The Oral Health Needs of Children, Adolescents and Young Adults Affected by a Mucopolysaccharide Disorder

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Abstract *Background:* As one of the 4 United Kingdom national centres for Lysosomal Storage Disorders, Birmingham Children's Hospital (BCH) cares for 49 patients with a mucopolysaccharide (MPS) disorder. Presently, their oral health needs have never been fully investigated. Enzyme therapies are revolutionising medical treatment, and will prolong life expectancy. Therefore, oral health and its impact on quality of life are increasingly important.

Hypothesis: Patients with an MPS disorder have greater oral health needs in comparison with the general population.

Design: Forty-six patients with an MPS disorder were investigated for caries, gingival health and enamel opacities. Questionnaires to establish the utilisation of dental services and assess the perceived difficulties in achieving adequate oral health care were completed.

Results: Patients with an MPS disorder have specific oral health needs depending on the type of MPS experienced. This study found 76% of patients with MPS IV had experienced dental caries and they all showed evidence of a generalised unspecified enamel defect. Subjects with MPS I, II and III did not have an increased caries rate; 50% of the study group had received dental treatment in the past,

of which 74% (17, $n = 23$) required a general anaesthetic.

Conclusion: The MPS disorders can have a significant effect on the developing dentition. Subjects with MPS IV do have an increased oral health need in comparison with the general population and the other MPS groups due to their increased caries rate and enamel defects. Further research is required to fully assess their needs and investigate any structural tooth defects.

Introduction

The mucopolysaccharide (MPS) diseases comprise a set of rare inherited disorders caused by the deficiency of particular lysosomal enzymes, which determine the type of MPS exhibited. A lysosomal enzyme deficiency results in disturbances in the catabolism of glycosaminoglycans (mucopolysaccharides) and leads to increased storage of mucopolysaccharides in the lysosomes of cells in various tissues throughout the body. The clinical effects are wide ranging and are dependent on the type of stored mucopolysaccharide (Wraith 1995). Severe physical and neurological developmental problems can arise including: abnormal upper airways, restrictive lung disease, skeletal abnormalities, cervical spine deformities and behavioural difficulties (Kircher et al. 2007; Kumar and Clark 1998). The MPS diseases include seven different disorders classified into various sub-types each exhibiting specific phenotypes (Table 1) (Wraith 1995; Kircher et al. 2007; Santos and Hoo 2006; Soong et al. 1988). All MPS diseases are caused by a recessive gene inheritance with the exception of MPS II or "Hunters disease", which is X-linked (Wraith et al. 2008).

As a consequence of the multiple effects of each disease, patients with an MPS disorder are often managed in a multidisciplinary setting comprising specialised

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Table 1 Classification of mucopolysaccharide diseases

Syndrome (OMIM ref)	Eponym	Enzyme deficiency	Stored material
MPS I H #607014	Hurler syndrome	Alpha-L-iduronidase	Dermatan sulphate Heparan sulphate
MPS I S #607015	Scheie syndrome	Alpha-L-iduronidase	Dermatan sulphate Heparan sulphate
MPS II A +309900	Hunter syndrome (severe)	Iduronate sulfatase	Dermatan sulphate Heparan sulphate
MPS II B +309900	Hunter syndrome (mild)	Iduronate sulfatase	Dermatan sulphate Heparan sulphate
MPS III A #252900	Sanfillipo syndrome A	Sulfamidase	Heparan sulphate
MPS III B #252920	Sanfillipo syndrome B	N-acetyl-alpha-glucosaminidase	Heparan sulphate
MPS III C #252930	Sanfillipo syndrome C	N-acetyl-transferase	Heparan sulphate
MPS III D #252940	Sanfillipo syndrome D	N-acetylglucosamine-6-sulfatase	Heparan sulphate
MPS IV A #253000	Morquio syndrome A	n-acetyl-galactosamine-6-sulfatase	Keratan sulphate
MPS IV B #253010	Morquio syndrome B	Beta-galactosidase	Keratan sulphate
MPS VI A #253200	Maroteaux–Lamy syndrome A	Arylsulfatase B	Dermatan sulphate
MPS VI B #253200	Maroteaux–Lamy syndrome B	Arylsulfatase B	Dermatan sulphate
MPS VII #253220	Sly syndrome	Beta-glucuronidase	Dermatan sulphate Heparan sulphate Chondroitin sulphate
MPS IX #601492	No eponym	Hyaluronidase	
MSD #272200	Multisulphatase deficiency	Multiple sulphatase deficiencies	Numerous materials including: sulfatides, glycosaminoglycans, sphingolipids, steroid sulphates

paediatric teams including cardiology, neurology, psychiatry, orthopaedics, physiotherapy and ophthalmology. Recently, significant advances in enzyme therapies have revolutionised the medical management of a number of MPS disorders with hopes of substantially prolonging life expectancy and the interim quality of life. As a major contributor to quality of life, the management of the oral health of these patients is becoming increasingly important (Sheiham 2005).

A wide range of craniofacial and dental abnormalities have been described in the literature as occurring in patients with an MPS disorder, which may or may not predispose to an increased risk of dental disease. Children with an MPS disorder would also be considered to be a population with various special healthcare needs depending on the severity of their disease. Those with MPS I, II and III will usually have significant cognitive impairment and behavioural difficulties, whereas those with type IV disease will be within the normal range of intelligence (Kircher et al. 2007). Various oral health studies over the world acknowledge that vulnerable populations often have particular oral health needs in

comparison with the general population. Many studies show a higher prevalence of caries, malocclusions, and poorer periodontal health. Access to dental care is often reported to being more difficult and therefore there is a larger unmet restorative need. (Lewis 2009; Shaw et al. 1986; Purohit et al. 2010). The literature to date investigating MPS disorders suggests there are alterations in the structure of the enamel and dentine and in particular the enamel/dentine junction in MPS type I (Guyen et al. 2008) and type IV presentations (Lustmann 1978) however, the extent and significance of this is unclear. (Table 2). Patients with an MPS disorder represent a challenge for dentists to treat due to the complicated medical and physical disabilities. Many, and in particular those with MPS III (Kircher et al. 2007) also exhibit behavioural problems which are progressive with the disease process. When general anaesthesia is required to deliver, essential health-care surgical units with adequate intensive care facilities and paediatric anaesthetists are required as patients with an MPS disorder present complex anaesthetic difficulties and particularly with intubation (Wraith 1995). The management of dental and

Table 2 Dental anomalies described in the literature to date are described below

Author/date	MPS disease	Number	Reported dental anomalies
McGovern et al. (2008)	MPS I	25 cases	Delayed dental development Spaced dentition Hypodontia Microdontia
Güven et al. (2008)	MPS I	1 case	Thick gingivae Hypoplastic teeth primary teeth Cysts around unerupted teeth Obliterated pulp canals Taurodont molars Hypoplastic mandibular condyles
Thomas and Tandon (2000)	MPS I	1 case	Large tongue Thick gingivae Spaced dentition Delayed eruption of permanent dentition
Keith et al. (1990)	MPS I Hurler-Scheie	2 cases	Broad maxilla and forehead Minor hypertelorism Broad chin Short ramus and deficient condyles Broad dental arches Dentigerous cysts Gingival hyperplasia Macroglossia
Schmidt et al. (1987)	MPS I	2 cases	Short mandibular necks Flattened condyles Hypertelorism Spaced teeth Dentigerous cysts
Gardner (1971)	MPS I and II	12 cases	Radiolucent mandibular lesions (7 cases) Spaced dentition Histologically normal teeth Hyperplastic gingivae (6 cases)
Worth (1966)	MPS I	24 cases	16 had condyle abnormalities All had small teeth, some peg shaped Spacing of the teeth in most cases All had short narrow rami Many had a reduplicated chin 13 showed mandibular bone destruction
Hopkins et al. (1973)	MPS II	2 cases	Anterior open bite Large protuberant tongue Thickened lips Limited neck extension and mouth opening (1 case) Coronoid hyperplasia Abnormal condyles Increased bone density Low caries incidence Spaced dentition
Webman et al. (1977)	MPS III	1 case	Obliteration of pulp canals in primary and permanent teeth
Oncag et al. (2006)	MPS IV	1 case	Flattened nasal bridge Flared nasal alae Prominent lower face Broad mouth Anterior open bite
Kuratani et al. (2005)	MPS IV	1 case	Spaced dentition Thin enamel
Rolling et al. (1999)	MPS IV	3 siblings	Pointed cusps Spade-shaped incisors Thin enamel Pitted buccal surfaces Condylar resorption

Table 2 (continued)

Author/date	MPS disease	Number	Reported dental anomalies
Smith et al. (1995)	MPS IV	8 cases	Delayed eruption Hyperplastic tooth follicles Unerupted and impacted permanent teeth
Kinirons and Nelson (1990)	MPS IV	9 cases	Thin enamel Microdont and opaque teeth Pointed cusps of molars Concave occlusal surfaces Absence of normal fissure patterns Spade-shaped incisors
Lustmann (1978)	MPS IV	2 cases	Lab examination of teeth only: Partial calcification at the enamel- dentine membrane
Levin et al. (1975)	MPS IV	12 cases	Prominent lower face Flat nasal bridge Broad flat palate DMF index average 4.5 Spaced anterior teeth, yellow colour Tapered teeth and pointed cusps Defective enamel in 10 patients
Sela et al. (1975)	MPS IV	2 siblings	Thin enamel Molar cusps small and pointed Generalised enamel hypoplasia Tongue showing geographic features Flattened condyle
Alpoz et al. (2006)	MPS VI	1 case	Enlarged tongue Delayed eruption of anterior permanent teeth Enlarged alveolar process High arched palate with a deep mid groove Unerupted teeth with dentigerous cysts
Smith et al. (1995)	MPS VI	2 cases	Delayed tooth eruption Thickened dental follicles
Roberts et al. (1984)	MPS VI	1 case	Macroglossia Hyperplastic fibrotic gingivae Dentigerous cysts

periodontal disease in patients with an MPS disorder can be extremely challenging in the conscious patient and as such poor oral health not only impacts on quality of life (Sheiham 2005) but can necessitate high risk anaesthesia. To date the limited literature available regarding the oral health of this group of patients is provided by sporadic case reports and epidemiological studies of small cohorts (Table 2). Therefore, the aim of the current investigation was to systematically assess the oral health of all patients under treatment for MPS disorders in a major metabolic disease referral centre.

Materials and Methods

A cross-sectional investigation was undertaken in the Department of Clinical Inherited Metabolic Disorders at Birmingham Children's Hospital, United Kingdom between December 2008 and July 2009. Ethical approval was obtained through the UK National Research Ethics Service prior to the commencement of the study (REF: 08/H1202/

119). All patients diagnosed with an MPS disorder and under care of the metabolic department were invited to participate resulting in 49 invitations. If a patient was too un-cooperative to successfully complete an element of the oral examination, the patient was excluded from this part of the study. Attempts were made to recruit an unaffected sibling control group but unfortunately compliance was poor and therefore the national epidemiological data from the most recent child dental health survey in 2003 (White and Lader 2004; Pitts and Harker 2005) matched to age groups was referred to for control data.

Clinical oral examinations were undertaken by a single Paediatric Dentist trained in epidemiological examinations. A validated screening tool using the criteria of diagnosis of the British Association for the Study of Community Dentistry (BASCD 2005) was employed. Due to practical constraints of the multidisciplinary clinic setting, the oral examination was performed under artificial lighting, either on a hospital trolley or where the child was unable to co-

operate for this, in their wheelchair. Data recorded included a dental charting which detailed the number of, decayed, missing and filled teeth (coded as DMFT for adult dentition and dmft for deciduous dentition). The mouth was subsequently divided into sextants and the gingival health was qualified by observing gingival redness (an indirect measure of gingival inflammation) and visible plaque and calculus representative of the level of oral hygiene maintenance. The presence of any gingival overgrowth, enamel opacities and structural anomalies of the dental hard tissues were also recorded. A simple questionnaire (simplified and modified from a previous audit) was provided to the parents or guardians in order to establish the current awareness and uptake of available primary and secondary dental care services and to assess the perceived difficulties in achieving adequate oral health care for their child. These were completed by the parents/guardians independently in the waiting area before their appointment; any questions were answered by the research nurses.

Results

Of the 49 invited patients with an MPS disorder, 46 agreed to take part in the study. This group comprised of 22 females and 24 males, aged between 2 and 28 years old. The groups included 5 subjects with MPS I, 6 with MPS II, 15 with MPS III, 17 with MPS IV, 2 with MPS VI and 1 patient with multi-sulphatase deficiency. All patients with MPS I, II and VI were currently receiving enzyme replacement therapy.

Experience of Dental Caries

All 46 patients were examined for dental caries. Overall 23 (51%) patients had no decayed, missing or filled teeth, 22 (49%) had decay experience. The level of dental decay was inconsistent between the different groups of MPS disorders with the patients with an MPS type IV disorder having experienced an increased level of dental caries (Table 3).

The MPS I and IV groups did experience considerable dental caries. Group IV ranged from 3 to 28 years old and the number of decayed teeth ranged from 0 to 11. The average dmft (deciduous dentition) was 3.21 (45/14, $n = 14$ with teeth in the primary dentition) and the average DMFT (permanent dentition) was 1.67 (14/12, $n = 12$ with erupted first permanent molar teeth). The total number of dmft and DMFT is over 17 because some subjects are in the mixed dentition and therefore the coding system allows them to have both a dmft and DMFT. Figures 1 and 2 show the level of dental decay experienced by the study group as a whole and the type IV group specifically against the Child Dental Health survey levels of decay in both the West Midlands and the UK as a whole for both the primary and secondary dentition. Both the West Midlands data and the UK data are useful for comparison because the study group has been recruited from a regional centre and therefore not all the recruited patients will reside in the West Midlands.

Gingival Health

As a whole group (40 patients were examined, 6 were poorly co-operative and accurate observations were not possible): 17 (43%) exhibited marginal gingivitis, 24 (60%) had evidence of plaque deposits and 19 (48%) had evidence of calculus. Aged matched comparisons were performed

Table 3 Decay experience stratified according to MPS diagnostic group

Research group	No of patients with caries experience	Total patients in group	% patients experiencing dental caries
MPS I	3	5	60
MPS II	1	6	17
MPS III	4	15	27
MPS IV	13	17	76
MPS VI	0	2	0
MSD	1	1	100

Fig. 1 A graph comparing the level of decay experience in primary teeth of the study group, MPS IV and the general population

Fig. 2 A graph showing the level of decay experience in the adult dentition of the study group, MPS IV and the general population

Table 4 Child dental health survey 2003 results

Age	Gingivitis %	Plaque %	Calculus %
5	32	50	5
8	63	76	16
12	65	73	20
15	52	63	32
Study group	43	60	48

against National epidemiological data and increased levels of plaque and calculus deposits were observed in the study group but no increase in gingivitis was evident (White and Lader 2004). Table 4 shows the Child dental health survey 2003 results.

Opacities and Enamel Defects

Enamel opacities were recorded in patients with permanent incisor teeth only (19 patients) of which 10 patients exhibited opacities on their teeth. Although not included in the criteria of diagnosis, it was noted that all patients with MPS IV exhibited enamel defects. In both the primary and permanent dentition, the defects gave the appearance of generalised white chalky enamel and the teeth had pronounced sharp pointed cusps.

Oral Health Maintenance

The parents or carers of all patients ($n = 46$) responded to the oral health maintenance questionnaire. Despite being subject to both recall bias and the possibility that some of the answers given were provided to “please the researchers”, it suggested some interesting thoughts worthy

of mentioning in this report; 48% of the study population considered themselves to regularly access dental care for their child. Of the 46 patients, 23 had visited a dentist in the preceding 6 months and a further 12 within the past year. Five parents reported only accessing dental care when they believed their child was in pain and of concern, 9 reported never having visited the dentist. Of the reported regular dental attendees, 47% accessed their care through the Children’s Hospital, 44% in a local community setting and 9% visited both services. When questioned whether they had ever received advice on how to maintain their child’s oral hygiene 67% reported they had and 59% reported to have received advice regarding preventing tooth decay. The parent/guardians recall of patient brushing habits were as follows: 2 patients never brushed their teeth, 1 managed once a week, 4 once or twice a week, 24 once a day, 13 twice a day and 2 reported to brush more than twice a day. It was reported that 23 patients had experience of having dental treatment carried out of which 17 patients required a general anaesthetic for this purpose. Parents commented that cleaning their child’s teeth can be extremely difficult and that they would be concerned if their child required dental restorations.

Discussion

The series of 46 patients with an MPS disorder described is the largest cohort to undergo a detailed oral health assessment reported in the medical and dental literature to date. However given the rarity of the diseases and the large number of clinical and patient-based variables, it was accepted that the power of any statistical enquiries to compare with national epidemiological data for unaffected individuals would be too weak for a valid analysis. At the outset, attempts were made to recruit sibling controls to

account for familial dietary and hygiene patterns but unfortunately few siblings, although invited, attended the dental examination. In order to provide the most valid comparison with national epidemiological data, where possible the conditions of examination matched those of the 2003 UK Child Dental Health Survey.

The group of patients described had significant oral health needs as a consequence of the effects of both their MPS disorder and the special measures required providing care for them on a day-to-day basis. The study highlights that access to regular professional dental care is important in order that problems in the form of developmental anomalies or disease are identified and that appropriate preventative interventions can be provided. With the exception of MPS IV patients, there was considerable heterogeneity in the prevalence of predisposing dental anomalies and poor hygiene and in the incidence of decay and gingivitis between and within classes of MPS. Therefore, given the serious challenges in providing dental treatments, and considering the evidence from the literature about increased oral health needs in vulnerable groups of patients (Lewis 2009; Shaw et al. 1986; Purohit et al. 2010) the authors recommend that dental professionals should consider all patients with an MPS disorder as being at high-risk of dental disease. Failure by parents and carers to access dental care needs to be addressed. According to the questionnaire results; 5 parents reported only accessing dental care when they believed their child was in pain and of concern, 9 reported never having visited the dentist showing that despite attending a unit where access to dental care is possible many are not receiving regular oral health care. The identification of oral health problems is often particularly important to rule out/identify issues when behaviour has changed e.g. teething or drooling, this is particularly important in patients with an MPS III disorder as their disease symptoms progress and disruptive behaviour becomes evident.

Within the limitations of the current study, the findings support the observations of Mc Govern et al. (2008) that MPS I patients do not have an increased dental caries rate. The MPS groups II, III and VI also show a low caries rate though firm conclusions are difficult to justify given the small sample size. The MPS IV group did appear to show an increased caries rate in comparison with the other MPS groups and the national epidemiological studies. The group also displayed developmental anomalies of both the permanent and primary dentition. Such defects in the appearance of the enamel in patients with MPS IV have been reported previously (Lustmann 1978) and have been described as being similar in appearance to that of amelogenesis imperfecta (Sela et al. 1975). However, to date no

studies have commented on an increased caries rate. Given the structural defects, one could conceive these teeth may be more prone to caries in an unfavourable oral environment; however, further studies would be required to confirm this finding. It is important to note that the development of the dental enamel of the primary dentition and of the several permanent successor teeth occurs largely *in-utero* or soon after birth. Therefore, despite the advances in enzyme replacement therapies, the management of such dental anomalies is likely to remain a concern and problem.

The current investigation demonstrated that despite the special needs and physical difficulties of patients with an MPS disorder, a similar level of oral hygiene to the general population was maintained. Within the study population, only a slight increase in the levels of plaque and calculus was observed. Although this measure of oral health is relatively crude and based only on visual assessment, the observation was surprising and indicates that despite the adversities patients are still managing a reasonable level of oral hygiene indicating the possible increased caries rate is due to other factors. Any gingival hypertrophy was considered the dental assessment but none was noted. In the past, this has been mentioned as a feature of MPS I (Güven et al. 2008; Thomas and Tandon 2000). This finding is possible due to the fact that the MPS I patients in our study were all on enzyme therapy, and this perhaps is prevented or reduced to an undetectable level by the enzyme therapy. As a group the patients with an MPS disease do use the BCH dental services and with so many medical appointments it is often convenient for the families to attend at BCH; 50% of the study group had already received some dental treatment and 43% required this to be carried out under a general anaesthetic. Despite this, a significant number were still not accessing the dental services. It is therefore important that we continue to work with these patients in order to improve the oral health care they receive.

Summary

- MPS disorders do have an effect on the developing dentition and to date the effect of enzyme therapy is largely unknown.
- Maintaining good oral health is challenging; however, prevention of dental decay, periodontal disease and erosion is extremely important.
- Regular visits to the dentist are recommended.
- We need to work together to improve existing services and create a service for the future generation, including adolescent and adult services.

Synopsis

Synopsis: MPS disease does have an impact on oral health and the developing dentition, the extent of which varying between disease type. To date the effect of enzyme therapy on the oral health is largely unknown.

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