Oral manifestations of patients with hypophosphatasia

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Abstract  Hypophosphatasia is a rare inherited disorder characterized by defective bone mineralization and deficiency of tissue non-specific alkaline phosphatase (TNSALP) activity. The disease is caused by mutations in the liver/bone/kidney alkaline phosphatase gene (ALPL) encoding TNSALP. As for dental manifestations, premature loss of deciduous teeth due to disturbed cementum formation is well known. However, few reports of multiple cases have been presented. The oral manifestations of patients diagnosed with hypophosphatasia were analyzed by collecting clinical records of cases from a nationwide survey of pediatric dentistry clinics affiliated with 29 university dental hospitals in Japan. We inquired regarding the number of cases and clinical findings of diagnosed patients. We obtained information for 9 children diagnosed with hypophosphatasia from our university and 10 from 6 other universities. The main oral manifestation was early exfoliation of deciduous teeth, which was found in 15 of the 19 cases. Early exfoliation of mandibular deciduous anterior teeth was recognized in 14, whereas there were no cases of early exfoliation of a permanent tooth. The main oral finding of hypophosphatasia was early exfoliation of deciduous teeth, predominantly in the mandibular anterior region of children aged 1 to 4 years old.

Key words  Cementum, Early exfoliation, Hypophosphatasia, Mandibular anterior teeth, Primary teeth

Introduction

Hypophosphatasia is a rare inherited disorder related to deficiency of tissue non-specific alkaline phosphatase (TNSALP) activity and characterized by defective bone mineralization⁶. The frequency of severe forms of hypophosphatasia has been estimated to be 1 per 100,000 newborns, while mild forms of the disease are considered to be more common²⁻⁴. Hypophosphatasia is inherited as an autosomal recessive trait, though autosomal dominant inheritance has been reported in some milder cases⁵. The disease is caused by mutations in the liver/bone/kidney alkaline phosphatase gene (ALPL) encoding TNSALP⁶, with more than 200 mutations in the ALPL gene reported⁷. In Japanese patients, the F301L and T1559del mutation types are commonly found in the TNSALP gene⁷, of which the former is reported to be associated with relatively mild forms and the latter type with the lethal form⁹.

Six clinical forms of hypophosphatasia, perinatal lethal, perinatal benign, infantile, childhood, adult, and odonto-hypophosphatasia, are currently recognized, which are classified based on the age at diagnosis, and the severity of associated signs and symptoms³⁴. The severity of the disease is generally correlated with the onset period, except for the odonto type⁷. Symptoms in patients with hypophosphatasia range from stillbirth without mineralized bone to isolated premature loss of primary teeth³⁴.
Most common oral manifestations in patients with hypophosphatasia are known to be premature loss of primary teeth due to impaired formation of the cementum, especially in childhood cases and odonto-hypophosphatasia type, with the latter not associated with abnormalities of the skeletal system\(^3,4\). Histopathological examinations of spontaneously exfoliated teeth have shown the lack of both cellular and acellular cementum\(^8,9\). In general, hypophosphatasia in childhood is often recognized by pediatric dentists when the patient visits a dentist for early and spontaneous exfoliation of a primary tooth\(^9\).

In the present study, the clinical records of 19 hypophosphatasia cases from 7 pediatric dental clinics of 29 university dental hospitals were examined and the oral manifestations presented are summarized.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Phenotype</th>
<th>First and last examination</th>
<th>Early exfoliated or extracted teeth</th>
<th>Genetic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>F</td>
<td>Perinatal (benign)</td>
<td>2Y7M–14Y3M</td>
<td>A</td>
<td>F301L</td>
</tr>
<tr>
<td>2a</td>
<td>F</td>
<td>Childhood</td>
<td>7Y0M–18Y0M</td>
<td>None</td>
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</tr>
<tr>
<td>3b</td>
<td>M</td>
<td>Odonto</td>
<td>3Y0M–8Y9M</td>
<td>A</td>
<td>A23V/E174G</td>
</tr>
<tr>
<td>4b</td>
<td>M</td>
<td>Childhood</td>
<td>3Y0M–8Y9M</td>
<td>CBA</td>
<td>A23V/E174G</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Perinatal (benign)</td>
<td>8Y8M–12Y4M</td>
<td>None</td>
<td>F301L</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Childhood</td>
<td>2Y2M–3Y9M</td>
<td>C</td>
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<tr>
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<td>M</td>
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<td>2Y2M–3Y7M</td>
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<tr>
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<td>4Y5M</td>
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<tr>
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<tr>
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<td>M</td>
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<td>12</td>
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<td>Odonto</td>
<td>5Y2M–23Y11M</td>
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<td>Exon 10 point mutation</td>
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<td>13</td>
<td>F</td>
<td>Odonto(^b)</td>
<td>4Y0M–8Y10M</td>
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<td>E218V/1559delT</td>
</tr>
<tr>
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<td>1Y5M–7Y</td>
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<td>17</td>
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<td>p327L/1559delT</td>
</tr>
<tr>
<td>18</td>
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<td>Childhood</td>
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</tr>
<tr>
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<td>F</td>
<td>Childhood</td>
<td>2Y7M–</td>
<td>BA</td>
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</tr>
</tbody>
</table>

\(^a\): Siblings, \(^b\): Fraternal twins, \(^c\): Odonto type, possibly childhood type, general information is lacking.
**Subjects and Methods**

**Collection of subjects with hypophosphatasia**

There were 9 children diagnosed with hypophosphatasia at our clinic, with the clinical oral features of 4 of those previously reported (Cases 1 to 4 in Table 1)\(^{10}\). In order to collect information from additional cases, we contacted clinics of pediatric dentistry at 28 other university dental hospitals in Japan and inquired regarding the existence of patients diagnosed with hypophosphatasia. In reply, we received information for 10 children from 6 universities, thus the total number of cases analyzed was 19 (11 males, 8 females). There were no cases reported from the other 22 university dental hospitals contacted.

**Clinical analyses**

The patient information was summarized in regard to gender, phenotype, chronological age at the
time of the first and last examinations, location of spontaneous early exfoliated teeth, and genotypes. An early exfoliated or extracted tooth was defined as a primary tooth exfoliated or extracted because of periodontal disease within 3 years after eruption of the primary tooth, which was determined from the mean eruption time of primary teeth in Japanese children.\(^{11}\)

**Results**

**Phenotypes**

The most frequent phenotype seen in the present study was the childhood type (9 cases), followed by odonto (n = 6), perinatal benign (n = 3), and infantile (n = 1) types. In addition, general information was not available for 1 of the patients (Case 13), who was classified as childhood type.

**Oral manifestations**

Early exfoliated or extracted primary teeth were found in 15 cases (Table 1). Most of those were identified in the anterior region, while there were no cases of early exfoliated or extracted permanent teeth.

The time of early exfoliation of primary anterior teeth is illustrated in Figs. 1 and 2, with findings for the right and left mandibular primary incisors and canines shown in Fig. 1. Early exfoliation of the mandibular primary central incisors before 4 years of age was seen in 74% (14/19 cases) of all cases and comprised 66% (25/38 teeth; 2 teeth per case) of all exfoliated teeth. In addition, the rate of early exfoliation of mandibular primary lateral incisors was 47% of all cases and comprised 40% of the total number of mandibular primary central incisors. On the other hand, early exfoliation of the mandibular primary canines before 4.5 years of age was seen in 37% of all cases and comprised 26% of all exfoliated teeth. Figure 2 shows the period of time required for spontaneous exfoliation of the right and left maxillary primary incisors and canines. Early exfoliation of maxillary primary anterior teeth was seen in 47% of all cases and comprised 18% of all exfoliated teeth. In addition, the abnormalities of the numbers and the shape of teeth were not observed in all cases.
Genetic findings

Information from results of genetic analyses was available for 7 cases and is summarized in Table 1. The F301L mutation type was associated with 2 perinatal lethal cases (Cases 1 and 5). In those, 2 early exfoliated teeth were noted in Case 1, whereas no teeth were spontaneously exfoliated in Case 5. In addition, an A23V/E174G type mutation was found in fraternal twins (Cases 3 and 4) (Fig. 3), in whom a mandibular central incisor (Case 3) and 5 primary mandibular anterior teeth (Case 4) were exfoliated. Furthermore, an E218V/1559delT type mutation was identified in Case 13, which showed 7 early exfoliated teeth, while a p327L/1559delT type mutation was identified in case 17 without early exfoliated teeth.

Discussion

The frequency of severe forms of hypophosphatasia in the general population is estimated to be 1 per 100,000 individuals\(^2,6\), whereas that of moderate forms is expected to be much higher due to the number of patients with dominant forms of the disease\(^2,3,12\). In the present study, we analyzed 19 cases of hypophosphatasia from information collected at pediatric dentistry clinics of 29 university hospitals throughout Japan including ours. However, 9 of the cases were treated at our medical hospital by pediatricians engaged in management of child patients with hypophosphatasia. We consider it important to collaborate with medical doctors when treating children with hypophosphatasia, since oral manifestations can be identified in most of these patients. Patients in this study referred to our clinic were treated as soon as they were diagnosed with hypophosphatasia by a pediatrician. In addition, a few of the patients were suspected to have hypophosphatasia based on findings in our dental clinic and referred to a pediatrician.

It is generally known that one of the common findings of this disease is early spontaneous exfoliation of primary teeth and the present analysis revealed that exfoliation of a primary incisor was identified by 4 years of age at a frequency of 74%. Since exfoliation of a primary incisor is generally observed at around 6 years of age, early exfoliation occurring at an age younger than 4 years may be an indicator of hypophosphatasia for general dentists as well as medical doctors.

A feature of premature loss of primary teeth is considered to be derived from disturbed cementum formation\(^13–25\). The present findings showed that early exfoliated teeth generally occur in the area of the primary central incisors, especially the mandibular primary central incisors, which are the first to erupt into the oral cavity among primary dentition. The primary incisors are small in size and have a single root as a morphological feature. In addition, a short time after their eruption, the mandibular central incisors receive high levels of occlusal force from peripheral soft tissues. Although incisors with intact cementum can accept such pressure, those with impaired cementum, such as that seen in hypophosphatasia patients, cannot accept high pressure levels, possibly resulting in irreversible impairment of periodontal tissues and induction of bone loss.

We found no cases of early exfoliated permanent teeth in this study, though a few case reports have described such affected permanent teeth\(^26–29\). In those cases, in addition to the primary incisors and canines, the primary molars were also exfoliated.
before the permanent teeth began to erupt. Hence, a few primary teeth remain in the oral cavity when the permanent incisors and/or first molars erupt into the oral cavity. As with the mandibular central incisors, these permanent teeth in patients with hypophosphatasia also receive high levels of pressure, which may induce early exfoliation. To prevent early exfoliation of permanent teeth in hypophosphatasia patients, a denture should be applied to reduce pressure before the permanent teeth begin to erupt.

To our knowledge, no effective approaches for early exfoliation of primary teeth in cases with hypophosphatasia have been presented. Thus, it is important to pay special attention to changes in periodontal conditions to discern the onset of periodontitis as early as possible. It is generally considered that periodontitis in children is a quite rare clinical finding, though cases of gingivitis are commonly found\textsuperscript{30}. When conditions similar to periodontitis are found in these patients, it is important to pay special attention to prevent the development of lesions. Since impaired cementum tissue may produce favorable sites for colonization of periodontitis-related bacteria\textsuperscript{10}, maintenance of oral hygiene is most vital. In the present study, we noted predominant periods for early spontaneous exfoliation of primary teeth, which might be also important for monitoring the periodontal conditions of patients with hypophosphatasia.

When cases with early exfoliation of primary teeth are encountered, application of a partial denture is recommended to disperse occlusal pressure and resolve esthetic problems. However, it is possible that the wire clasps of a partial denture may impose a severe burden on the remaining primary teeth. Therefore, it is important to confirm the mobility of teeth with clasps during periodic examinations, otherwise a non-clasp denture may be more suitable.

Presently, there is no radical treatment recommended for cases of hypophosphatasia. On the other hand, several possible treatments have been presented, including enzyme replacement therapy using the serum of a patient with Paget’s disease\textsuperscript{31}, administration of parotid hormone\textsuperscript{32,33}, transplantation of bone fragments and cultured osteoblasts\textsuperscript{34}, and allogenic mesenchymal stem cell transplantation\textsuperscript{35}. Furthermore, animal experiments using \textit{TnAlp} knockout mice, a model of infantile hypophosphatasia\textsuperscript{36}, showed that enzyme replacement therapy with a deca-aspartate-tagged enzyme was successful\textsuperscript{37}. That therapy also prevented hypomineralization of alveolar bone, dentin, and cementum\textsuperscript{38}. Clinical trials with this modified enzyme are now in progress, though the therapy requires repeated administrations of large amounts of enzymes for long-term correction\textsuperscript{39}. Gene therapy by means of a single injection may prove to be a better treatment. In previous studies, \textit{TnAlp} knockout mice were treated with lentivirus gene therapy\textsuperscript{39} and adeno-associated virus serotype 8 mediated gene therapy\textsuperscript{40}. Accumulation of such experimental findings may result in novel approaches for patients with hypophosphatasia in the near future.

Four of the present cases with different types of disease did not show early exfoliation of primary teeth. However, the present results did not reveal information regarding the relationships between early exfoliation and subtypes. The two most common types of mutations for \textit{Alpl} (F301L and T1559delT) are reported to be associated with relatively mild and lethal forms, respectively, of hypophosphatasia in Japanese patients\textsuperscript{7}. That study also noted that the genotype-phenotype relationship is consistent with the enzymatic activities of mutant ALP proteins. Furthermore, patients with F301L type were found to retain some residual activities of ALP, whereas those with the T1559del type had a complete loss of those activities. In addition, they showed that F301L is associated with relatively mild forms of hypophosphatasia, whereas T1559 is associated with lethal forms. In the present study, the F301L mutation was detected in Cases 1 and 5 with the perinatal benign type, though their dental phenotypes were different. In addition, Cases 3 and 4, fraternal twins, had the same mutation, while their dental phenotypes were completely different. It was previously reported that the relationships between phenotypes and genotypes are not fully understood\textsuperscript{5}, and additional studies are required.

Child onset hypophosphatasia is often recognized first by pediatric dentists, who are generally consulted for premature spontaneous exfoliation of fully rooted primary teeth\textsuperscript{9}. In the present study, most of the cases of child and odonto types treated at our clinic were suspected to be hypophosphatasia based on dental findings. Pediatric dentists should refer patients suspected to have hypophosphatasia based on premature exfoliation of a primary anterior tooth to a pediatrician as early as possible for additional examinations.
Conclusion

The main oral finding of hypophosphatasia was early exfoliation of deciduous teeth, predominantly in the mandibular anterior region, at the age of 1 to 4 years old. Pediatric dentists should investigate the possibility of hypophosphatasia when an uncommon case of early exfoliation of a primary tooth is encountered in a young patient.

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References

24) Lynch, C.D., Ziada, H.M., Buckley, L.A., O’Sullivan,


