

Report of Two Dental Patients Diagnosed with Hypophosphatasia

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Abstract

Hypophosphatasia is a rare inherited skeletal disorder characterized by defective bone mineralization and tissue non-specific alkaline phosphatase (TNSALP) deficiency, with mutations in the gene encoding the TNSALP isozyme the cause. As for dental manifestations, premature loss of primary teeth due to disturbed cementum formation is well known and tooth roots in affected patients are not able to adequately attach to absorbed alveolar bone due to malformed cementum. We report spontaneous early exfoliation along with mild to severe mobility of primary anterior teeth in 2 child patients referred to pediatric dentists from a general dental practitioner. Case 1 was a 1-year-7-month-old boy with 3 mandibular incisors exfoliated, while Case 2 was a 3-year-3-month-old girl with 1 mandibular central incisor exfoliated. The possibility of hypophosphatasia was considered and the patients were referred to the Pediatric Clinic of Osaka University Medical Hospital, where each was diagnosed with hypophosphatasia (odonto type). We performed repeated periodontal treatments and applied removable partial dentures in both cases, which solved esthetic and functional problems. Although the incidence is quite low, it is important to diagnose hypophosphatasia as early as possible for planning general and dental preventive approaches. In patients with mild forms, such as odonto and childhood types, early exfoliation of primary teeth identified in a dental examination can occasionally lead to early diagnosis of hypophosphatasia. In addition, dental findings obtained by a dentist are useful to identify patients with a risk of hypophosphatasia, who can then be immediately referred to a pediatrician for more detailed systemic examinations. Thus, a cooperative relationship between pediatricians and pediatric dentists should be regarded as necessary. This is the first known report to describe cases of hypophosphatasia diagnosed after referral from a pediatric dentist because of typical dental findings for the disorder.

Keywords: Alkaline phosphatase; Cementum; Early exfoliation; Hypophosphatasia; Primary teeth

Introduction

Primary teeth generally begin to emerge into the oral cavity at around 8 months of age, typically starting from the lower anterior teeth, with all emerging into the oral cavity by approximately 2.5 years old [1]. At around 5 or 6 years of age, the first permanent tooth begins to emerge into the oral cavity, typically a lower anterior tooth with replacement of the corresponding primary teeth, followed by posterior teeth with addition of distal positioning of the most distal primary molar tooth [1,2]. Thus, most general dentists consider it to be quite uncommon to encounter cases of spontaneous exfoliation of primary teeth in patients under the age of 4 years.

Hypophosphatasia is a rare inherited skeletal disorder characterized by defective bone mineralization and deficiency of tissue-nonspecific alkaline phosphatase (TNSALP) [3]. The disease is caused by mutations in the gene encoding the TNSALP isozyme and frequency has been estimated at 1 per 150,000 newborns [4]. Hypophosphatasia is classified into 6 clinical forms, perinatal lethal, perinatal benign, infantile, childhood, adult, and odonto-hypophosphatasia, based on the age at diagnosis, as well as severity of associated signs and symptoms [5]. As for dental manifestations, early exfoliation of primary teeth due to disturbed cementum formation has been reported [5].

It is known that some systemic diseases present unique dental findings, leading the attending dentist to suspect several different causes, among which hypophosphatasia is well known. However, there have been few reports describing details of patients with hypophosphatasia who were ultimately diagnosed after being referred based on dental findings. Here, we present 2 cases of hypophosphatasia diagnosed by pediatricians following referral from pediatric dentists because of typical dental findings.

Case Reports

Brief information regarding the present cases is described in the

Table. Both patients were referred to the Pediatric Dentistry Clinic of Osaka University Dental Hospital by general dental practitioners for detailed examinations of spontaneous early loss of primary anterior teeth.

Case 1

Male: An intraoral examination at the first visit demonstrated that 3 mandibular primary incisors were already exfoliated (Figure 1a). According to his mother, the mandibular primary central incisors were spontaneously exfoliated at the age of 1Y2M, while the mandibular primary left lateral incisor was exfoliated at 1Y6M without trauma. We were shown 2 of the exfoliated teeth and it was noted that the roots had not been absorbed (Figure 1b). In addition, prominent mobility was observed in 2 anterior teeth. Although his mother did not report any systemic problems, we suspected that the patient might be complicated with a systemic disease such as hypophosphatasia. Therefore, he was referred to the Pediatric Clinic of Osaka University Hospital for further consultation, where he was diagnosed with hypophosphatasia (odonto type) with a low level of Alkaline Phosphatase (ALP) in serum (192 IU/l) and a high level of phosphoethanolamine (PEA) in urine (898.8 nmol/mg Cr). On the other hand, radiological examinations of the lower extremities and hands at 1Y6M did not show the metaphyseal irregularity rickets (Figures 1c-1e), though the patient was short

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in stature (-2.5 SD) and TNSALP gene sequencing demonstrated a heterozygous c.550C>T (p.Arg184Trp) mutation.



Figure 1a: Intraoral photograph taken at first visit (1Y7M).



Figure 1b: Exfoliated primary teeth.



Figure 1c: Radiograph of lower extremities (1Y8M).



Figure 1d: Radiograph of left hand (1Y8M).



Figure 1e: Radiograph of right hand (1Y8M).

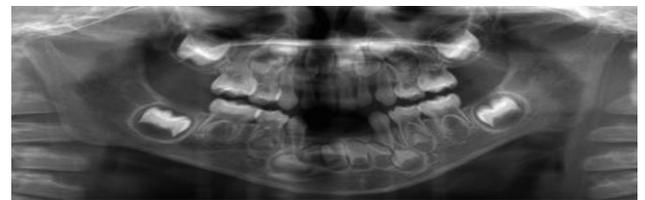


Figure 1f: Orthopantomograph taken at 3Y5M.



Figure 1g: Intraoral photograph before application of partial denture (3Y11M).



Figure 1h: Intraoral photograph after application of partial denture (3Y11M).

At 2Y11M, the mandibular primary right lateral incisor was exfoliated and orthopantomograph findings obtained at the age of 3Y5M showed mild absorption of the alveolar bone at the corresponding location (Figure 1f). Thereafter, the patient gradually responded to various dental procedures and we began to manufacture removable partial dentures (Figure 1g), which were applied at the age of 3Y11M (Figure 1h). At 4Y1M, the maxillary primary left central incisors were spontaneously exfoliated (Figure 1i), even though the roots were not resorbed (Figure 1j). A histopathological examination at that time revealed disturbed cementum formation (Figure 1k). Finally, we produced a maxillary partial denture and applied it for the patient (Figures 1l and 1m).

Case 2

Female: An intraoral examination at the first visit demonstrated that 1 mandibular primary central incisor was already exfoliated

(Figure 2a), while orthopantomograph findings showed mild absorption of alveolar bone at the corresponding location (Figure 2b). According to the mother of the patient, the mandibular primary left central incisor had spontaneously exfoliated at the age of 3Y0M. Periapical radiography showed severe absorption of the alveolar bone (Figures 2c-2e). Furthermore, the other 4 incisors demonstrated prominent mobility (Table 1). Although her mother did not report any



Figure 1i: Intraoral photograph before application of partial denture (4Y1M).



Figure 1j: Exfoliated primary teeth.



Figure 1k: Histopathological appearance of roots of primary teeth.



Figure 1l: Partial denture.



Figure 1m: Intraoral photograph after application of partial denture (4Y3M).



Figure 2a: Intraoral photograph taken at first visit (3Y3M).



Figure 2b: Orthopantomograph taken at 3Y3M.



Figure 2c: Periapical radiograph taken by general practitioner prior to referral to our clinic at 2Y10M.



Figure 2d: Periapical radiograph taken by general practitioner prior to referral to our clinic at 3Y2M.



Figure 2e: Periapical radiograph taken by general practitioner prior to referral to our clinic at 3Y3M.

systemic problems, we suspected that the patient might be complicated with a systemic disease such as hypophosphatasia and referred her to the Pediatric Clinic of Osaka University Hospital for consultation. Low serum

Case	Sex	First visit to dentist	Primary dentition conditions at first visit										ALP value (IU/l)	PEA value (nmol/mgCr)	Final visit to dentist	
			E	D	C	B	A	A	B	C	D	E				
			E	D	C	B	A	A	B	C	D	E				
1	M	1Y7M	NE										NE	192 (1Y8M)	898.8 (1Y8M)	5Y2M
			NE										NE			
2	F	3Y3M												254 (3Y5M)	Not Detected	4Y11M

Spontaneously exfoliated
 Severe mobility
 Mild mobility
 NE: Not yet emerged into oral cavity

Table 1: Summary of present patients with hypophosphatasia.



Figure 2f: Radiograph of lower extremities (3Y5M).



Figure 2g: Radiograph of right hand (3Y5M).



Figure 2h: Exfoliated primary teeth.

ALP (254 IU/I) was found and a diagnosis of hypophosphatasia (odontotype) was made. Radiological examinations of the lower extremities and hands at 3Y5M did not show any signs of rickets (Figures 2f and 2g).

The mandibular primary right central incisor was extracted at the age of 3Y6M due to severe mobility. The root of the extracted tooth was not absorbed (Figure 2h) and histopathological findings revealed a



Figure 2i: Histopathological appearance of roots of primary teeth.



Figure 2j: Intraoral photograph before application of partial denture (3Y8M).



Figure 2k: Partial denture.



Figure 2l: Intraoral photograph after application of partial denture (3Y8M).

near total lack of cementum (Figure 2i). We applied removable partial dentures at the age of 3Y8M (Figures 2j-2l) and then refashioned them at 4Y11M because of incompatibility due to mandible growth.

Discussion

This is the first known report to describe cases of hypophosphatasia diagnosed following referral from a dentist based on findings of spontaneous early exfoliation of primary teeth. In normal individuals, the tooth root surface is covered with cementum tissue, which attaches to alveolar bone via the periodontal ligament. However, in those with hypophosphatasia, the root is not able to adequately attach to absorbed alveolar bone due to disturbed cementum, leading to spontaneous early exfoliation of the affected tooth [5-8]. Dentists can screen for possible cases of hypophosphatasia if they have such knowledge and then refer the suspected patient to a pediatrician for more detailed examinations.

In both of the present cases, exfoliation of primary anterior teeth had started before the age of 4 years and the roots of those teeth appeared to have not undergone resorption, both of which should be regarded as typical dental findings in hypophosphatasia cases. Our patients were ultimately diagnosed with odonto type and no treatments were performed by the attending pediatricians. Mild forms of hypophosphatasia, such as odonto type, are thought to occur most often, with a frequency of 37% reported [9]. Although no medical approaches for cases with odonto type have been reported, affected patients may develop possible problems in the jaw bones. Thus, we consider it necessary to develop some options for improvement of the condition and its associated symptoms by accumulation of similar case reports. In addition, communication between pediatric dentists and pediatricians is important to better treat patients with hypophosphatasia.

Although the present patients were diagnosed as odonto type and no treatment was performed by their respective pediatricians, it is possible that dentists will encounter other mild cases, such as childhood and adult types, which will require medical intervention as soon as possible. Thus, it is important to find patients with a risk of hypophosphatasia based on dental findings by a dentist, who can then immediately refer them to pediatricians for more detailed examinations. A cooperative

relationship between pediatricians and pediatric dentists is also necessary for such cases.

As for dental treatment for hypophosphatasia patients, periodontal therapy is important for teeth with mobility. Although that may not recover a healthy condition, it can maintain the stability of the current condition, thus enabling preservation of affected teeth as long as possible. In addition, application of a partial denture is a useful treatment modality for cases with tooth loss, as that can solve not only esthetic but also functional problems, such as mastication and speech. We were able to adequately perform those treatments for the present cases. For patients referred by a pediatrician, it often takes time to initiate such treatment, thus pediatricians should also refer these patients to pediatric dentists if their condition is adequate to undergo dental examinations.

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