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Hurler's syndrome: dental findings in a case treated with bone marrow transplantation in infancy

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Summary. Hurler's syndrome, also known as mucopolysaccharidosis I (MPS I-H), is a rare condition inherited as an autosomal recessive trait. It is caused by a deficiency in alpha-L-iduronidase, an enzyme that participates in the degradation of the glycosaminoglycans (GAGs) heparin sulphate and dermatan sulphate. Children with Hurler's syndrome appear nearly normal at birth but, left untreated, show a progressive mental and physical deterioration caused by a build-up of GAGs in all organs of the body. Death is often caused by cardiac or respiratory failure and usually occurs before the second decade of life.

In recent years, bone marrow transplantation (BMT) has been employed in the management of patients with Hurler's syndrome. However, the dental findings observed in these cases have not previously been reported in the dental literature. Here we report a patient aged 11 years and 6 months, presented to a Specialist Paediatric Dentistry Unit, who was successfully treated by BMT at 18 months of age.

Introduction

The mucopolysaccharidoses (MPS) are a group of syndromes characterized by inadequate metabolism of mucopolysaccharides (also known as glycosaminoglycans or GAGs). Hurler's syndrome (MPS I-H; Mendelian Inheritance in Man #607014 was first described in 1919 by the German paediatrician Gertrud Hurler and is the most severe of the MPS syndromes. Inherited as an autosomal recessive trait, it is characterized by a deficiency in alpha-L-iduronidase. This enzyme is responsible for the degradation of the glycosaminoglycans heparin sulphate (HS) and dermatan sulphate (DS), and a deficiency in the enzyme leads to a build-up of these substances in all organs of the body. The chief pathological finding is accumulation of membrane-enclosed storage material (more DS than HS) in parenchymal and mesenchymal cells [1].

In 1990, the incidence of Hurler's syndrome was described as 1 : 144,000 [2]; more recently, it has been described as 1 : 76,000 [3]. Affected children appear nearly normal at birth and the most common early-presenting features are the nonspecific symptoms of rhinitis and inguinal hernia [4]. Most often, the diagnosis of Hurler's syndrome is contingent upon the recognition of the initial pattern of musculoskeletal abnormalities, which become increasingly pronounced after the sixth month [5]. Left untreated, affected children show a gradual mental and physical deterioration, with death usually occurring before the second decade of life [6].

The dental findings of the syndrome include spaced, hypoplastic, peg-shaped teeth with retarded eruption, flattened alveolar ridges with hyperplastic gingivae, macroglossia, and a high-arched palate. The mandible is short and broad, with abnormal condyles; localized dentigerous cyst-like radiolucencies are also often present [5–11].

Bone marrow transplantation (BMT) was first described in 1980 as a means of reversing the deposition of excess GAGs in the tissues [12]. In this process, the patient's diseased bone marrow is destroyed by chemo- and/or radiotherapy prior to the infusion of healthy marrow into the blood stream. In a successful transplant, the new bone marrow migrates to the cavities of the large bones, engrafts, and begins producing normal blood cells. Thereafter, the cells of donor haematopoietic origin assist in the removal of GAGs from the host tissues.

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Unfortunately, because of a lack of matched related donors and unacceptable morbidity of matched unrelated transplants, this therapy is not available to all patients. An alternative approach based on transfer and expression of the normal gene in autologous bone marrow has been used to restore normal GAG metabolism in deficient fibroblasts by introducing retrovirally transduced cDNA encoding alpha-L-iduronidase [13].

The treatment of choice for a child diagnosed with Hurler's syndrome before the age of 2 years, with minimal or no central nervous syndrome damage, is haematopoietic stem-cell transplantation. The patient's life expectancy is increased, hepatosplenomegaly resolves, cardiac disease is stabilized, and there is improvement in the range of motion of the joints, airway disease, and hearing [14]. Cord-blood transplantation appears to be as effective as bone marrow transplantation [15]. In a study by Fleming *et al.* [16], all patients with sustained engraftment experienced improvement in physical manifestations, such as corneal opacity, gingival and tongue hypertrophy, hepatosplenomegaly and joint mobility. Skeletal abnormalities, such as dysostosis multiplex, were stabilized but not reversed. Some patients continued to show decline in neuropsychometric testing, whereas others appeared to stabilize, and one demonstrated improvement [16].

Cardiac valvular disease is a primary systemic feature of Hurler's syndrome and is caused by accumulation of mucopolysaccharides in the tunica intima of the coronary arteries and the heart valves [6]. A recent study describes the cardiac ultrasound findings of 10 individuals with Hurler's syndrome more than 10 years after a successful BMT [17]. The investigators found that a BMT had a positive effect on the heart; as cardiac function was preserved, hypertrophy regressed and chamber dimensions tended to normal. In some patients, however, the left-sided cardiac valves continued to thicken and prolapse and insufficiency developed despite success of the BMT.

Another study reported poor penetration of the musculoskeletal tissues by the enzyme produced by the leucocytes of donor haematopoietic origin following BMT [18]. This resulted in abnormal bone modelling, focal failures of ossification, and an avascular disorder of the femoral head in all 11 children examined. Despite successful BMT, the children experienced loss of mobility as they entered adolescence, caused mainly by an increasing knee deformity and progressive generalized myopathy.

The dental findings observed in transplanted cases have not previously been described in the literature. This paper therefore presents the oral and dental findings in a female patient with Hurler's syndrome who underwent a successful bone marrow transplant at 18 months of age.

Case report

A female aged 11 years and 6 months was referred to the University Dental Hospital, Cardiff by her general dental practitioner regarding generalized crowding of her dentition.

Medical history

A comprehensive medical history revealed that she was diagnosed with Hurler's syndrome at 1 year of age and had received a successful bone marrow transplant at the age of 18 months. The immediate post-transplant regimen of immunosuppresants, antivirals, antibacterials, and calcium channel-blockers had been stopped 1 year post-transplant.

At the time of presentation, the patient had moderate aortic valve incompetence and will require prosthetic valve replacement in the future. The patient had also undergone several orthopaedic operations to her spine in an attempt to improve mobility. All joints were affected by GAG deposition within the joint structure. Interestingly an inguinal hernia, one of the classical early-presenting features of the syndrome, had been repaired.

Clinical examination

Extra-oral examination revealed the patient to be of short stature (121·5 cm, well below the 0·4th centile) and low weight (23·8 kg, in the 0·4th centile) with a large head and short neck. Her facial appearance was typical of patients with Hurler's syndrome, exhibiting a depressed nasal bridge, broad nasal tip, corneal clouding, and long upper lip with relative flattening of the philtrum (Figs 1 and 2). The patient was socially adept and attending mainstream school.

Intra-oral examination (Figs 3–5) revealed poor oral hygiene with associated marginal gingivitis. The occlusion was class I with incisor crowding, the upper left permanent lateral incisor being rotated through 90 degrees to facilitate its accommodation within the arch. The skeletal base relationship was

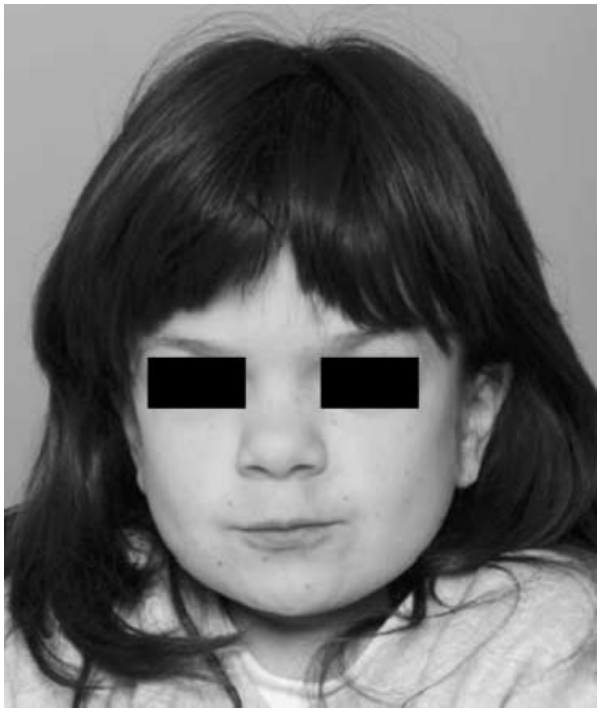

Fig. 1. Frontal extra-oral facial view.

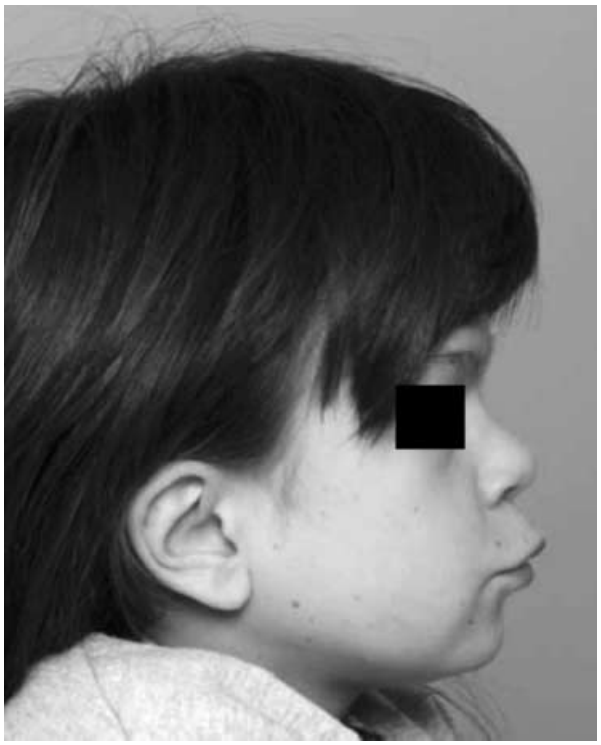

Fig. 2. Lateral extra-oral view.

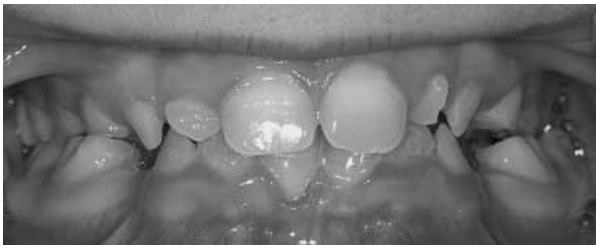

Fig. 3. Intra-oral view – upper and lower arches in occlusion.

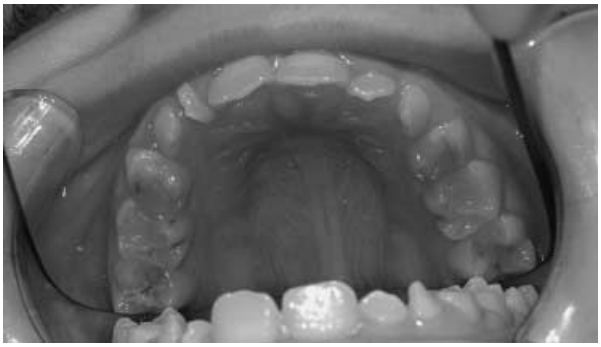

Fig. 4. Intra-oral view – upper occlusal.

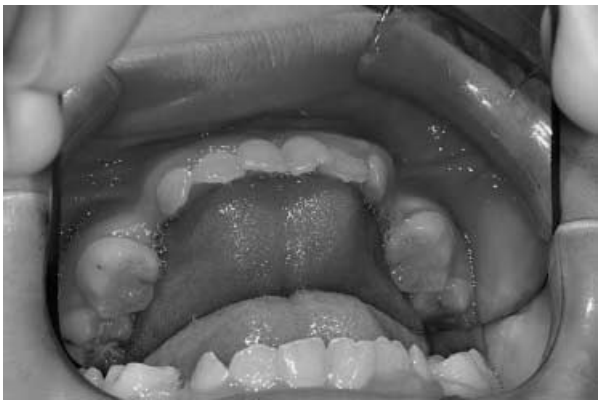

Fig. 5. Intra-oral view – lower arch.

difficult to determine. While the gingivae were of relatively normal appearance, the palatal mucosa was fibrous with pronounced rugae. The upper alveolar process appeared broad and flattened in the anterior region. Some dental dysmorphology was noted; whereas the molars were of normal morphology, the upper central incisors appeared 'short', and the partially erupted upper permanent canines were very conical, small, and pointed. The general dental practitioner extracted the lower first primary molars 2 years previously because of caries.

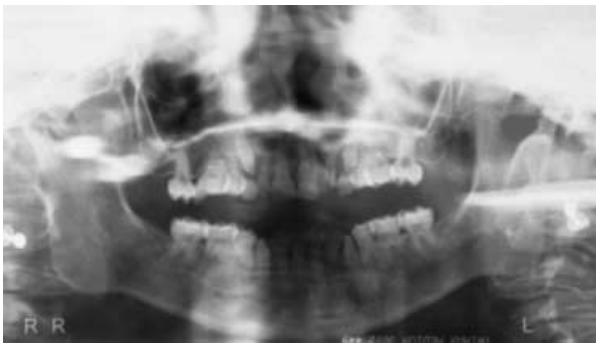

Fig. 6. Dental panoramic tomograph taken at age 9 years.

Radiographic findings

A previous dental panoramic tomograph (Fig. 6) taken at the age of 9 years showed the mandible to be generally small, with reduced height of the ascending ramus and small condylar heads. Notably, the articular eminence and glenoid fossa were normal and there was no obvious calcification of the stylohyoid ligament. The primary molars and the upper deciduous canines were retained and showed marked root resorption but normal crown form. In the permanent dentition, there were multiple missing teeth, with no evidence of development of the premolars and second or third molars. The permanent teeth demonstrated small crowns and short roots, with the first permanent molars showing a marked cervical constriction. Enamel and dentine in both dentitions showed normal density. The upper permanent canines showed follicle sizes just within the normal limits.

Management

The management of this patient was centred on prevention. Fissure sealants were applied to the first permanent molars on eruption, and regular intensive oral hygiene instruction and dietary advice continue to be given to the patient and her family. The main aim of this patient's dental treatment is to maintain her dentition for as long as possible. Unfortunately, it is not known how long the deciduous molars will be retained and further assessment would have to be made should these teeth become mobile.

No dentigerous cyst-like lesions, characteristic of the syndrome, have been identified in this patient. The failure of development of such a lesion to develop in this case may be due to the success of the BMT. Should a dentigerous cyst-like lesion arise, it has been recommended that the cyst and associated tooth should be extracted, as these areas of destruction tend to worsen with age [19].

If patients with Hurler's syndrome require dental intervention, the consultant cardiologist responsible for the patient should be consulted, as many patients require antibiotic cover as outlined in the Dental Practitioners Formulary, due to the cardiac damage produced during management of the syndrome.

Discussion

One of the most widely reported dental features of Hurler's syndrome has been spacing of the teeth. This is usually most marked in relation to the posterior teeth, the latter being spaced even in the presence of anterior crowding. This spacing has been attributed to both a relatively posterior position of the molars and to distoangular tipping of these teeth [10]; it is of note that these features are absent in this case. In Hurler's syndrome the teeth have often been described as peg-shaped and poorly formed [11] and may be hypoplastic [7]. In this case the incisors were slightly conical and the permanent canine teeth extremely pointed.

The flattening of the anterior region of the patient's hard palate is classical of Hurler's syndrome and is thought to be due to pressure from the tongue, which exhibits macroglossia due to deposition of GAGs within its structure [8]. Although absent in this case, many patients with Hurler's syndrome are described as having an anterior open bite with the same aetiology.

The radiographic findings seen in Hurler's syndrome classically include a short ramus and abnormal condyles [8]. While the ramus height of this patient did appear shortened, the condyles were small but otherwise of normal morphology. Other features seen in Hurler's syndrome but not observed in this case were absence of the articular eminence and calcification of the stylohyoid ligament. Dentigerous cyst-like lesions are also reported; these are almost always bilateral, appear to start within the dental follicle, and occur chiefly in the mandible [8]. Although the follicles of the unerupted canine teeth were obvious, their dimensions lay just within the normally accepted limit of 3 mm [20].

The patient had a successful BMT at 18 months of age. The preparatory chemotherapy associated with

this procedure may cause agenesis and hypoplasia of the teeth [21], this may explain the absence of the premolars and molars and the abnormal root form of the canine and permanent molars. It is surprising, however, that the crowns of the teeth developing at the time of chemotherapy are not affected to a greater extent.

Hurler's syndrome is a previously fatal childhood disease now being successfully managed with bone marrow transplantation. While the effects of the presenting condition may be attenuated, or even eliminated, by treatment, such children will inevitably suffer side-effects. The developing dental tissues are extremely sensitive to the effects of chemotherapy and all teeth developing at the time of treatment will be affected.

The input of the general dental practitioner is essential in the care of such patients. He must provide dietary and oral hygiene advice, as well as preventive measures such as fissure sealants and appropriate fluoride supplementation to prevent the development of caries. The general dental practitioner is well placed to detect dental caries at an early stage and prevent their progression. If dental treatment becomes necessary, the general dental practitioner must liase with the medical consultants responsible for the patient, prior to provision of treatment. If treatment under general anaesthetic becomes necessary, the practitioner should be aware of the anaesthetic risks involved in the management of these patients. Computerized tomography (CT) was used to evaluate the airway changes in 13 patients with one of the mucopolysaccharidoses [22]. Over half (54%) of the patients had abnormalities of the vocal cords and all of these seven patients, as well as a further two, had a U- or worm-shaped trachea (the trachea is usually round in cross-section). The change in tracheal shape is thought to be caused by abnormal submucosal storage producing structural alterations. The mean tracheal surface area at the level of T1 was reduced in the patient group compared to the control subjects. Care must therefore be exercised when considering endotracheal intubation in these children and, if possible, a general anaesthetic should be avoided when providing dental care for this vulnerable group.

What this paper adds

- Bone marrow transplantation (BMT) in infancy can be used to successfully manage some of the effects of Hurler's syndrome.
- The dental characteristics of children with Hurler's syndrome are altered by BMT in infancy.
- The medical management of this syndrome can cause agenesis of multiple permanent teeth.

Why this paper is important for paediatric dentists

- Paediatric dentists may be asked to give advice on the dental management of this unusual group of children.
- Children with Hurler's syndrome often require complex multi-disciplinary care may be best managed in a specialist department.

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