Sara L Hughes

Rachel C Parkes, Nicholas Drage and Mechelle Collard

Early Tooth Loss in Children: A Warning Sign of Childhood Hypophosphatasia

Abstract: Premature exfoliation of primary teeth may be the first manifestation of this serious condition and the general dental practitioner plays an important role in recognizing dental anomalies and referring patients at an appropriate time. This is imperative to ensuring early diagnosis and good quality patient care. This article describes the case of a 4-year-old boy affected by childhood hypophosphatasia, who presented with premature exfoliation of his primary teeth as the first manifestation of this condition. An overview of the condition is outlined including a discussion of the likelihood of permanent dentition involvement.

CPD/Clinical Relevance: Oral manifestations of hypophosphatasia may be the first and the only signs of this condition and may be the basis upon which a diagnosis is made.

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Case report

A 4-year-old boy (JJ) was referred to the Unit of Paediatric Dentistry at the University Dental Hospital, Cardiff by a consultant paediatrician regarding premature exfoliation of his primary teeth. JJ's parents were concerned about the rapid loss of his teeth along with delayed growth, for which he was under the care of both a geneticist and a paediatrician. Despite numerous medical investigations, a definitive diagnosis had not been confirmed.

JJ's first tooth erupted at the age of 15 months, became progressively mobile and exfoliated shortly afterwards. A total of 11 primary anterior teeth excluding the URC exfoliated promptly after eruption and JJ's mother reported difficulties with speech and mastication. JJ has a fit and healthy 6-year-old brother and no known family history of dental abnormalities.

Extra-orally, JJ was of small stature with a dolichocephalic head shape. Intra-orally, the soft tissues were healthy, the dentition was caries free and oral hygiene was good. Teeth present included all primary molars and the URC, all other primary teeth having exfoliated (Figure 1). The URC was grade 2 mobile.

The roots of the exfoliated primary teeth were of a substantial length with only a small degree of root resorption (Figure 2).

Oblique lateral radiographs revealed mildly enlarged pulp chambers of the primary molars. In addition, the crown morphology of both lower first permanent molars was abnormal with enlargement of the lower part of the bony crypt of the lower right first permanent molar (Figure 3).

Systemic conditions associated with premature tooth exfoliation include Papillon-Lefèvre syndrome, Chediak-Higashi syndrome, Langerhans cell histiocytosis, neutropenia, leukaemia and hypophosphatasia.

The clinical and radiographic examination suggested a possible diagnosis of hypophosphatasia. A definitive diagnosis of 'Childhood' hypophosphatasia was confirmed by a consultant paediatric endocrinologist following a deficient serum alkaline phosphatase measurement of 35 IU/L. This was further supported by a quantitative urine amino acid screen and the presence of radiolucencies in the metaphyseal area of the bones.

Dental treatment focused on improving speech and eating difficulties and his lack of confidence associated with so many missing anterior teeth. This

Sara L Hughes, BDS, MFDS RCS(Glasg), Dental Foundation Trainee Year 2, Unit of Paediatric Dentistry, **Rachel C Parkes,** BDS, MFDS RCS(Glasg), Specialist Trainee in Paediatric Dentistry, Unit of Paediatric Dentistry, **Nicholas Drage,** BDS, FDS RCS(Eng), DDR RCR, Consultant in Dental and Maxillofacial Radiology, Department of Dental Radiology and **Mechelle Collard,** BDS, MPhil, FDS(Paed Dent) RCS(Eng), Consultant in Paediatric Dentistry, Unit of Paediatric Dentistry, University Dental Hospital, Cardiff, UK.

involved the fabrication of upper and lower removable partial dentures (Figure 4). Since undergoing this treatment, JJ unfortunately developed caries in the URE and ULE which, although restored, have developed periapical infections and are due to be extracted under general anaesthesia. Long-term, JJ will require regular 3–6 monthly follow-up appointments incorporating an intensive preventive regimen along with the fabrication of new partial dentures as he grows. Monitoring of the permanent dentition will be imperative.

Discussion

Hypophosphatasia is a rare inherited disorder caused by mutations in the bone/liver/kidney alkaline phosphatase gene encoding tissue non-specific alkaline phosphatase; an enzyme involved in bone mineralization.[1] The condition is characterized by a deficiency of bone and serum alkaline phosphatase activity leading to defective hard tissue mineralization.[2]

The mode of inheritance determines the severity of the condition, ranging from autosomal recessive transmission in severe forms to both autosomal recessive and dominant transmission in moderate forms.[3] It is estimated that 1 in 100,000 new-borns are born with a severe form of hypophosphatasia and that less severe forms are more prevalent.[1]

There are six clinical forms of hypophosphatasia.[4] These are based on the age of the patient at diagnosis and the severity of the condition and are classified as prenatal (benign), perinatal (lethal), infantile, childhood, adult and odonto-hypophosphatasia. Our patient presents with the childhood form of hypophosphatasia where onset is usually after 6 months of age.

Clinical features vary overall and within each subgroup. The childhood form is characterized by loss of teeth, short stature and may be accompanied by a delay in walking, a waddling gait and skeletal deformities.[2] Spontaneous remission of bone symptoms within this subtype have been reported but the disease may reappear in middle or late adulthood.[3,5]

The predominant oral manifestation is premature exfoliation of deciduous teeth, mainly in the anterior mandibular region.[1] This is accompanied by reduced alveolar bone height with lack of root resorption and inflammatory periodontal changes.[3,6] Microscopically, pre-dentine is widened, dentinal tubules are enlarged and reduced in number, pulp chambers are enlarged and root canals are short. The severity of tooth loss has been strongly correlated with the general severity of the condition.[6]

Patients with severe forms are more likely to lose both anterior and posterior primary teeth and at a younger age than those with moderate forms, where the primary anterior teeth alone are lost.[3] Delays in eruption should be considered as an indicator for severe cases.[3] JJ's first tooth did not erupt until 15 months of age, which strengthens concerns about the severity of his condition. These features could be helpful in determining involvement of the permanent dentition and should be considered as part of the long-term management of this patient.

Although not fully understood, the premature exfoliation of primary teeth is thought to be related to the impaired formation of the cementum. This is particularly marked in the childhood subgroup. Beumer *et al* reported diminished cementum formation in prematurely exfoliated teeth of patients with hypophosphatasia.[6] This was particularly observed along the roots of incisors compared with canines and molars, which could be related to heightened disease activity at the time these teeth were developing.

One possible theory behind premature exfoliation of, in particular, the mandibular primary incisors, relates to their small root anatomy and the occlusal pressure placed upon them by the peripheral soft tissues, being the first teeth to erupt.[1] The lack of cementum and subsequent loss of alveolar bone could mean that these teeth are unable to withstand these conditions in comparison to their unaffected counterparts.

Ultrasonography is used to diagnose pre-natal benign and peri-natal

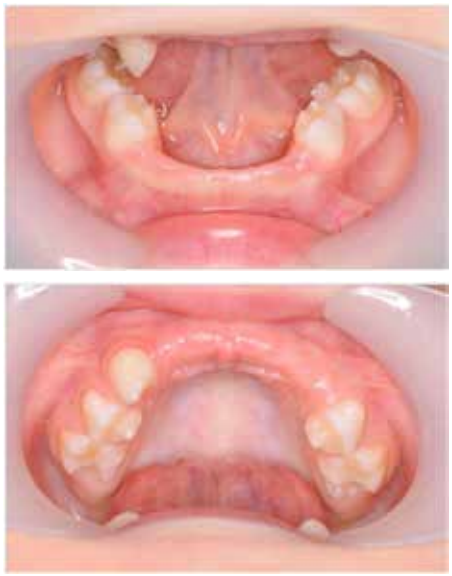

Figure 1. (a, b) Maxillary and mandibular occlusal views showing missing anterior teeth.

Figure 2. Exfoliated primary anterior teeth (excluding the URC).

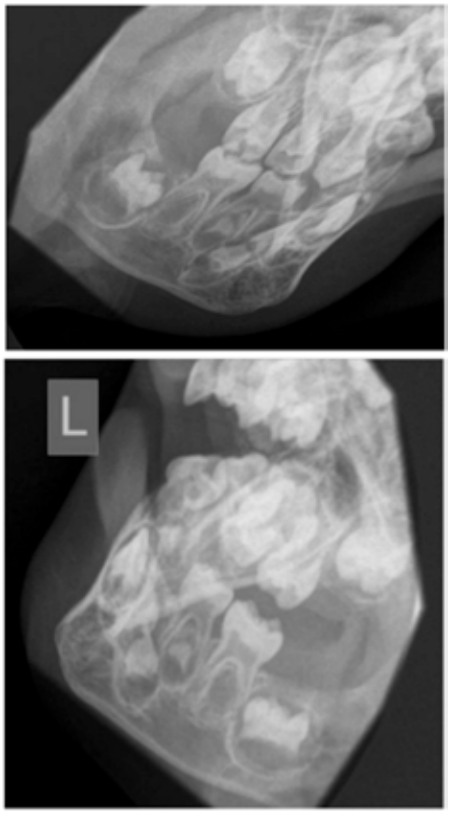

Figure 3. (a) Right and **(b)** left oblique lateral radiographs.

lethal forms of this condition. Clinical examination, radiography and biochemical testing of blood and urine are used in other forms. Two main diagnostic markers of this condition are excessive amounts of phosphoethanolamine in the urine and low levels of serum alkaline phosphatase activity.[2,6] Differential diagnosis includes pre-pubertal periodontitis, Langerhans cell histiocytosis and blood dyscrasias such as neutropenia and leukaemia.[7]

Currently, there is no accepted medical treatment for this condition and management focuses on symptomatic relief with the use of non-steroidal anti-inflammatories. In cases of bone fractures and skeletal deformities, orthopaedic intervention may be necessary. There is evidence to support the use of enzyme replacement therapy which, if applied early in post-natal life, could prevent accelerated tooth loss in patients with hypophosphatasia.[8] JJ was not eligible for this treatment owing to progress in his growth.

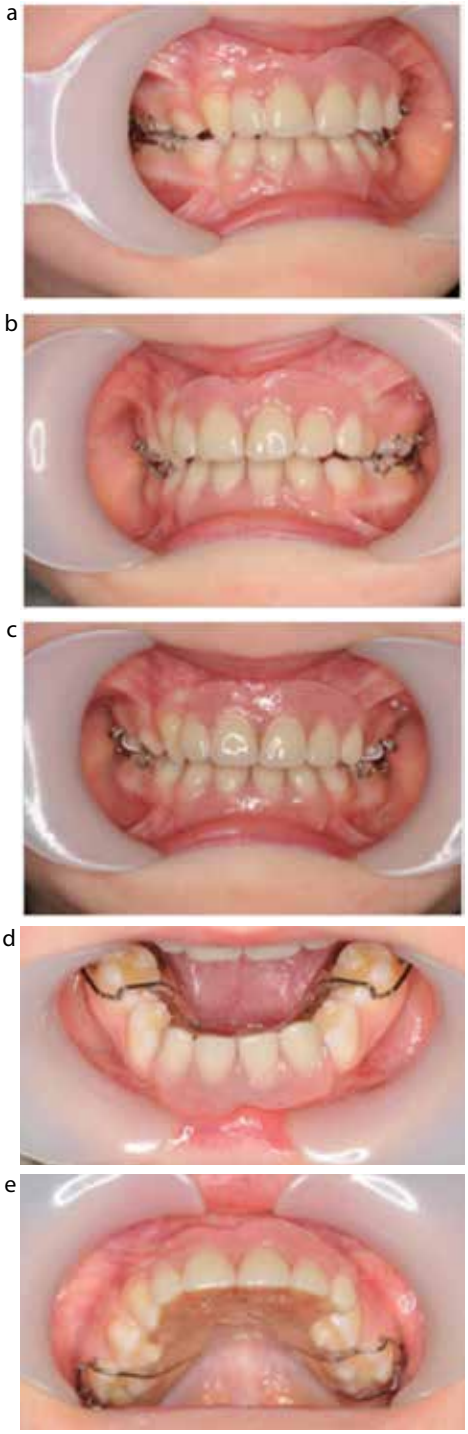

Figure 4. (a–e) Removable partial dentures fitted.

To reduce excessive loading on already compromised teeth, fabrication of removable partial dentures has shown to even out the occlusal forces around the arch and improve aesthetics, mastication and speech.[9]

Involvement of the permanent dentition

Literature on the effect of infantile and childhood hypophosphatasia on the permanent dentition is limited and varied. In this particular case there were differences in opinions between dental professionals and endocrinology specialists regarding the involvement of the permanent dentition.

There are case studies supporting the absence of permanent tooth involvement in patients with childhood hypophosphatasia,[1,3,6,10] including a study of three male siblings.[10] While results were promising, patients involved in these studies were often young adults and therefore the absence of dental anomalies in later life cannot be assumed. Despite this, there are reports of permanent dentition involvement including reduced alveolar bone height, premature loss of the maxillary central incisors, abnormal root cementum and large coronal pulp chambers of the molars.[11,12]

While anecdotal reports are useful, lack of robust long-term studies makes the understanding of permanent dentition involvement difficult. With more than 190 mutations involved in this complex condition,[5] it is not surprising that there is such variable clinical expressivity and could well account for why permanent dentition involvement is inconsistent among individuals.

The degree of dental involvement has been directly correlated with general disease severity[3] and therefore it could be reasonable to assume that permanent tooth involvement is more likely in individuals with more severe forms. Although there is no evidence to support this as an indicator of permanent tooth involvement, practitioners may consider this as part of their long-term management.

Conclusion

Patients with hypophosphatasia have significant dental needs and early recognition of the condition is essential for diagnosis. One of the first and only manifestations may be the premature exfoliation of primary teeth. Dental professionals should consider hypophosphatasia as part of the differential diagnosis in such cases. Literature regarding permanent tooth involvement in cases of infantile and childhood hypophosphatasia

is limited and varied, however, the potential for individuals to experience dental abnormalities later in life should be considered and long-term, regular monitoring of these patients is essential.

Acknowledgement

All images were taken at the photography department of the University Dental Hospital, Cardiff, with full signed consent from the patient's parents.

References

1. Okawa R, Nakano K, Matsumoto M. Oral manifestations of patients with Hypophosphatasia. *Paed Dent J* 2012; **22**: 155–162.
2. Haliloglu B, Guran T, Atay Z *et al*. Infantile loss of teeth: odontohypophosphatasia or childhood hypophosphatasia. *Eur J Paediatr* 2013; **172**: 851–853.
3. Reibel A, Manière M-C, Clauss F *et al*. Orodental phenotype and genotype findings in all subtypes of Hypophosphatasia. *Orphanet J Rare Dis* 2009; **4**: 6.
4. Hollis A, Arundel P, High AS, Balmer R. Current concepts in hypophosphatasia: case report and literature review. *Int J Paediatr Dent* 2013; **23**: 153–159.
5. Mornet E, Taillandier A, Peyramaure S *et al*. Identification of fifteen novel mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene in European patients with severe hypophosphatasia. *Eur J Hum Genet* 1998; **6**: 308–314.
6. Beumer J, Trowbridge HO, Silverman S. Childhood hypophosphatasia and the premature loss of teeth. *Oral Surg Oral Med Oral Pathol* 1973; **35**: 631–640.
7. Watanabe K. Prepubertal periodontitis: a review of diagnostic criteria, pathogenesis, and differential diagnosis. *J Periodont Res* 1990; **25**: 31–48.
8. McKee MD *et al*. Enzyme replacement therapy prevents dental defects in a model of hypophosphatasia. *J Dent Res* 2011; **90**: 470–476.
9. Grewal PS, Gupta KP. Prosthetic rehabilitation of a young patient with Hypophosphatasia – a review and case report. *Contemp Clin Dent* 2012; **3**: 74–77.
10. Lepe X *et al*. Absence of dental anomalies in familial hypophosphatasia. *J Periodont Res* 1997; **32**: 375–380.
11. Olsson A, Matsson L, Blomquist HK, Sjödin B. Hypophosphatasia affecting the permanent dentition. *J Oral Pathol Med* 1996; **25**: 343–347.
12. El-Labban NG, Lee KW, Rule D. Permanent teeth in hypophosphatasia: light and electron microscopic study. *J Oral Pathol Med* 1991; **20**: 352–360.