper PS: The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. Dev Med Child Neurol 25:481–89, 1983.
9. Young ID, Harper PS: Mild form of Hunter's syndrome: clinical delineation based on 31 cases. Arch Dis Child 57:828–36, 1982.
10. Stewart RE, Prescott GH: Oral facial manifestations of inborn errors of metabolism. Oral Facial Genetics. St Louis: CV Mosby Co, pp 392–96, 1976.
11. Lustmann J, Bimstein E, Yatziv S: Dentigerous cysts and radiolucent lesions of the jaw associated with Hunter's syndrome. J Oral Surg 33:679–85, 1975.
12. Clarke JT, Willard HF, Teshima I, Chang PL, Skomorowski MA: Hunter disease (mucopolysaccharidosis type II) in a karyotypically normal girl. Clin Genet 37:355–62, 1990.
13. Neufeld EF, Liebaers J, Epstein CJ, Yatziv S, Milunsky A, Migeon BR: The Hunter syndrome in females: is there an autosomal recessive form of iduronate sulfatase deficiency? Am J Hum Genet 29:455–61, 1977.
14. Yatziv S, Erickson RP, Epstein CJ: Mild and severe Hunter syndrome (MPS II) within the same sibships. Clin Genet 11:319–26,1977.
15. Young ID, Harper PS, Newcombe RG, Archer IM: A clinical and genetic study of Hunter's syndrome. 2. Differences between the mild and severe forms. J Med Genet 19:408–11, 1982.
16. Morehead JM, Parsons DS: Tracheobronchomalacia in Hunter's syndrome. Intern J Pediatr Otorhino 26:255–61, 1993.
17. Liu KL: The oral signs of Hurler-Hunter syndrome: report of four cases. ASDC J Dent Child 47:122–27, 1980.
18. Reilly WA, Lindsay S: Gargoylism (lipochondrodystrophy) review of clinical observations in 18 cases. Am J Dis Child 75:595–607, 1948.
19. McDonald RE, Avery DR: Bone marrow transplantation. In: Dentistry for the Child and Adolescent, 5th ed. St Louis: CV Mosby Co, pp 648–49, 1987.
20. Warkentin PI, Dixon MS Jr, Schafer I, Strandjord SE, Coccia PF: Bone marrow transplantation in Hunter syndrome: a preliminary report. Birth Defects 22:31–39, 1986.