Effects of Enzyme Replacement Therapy for Primary Teeth in a Patient with Infantile Hypophosphatasia

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Hypophosphatasia (HPP) is a skeletal disorder characterized by hypomineralization of bone, with early exfoliation of primary teeth. Alkaline phosphatase enzyme replacement therapy (ERT) has been shown to improve bone hypomineralization for patients with HPP, although its dental effects are unknown. A 20-month-old Japanese boy diagnosed with infantile HPP was referred to our clinic because of early exfoliation of primary teeth. The patient had been followed by a pediatrician since the age of 3 months, due to slow weight gain. At the age of 12 months, primary incisors showed sudden exfoliation; at the age of 19 months, a diagnosis of HPP was made based on bone and dental manifestations. ERT was initiated at the age of 21 months. The patient demonstrated stable periodontal conditions of primary molars that erupted after initiation of ERT, due to improved alveolar bone and tooth mineralization. Thus, ERT may improve both dental and systemic conditions.

***Keywords**: hypophosphatasia, enzyme replacement therapy, primary teeth, early exfoliation, poor weight gain.*

INTRODUCTION

Hypophosphatasia (HPP; OMIM entry #241500) is a rare metabolic disorder, characterized by defective mineralization of bone and/or teeth in the presence of low serum alkaline phosphatase (ALP) activity and caused by mutations in the *ALPL* gene encoding tissue-nonspecific ALP.[1-5] HPP is diagnosed on the basis of these clinical symptoms, radiological findings, and biochemical test results. For definitive diagnosis, ALPL gene testing is recommended.[6]

HPP is classified into six types according to onset and symptoms: perinatal severe (fetal-neonatal; characterized by respiratory insufficiency and hypercalcemia), perinatal benign (fetal-neonatal; characterized by prenatal skeletal manifestations that slowly resolve into a milder form), infantile (age <6 months; characterized by rickets and an absence of elevated serum ALP activity), childhood (age ≥6 months to <18 years; ranges from low bone mineral density for age with unexplained fractures to rickets, combined with premature loss of primary teeth with intact roots), adult (age ≥18 years, characterized by stress fractures and pseudofractures of lower extremities in middle age), and odonto (regardless of age, characterized by premature exfoliation of primary teeth without skeletal manifestations).[1-6] Early onset types of HPP (e.g., perinatal severe or infantile) exhibit generally severe phenotypes. All patients with perinatal severe HPP and half of the patients with infantile HPP have poor life prognoses without treatment.[6]

Early exfoliation of primary teeth is caused by disturbed cementum formation.[7-9] This symptom often begins with mandibular central primary incisors around the age of 12 months;[7] the teeth

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exfoliate with long roots.[7-9] Early exfoliation sometimes leads to diagnosis of mild HPP (e.g., odonto or childhood types), with or without mild bone symptoms.[9]

A recombinant bone-targeted ALP has been developed for use as enzyme replacement therapy (ERT), administered via subcutaneous injection; good outcomes have been reported, especially in patients with severe HPP.[10-14] However, the dental effects of this therapy in humans are unknown. Here, we describe a patient with infantile HPP who was diagnosed on the basis of early exfoliation of primary teeth; the patient has received ERT since the age of 21 months.

Case report

A 20-month-old Japanese boy diagnosed with infantile HPP was referred to our clinic by his pediatrician for specialized oral management related to early exfoliation of primary teeth (Fig. 1). His mother reported that no abnormal medical conditions had been apparent during the prenatal period or at birth. His birth height was 47.5 cm and weight was 2,750 g. He was the first child of his parents and neither parent reported a family history of HPP. However, because of slow weight gain after birth, the patient had been hospitalized at the age of 3 months for whole-body examinations; he had not been diagnosed with HPP despite the finding of a low serum ALP value.

At the age of 12 months, the patient exhibited sudden exfoliation of primary mandibular bilateral central incisors that had emerged into the oral cavity 2 months prior. His mother reported gingival retraction and tooth mobility were discernible soon after the tooth had erupted. The patient's parents took him to the dental clinic, where he was diagnosed with exfoliation due to dental trauma.

At the age of 19 months, the patient received a diagnosis of HPP based on bone hypomineralization and dental manifestations, as well as low serum ALP (167 I/U) (normal range in boys aged 1 year is 395–1339 U/L); the diagnosis of HPP was confirmed by genetic mutation findings. A compound heterozygous *ALPL* mutation (c.1559delT/p.H482Q/C) was detected. Nine teeth including four primary first molars were recognized in the oral cavity; seven primary incisors had exfoliated and five incisors showed severe mobility. The exfoliated tooth was in the process of forming. Oral hygiene was poor due to mobility of the primary teeth. We chose to control the patient's periodontal condition by oral hygiene guidance and periodontal treatment. In addition, we planned to apply dentures for missing primary teeth when the patient reached the age of approximately 36 months, as he could then cooperate in dental treatment.

Contact microradiograph imaging of a ground section from the exfoliated maxillary left primary central incisor revealed enamel dysplasia (Fig. 2A), as well as a wide pulp chamber and interglobular dentin caused by dentin dysplasia (Fig. 2B). Histopathological examination of the decalcified section revealed disturbed cementum formation (Fig. 2C, D).

The patient began ERT at the age of 21 months, after he had been diagnosed with HPP. His height and weight were 73.5 cm (-3.0 standard deviations) and 7.8 kg (-2.0 standard deviations), respectively, before the initiation of ERT. Growth and development showed gradual recovery. However, four additional primary incisors were lost before complete root formation (Fig. 3); the periodontal conditions of the mandibular bilateral first primary molars tended to worsen after initiation of ERT.

When the patient reached the age of 36 months, his mandibular primary second molar exhibited stable periodontal conditions; however, his mandibular primary left canine and bilateral first molar showed enhanced mobility (Fig. 4). His mandibular primary left canine and first molar did not demonstrate alveolar bone support. Thus, we performed orthopantomography to enable diagnosis of the patient's permanent tooth formation (Fig. 5). Orthopantomography revealed mineralization of permanent successors, except for second premolars and second molars. No remarkable delays were observed regarding permanent tooth development in relation to the patient's thin mandibular bone. The patient's mandibular primary second molars had erupted after initiation of ERT; these teeth exhibited root formation (Fig. 6). The line of alveolar bone was higher around the primary second molars than around the first molars. However, this root was thin and the pulp chamber was wide, as a result of dentin dysplasia. Thus, we decided to apply partial dentures and continue periodontal management for this patient.

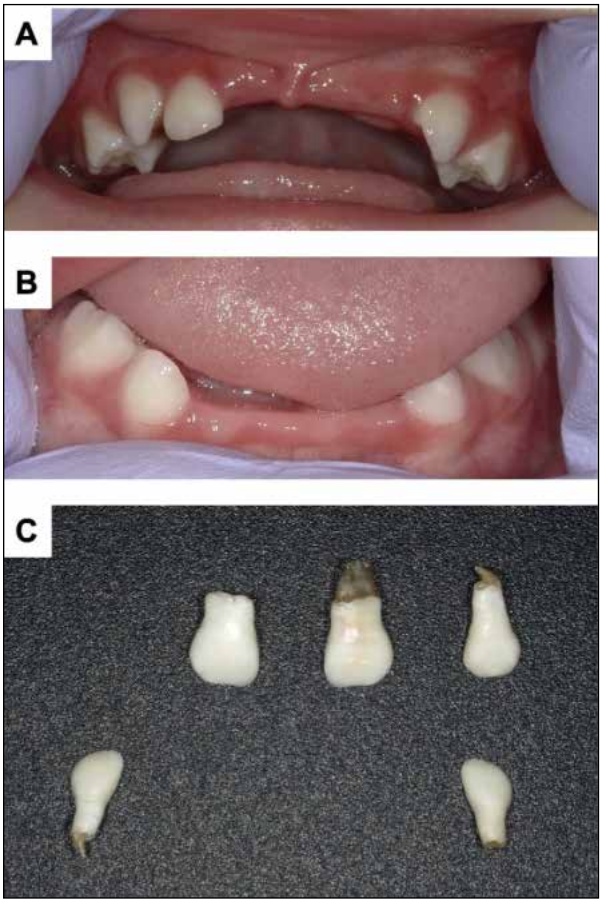

Figure 1. Findings on initial examination. A and B: Intraoral photographs taken at 20 months. Seven primary incisors had exfoliated and five incisors showed severe mobility. C: Exfoliated primary teeth provided by the patient's parents. The exfoliated tooth was in the process of forming.

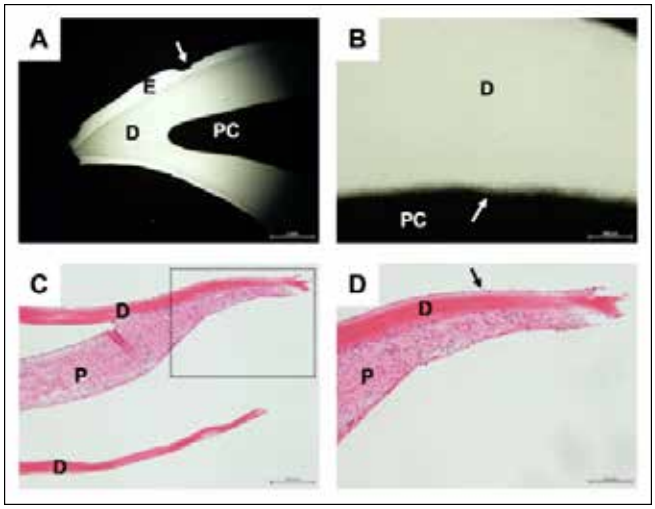

Figure 2. Analysis of exfoliated maxillary left primary central incisor. A and B: Contact microradiograph images of ground section (A, low magnification revealed enamel dysplasia [arrow]; B, high magnification revealed wide pulp chamber and interglobular dentin [arrow] caused by dentin dysplasia). C and D: Histopathological examination of decalcified section (hematoxylin and eosin staining) revealed disturbed cementum formation (arrow) (C, low magnification; D, high magnification of square in panel C). Abbreviations: E, enamel; D, dentin; PC, pulp chamber; P, pulp

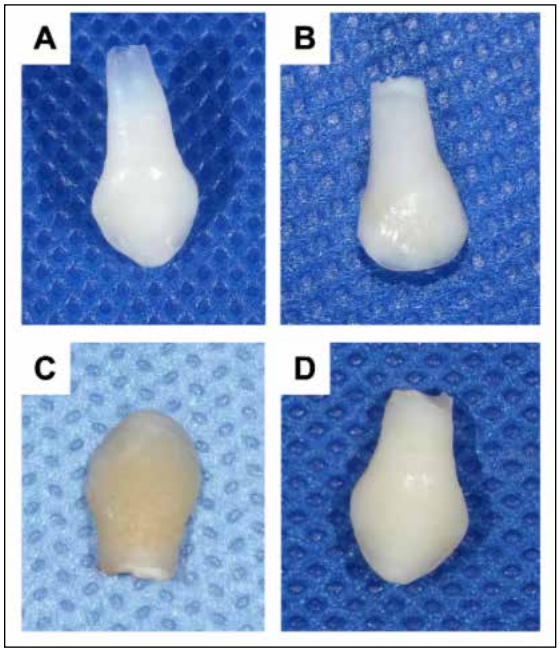

Figure 3. Exfoliated tooth after initial diagnosis. Four more primary incisors were lost before complete root formation. A: Maxillary primary left canine (exfoliated at 22 months). B: Maxillary primary left lateral incisor (exfoliated at 24 months). C: Mandibular primary right canine (exfoliated at 24 months). D: Maxillary primary right canine (exfoliated at 27 months).

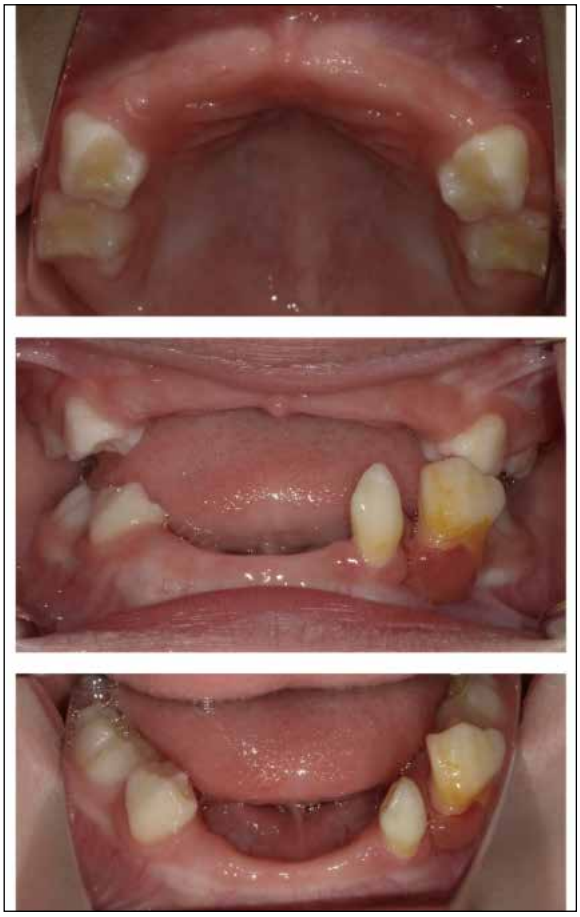

Figure 4. Intraoral photographs taken at 36 months. The periodontal condition of mandibular bilateral first primary molars tended to worsen after initiation of enzyme replacement therapy.

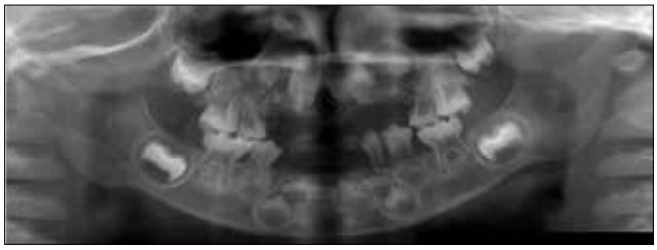

Figure 5. Panoramic radiograph taken at 36 months. Root formation of mandibular primary second molars, which had erupted after initiation of enzyme replacement therapy, was recognized.

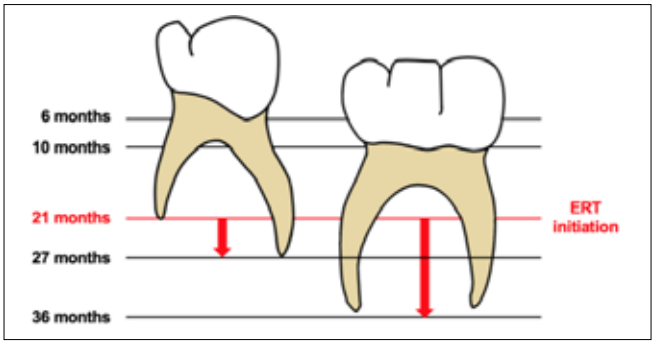

Figure 6. Image of relationship between tooth formation and enzyme replacement therapy. Abbreviation: ERT, enzyme replacement therapy

DISCUSSION

We have described a patient with infantile HPP who began receiving ERT in the stage of primary dentition. Early exfoliation of primary incisors is an important indicator for early diagnosis of HPP; our patient was diagnosed based in part on his dental findings. Since HPP is a rare disease, the patient could not be diagnosed until his primary teeth had exfoliated. Early exfoliation of primary teeth leads to diagnosis of mild HPP with or without mild bone symptoms.[7] In our patient, slow weight gain was recognized soon after birth; however, he was not definitively diagnosed until the age of 19 months. HPP is a progressive disease.[6] Therefore, diagnosis and early treatment are important for patients with HPP who exhibit severe growth and development manifestations.

To the best of our knowledge, there have been few reports regarding the effects of ERT on human dentition. After the patient began ERT, his primary second molars emerged into the oral cavity. Generally, the mandibular primary first molar initiates root formation at the age of 5.5 months, erupts at 12 months, and completes root formation at 27 months.[15] When the patient began ERT at the age of 19 months, more than two-thirds of the roots were presumably completely formed. The mandibular primary first molar had displayed mobility prior to initiation of ERT. In contrast, the mandibular primary second molar initiates root formation at the age of 10 months, erupts at 20 months, and completes root formation at 36 months.[15] When ERT was initiated, fewer than half of the roots had presumably been formed. ERT is not expected to recover periodontal conditions of already erupted teeth, although it may be effective for the development of unerupted teeth because it improves bone mineralization. Primary molars that erupted after initiation of ERT demonstrated stable periodontal conditions, due to improved alveolar bone and tooth mineralization in our patient. We suspect that ERT was effective for tooth germs and was not affected by external forces, such as occlusion. Mineralization of permanent teeth begins at birth. If ERT influences tooth germs, early initiation of ERT may be effective.

The patient also exhibited a skeletal manifestation of HPP in his jawbone. He will experience occlusal problems and require orthodontic treatment in the future. ERT has reportedly led to remarkable improvement of bone mineralization.[10-13] However, there have been few reports regarding occlusal problems and dental effects in patients receiving ERT. We plan to observe the growth of the patient's jaw, as well as the effect of ERT on his jawbone. Indications for ERT are decided by medical doctors on the basis of bone symptoms; however, there are no widely accepted criteria.[6] Recommendations regarding the length of ERT with respect to dental manifestations may be guided by further accumulation of case reports.

CONCLUSION

Early exfoliation of primary teeth is an important indicator for early diagnosis of HPP. When patients are encountered with early exfoliation of primary teeth, growth problems such as poor weight gain or short stature are important for evaluation of suspected HPP. ERT presumably cannot facilitate recovery of periodontal conditions for erupted teeth, although it may be effective for the development of unerupted teeth, because it improves bone mineralization. Our findings indicate that ERT can improve both dental and systemic conditions, although accumulation of further cases is necessary to confirm our findings.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

Informed consent was obtained from the patient for publication of this case report and accompanying images.

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