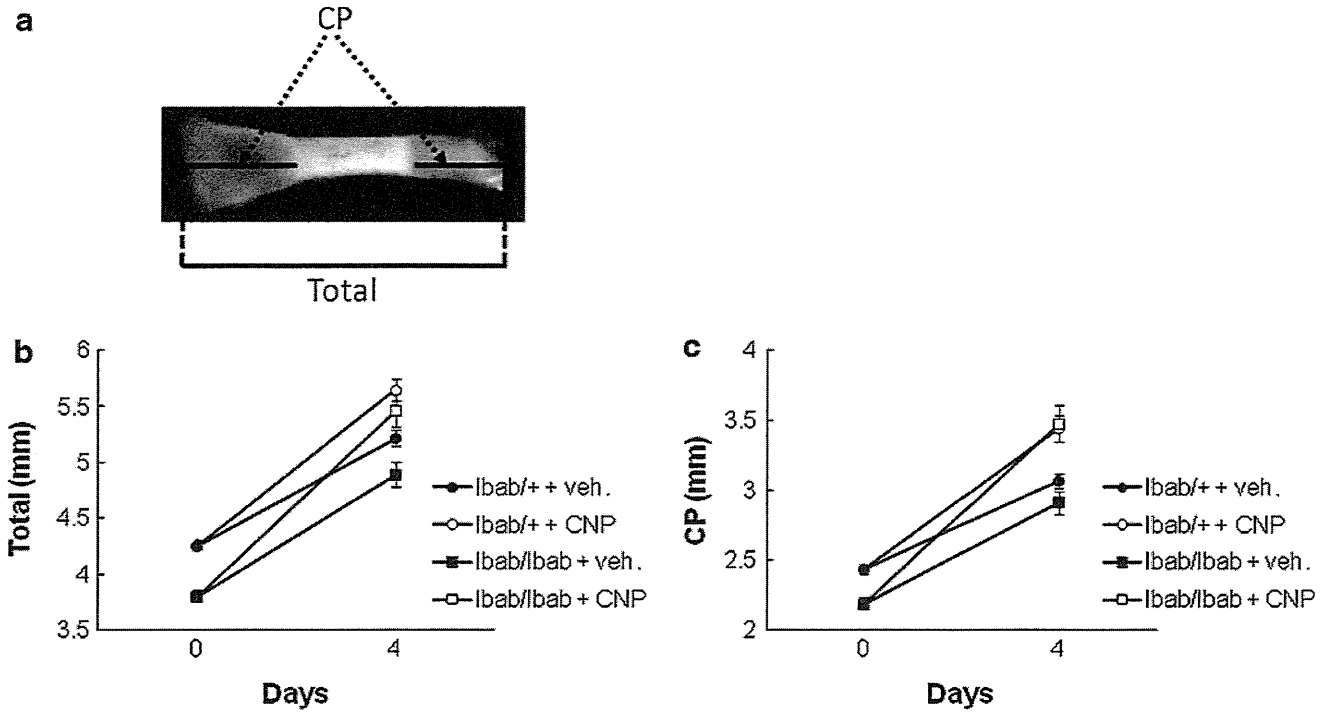

Fig. 6 Effect of CNP on cultured tibiae from fetal *lbab/+* and *lbab/lbab* mice. **a** A representative picture of a tibial explant from a fetal mouse. Total longitudinal length (*Total*) and the sum lengths of cartilaginous primordia (*CP*) are indicated. Graphs of total (**b**) and CP (**c**) lengths of cultured tibiae from *lbab/+* and *lbab/lbab* mice treated with vehicle (*veh.*) or 10^{-7} M CNP (*CNP*) for 4 days. *Circles* indicate *lbab/+* tibiae, and *squares* indicate *lbab/lbab* tibiae. At the end of culture, *closed symbols* indicate tibiae treated with vehicle and *open symbols* indicate those treated with CNP. $n = 8$–12 each

The reason the decreased proliferation of chondrocytes in the *lbab/lbab* growth plate was not rescued by CNP overexpression in chondrocytes is not clear, but it may be because of the weak and slow expression of the CNP transgene owing to the weak power of the promoter region. On the other hand, CNP could not increase the proliferation of growth plate chondrocytes in *lbab/lbab* explants in organ culture experiments in this study. The effect of CNP on chondrocyte proliferation might be so mild that other effects of CNP on growth plate chondrocytes, e.g., the stimulatory effect on matrix synthesis as we had previously reported [3, 4], might proceed to recover the thinned growth plate of *lbab/lbab* mice. The discrepancy between the effects on proliferation and matrix synthesis may explain in part the delayed recovery of bone length relative to growth plate thickness. On the other hand, immunohistochemical staining of type X collagen and Ihh in explanted growth plates at two different stages of endochondral ossification suggested that the progression of proliferative chondrocytes to hypertrophic chondrocytes was delayed in the *lbab/lbab* growth plate and recovered by addition of CNP. In addition to the result that the expression of MMP-13 was not different between the terminal hypertrophic chondrocytes of wild-type, *lbab/lbab*, and rescued growth plates, CNP might promote the hypertrophic differentiation of proliferative chondrocytes but not accelerate the terminal differentiation of hypertrophic chondrocytes.

In this study, we investigated the character of calcified bones of *lbab/lbab* mice using three-dimensional CT analysis: the bone volume of *lbab/lbab* mice was substantially decreased compared to that of wild-type mice and recovered by cartilage-specific CNP overexpression. The mechanism of decrease in bone volume of *lbab/lbab* mice is still unknown, but CNP may be expressed in and affect cells other than chondrocytes, i.e., osteoblasts or osteoclasts, in bone. Although overexpression of CNP was targeted to chondrocytes in our rescue experiments, early onset of CNP-Tg expression from the CP might have been able to affect bone metabolism at the earlier stage of skeletogenesis [17] and may have continued to affect osteoblasts or osteoclasts near the growth plate cartilage in the later stage of skeletogenesis. Whereas several in vitro effects of CNP on osteoblastic cell lineages or osteoclasts have been reported [18–28], the in vivo effects of CNP on bone metabolism remain elusive; and further experiments are now ongoing in our laboratory.

We previously discovered that in two strains of mice, *cn/cn* and *slw/slw*, dwarfism is caused by spontaneous

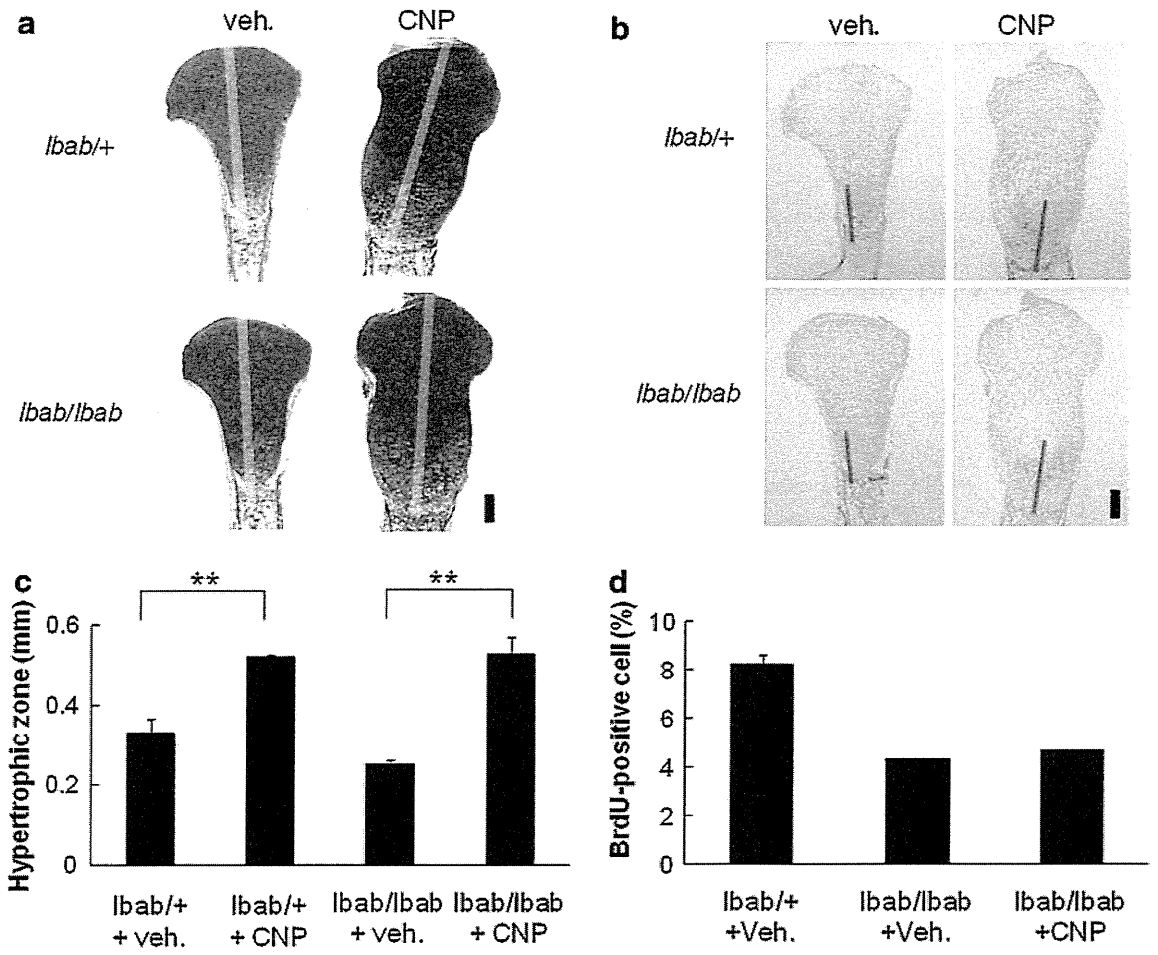

Fig. 7 Histological analyses of the growth plates of tibial explants from fetal *lbab/+* and *lbab/lbab* mice treated with vehicle (*veh.*) or 10^{-7} M CNP (*CNP*) for 4 days. Alcian blue and hematoxylin–eosin staining (**a**) and immunohistochemical staining for type X collagen (**b**). *Yellow bars* in **a** indicate lengths of cartilaginous primordial, and *red bars* in **b** indicate heights of hypertrophic chondrocyte layers. *Scale bars* 200 μm. Height of hypertrophic chondrocyte layer (**c**) and proportion of BrdU-positive cells (**d**) of the growth plate of tibial explant from fetal *lbab/+* or *lbab/lbab* mice treated with 10^{-7} M CNP or vehicle at the end of the 4-day culture period. $n = 3$ each. $^{**}P < 0.01$ in **c** and $n = 2$–3 each in **d** (Color figure online)

mutations in the GC-B gene [7, 8]. In humans, it has been identified that AMDM is caused by spontaneous loss-of-function mutations in the GC-B gene [9, 29]. The *lbab/lbab* mouse, the skeletal phenotype of which we have closely analyzed in the present report, has a spontaneous loss-of-function mutation in the CNP gene; by analogy to the GC-B gene, some forms of human skeletal dysplasia might be caused by mutations in the CNP gene. Thus far, no such conditions have been discovered [30]. In the event such a discovery is made, the *lbab/lbab* mouse would then be a novel model of a form of human skeletal dysplasia caused by a mutation in the CNP gene.

In contrast to mice homozygous for the *lbab* allele, the growth and skeletal phenotype of mice heterozygous for the *lbab* allele were not different from those of wild-type mice, as is the case with heterozygous CNP knockout mice. This confirms that haploinsufficiency for the CNP gene does not exist in mice. Likewise, heterozygotes for the GC-B knockout, the *cn* allele, or the *slw* allele exhibit no skeletal abnormalities [6–8]; thus, haploinsufficiency of the GC-B gene also does not exist in mice. Nevertheless, haploinsufficiency of the GC-B gene does exist in humans: heterozygous carriers of AMDM are reported to be shorter than expected for their population of origin [31]. The reason for the discrepancy is not clear at present, but it may have to do with differences between species or some other unknown mechanism(s). We will have to perform further investigations on the skeletal phenotypes of the aforementioned lines of GC-B mutant mice; such experiments are now ongoing in our laboratory.

In summary, in this study we more closely investigated the skeletal phenotypes of a novel CNP mutant mouse, *lbab/lbab*. The results of this study will be useful not only for further elucidation of the physiological role of CNP on

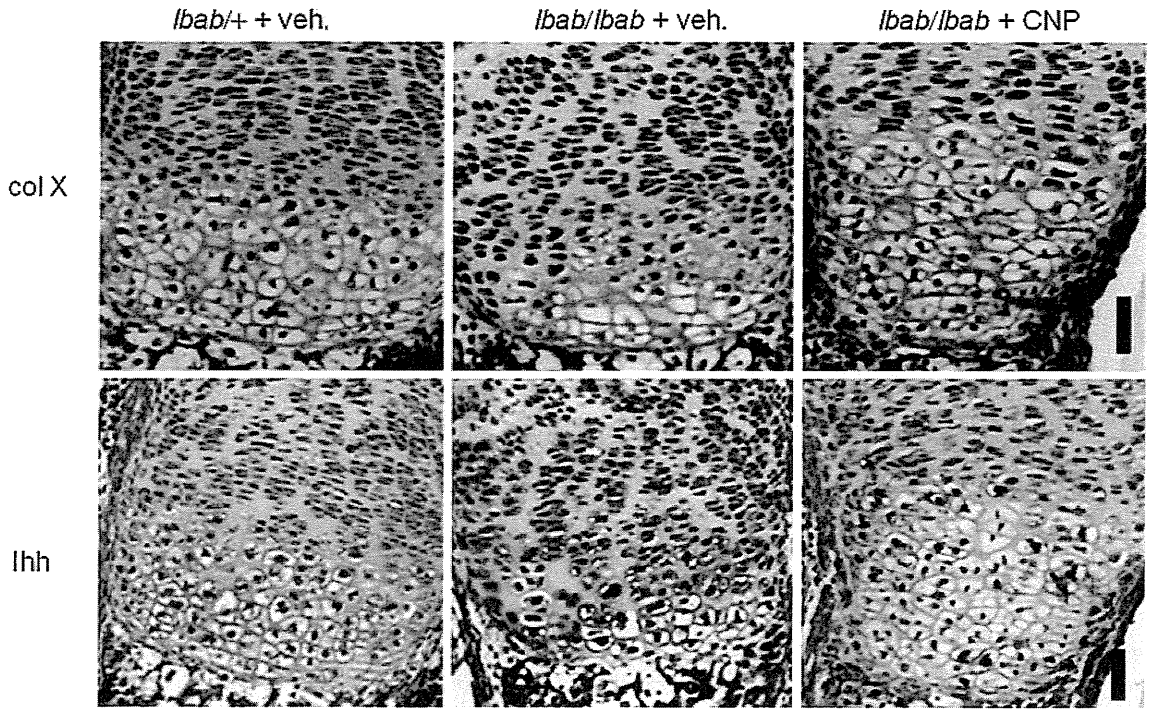

Fig. 8 Immunohistochemical staining of type X collagen (*upper panels*) and Ihh (*lower panels*) of the growth plates of metatarsal explants from fetal *lbab/+* and *lbab/lbab* mice treated with vehicle (*veh.*) or 10^{-7} M CNP for 4 days. *Scale bar* 50 μm

endochondral bone growth but also for the prediction of pathophysiology of a hypothetical chondrodysplasia caused by a mutation in the human CNP gene, which has not yet been discovered.

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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 mineralization[1]. 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 common[2–4]. Hypophosphatasia is inherited as an autosomal recessive trait, though autosomal dominant inheritance has been reported in some milder cases[5]. The disease is caused by mutations in the liver/bone/kidney alkaline phosphatase gene (*ALPL*) encoding TNSALP[6], with more than 200 mutations in the *ALPL* gene reported[5]. In Japanese patients, the F301L and T1559del mutation types are commonly found in the TNSALP gene[7], of which the former is reported to be associated with relatively mild forms and the latter type with the lethal form[8].

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 symptoms[3,4]. The severity of the disease is generally correlated with the onset period, except for the odonto type[7]. Symptoms in patients with hypophosphatasia range from stillbirth without mineralized bone to isolated premature loss of primary teeth[3,4].

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Table 1 Summary of patients diagnosed with hypophosphatasia

Case	Gender	Phenotype	First and last examination	Early exfoliated or extracted teeth	Genetic analysis
1[a]	F	Perinatal (benign)	2Y7M–14Y3M	A | A	F301L
2[a]	F	Childhood	7Y0M–18Y0M	None	Unknown
3[b]	M	Odonto	3Y0M–8Y9M	A |	A23V/E174G
4[b]	M	Childhood	3Y0M–8Y9M	CBA | AB	A23V/E174G
5	M	Perinatal (benign)	8Y8M–12Y4M	None	F301L
6	M	Childhood	2Y2M–3Y9M	C C / CBA | ABC	Unknown
7	M	Odonto	2Y2M–3Y7M	BA | AB	Unknown
8	F	Odonto	4Y5M	A |	Unknown
9	F	Perinatal (benign)	1Y9M–4Y4M	C | BA	Unknown
10	F	Odonto	2Y8M–15Y6M	A / CBA | AB	Unknown
11	M	Childhood	3Y10M–4Y8M	B / A | A C	Unknown
12	M	Odonto	5Y2M–23Y11M	None	Exon 10 point mutation
13	F	Odonto[c]	4Y0M–8Y10M	BA | A C / BA | A	E218V/1559delT
14	M	Childhood	1Y5M–7Y	BA / C A | C	Unknown
15	F	Childhood	1Y7M–10Y2M	| A / CBA | ABC	Unknown
16	M	Childhood	3Y5M–11Y	CBA | ABC / A | A	Unknown
17	M	Infantile	7Y8M–12Y8M	None	p327L/1559delT
18	M	Childhood	3Y2M–7Y3M	BA | A	Unknown
19	F	Childhood	2Y7M–	| AB / BA | AB	Unknown

[a]: Siblings, [b]: Fraternal twins, [c]: Odonto type, possibly childhood type, general information is lacking.

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.

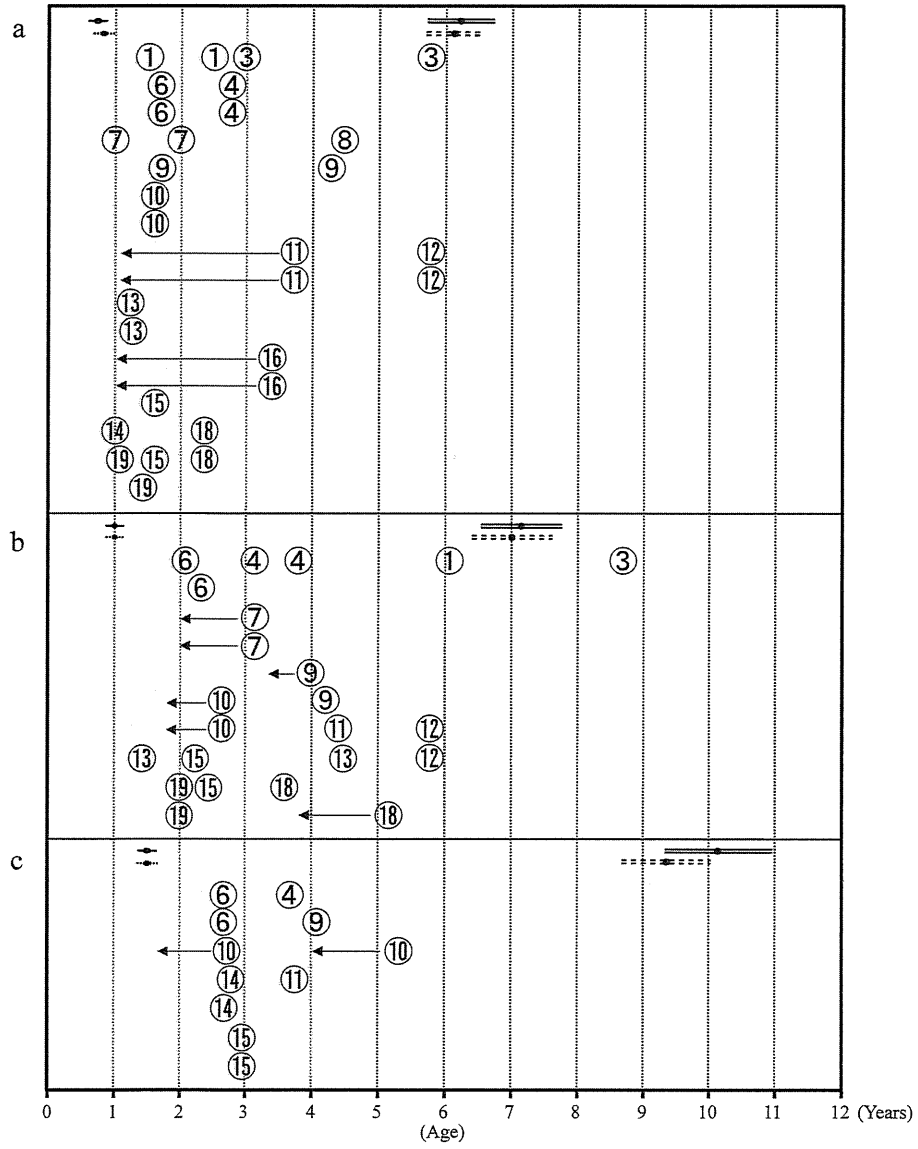

Fig. 1 Time of spontaneous exfoliation of right and left mandibular primary incisors and canines

Numbers in circles indicate case numbers. Arrows indicate estimated periods of exfoliation. Bold line indicates the mean time (center dot) of emergence of mandibular primary incisors and canines in boys, with an SD of 1. The double bold line indicate the same for the permanent successors and the center dot indicates the mean. Bold dotted and double-dotted lines indicate results for girl patients. Shadow indicates the term within 3 years after eruption of the primary tooth.
a: Central incisors, b: Lateral incisors, c: Canines.

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

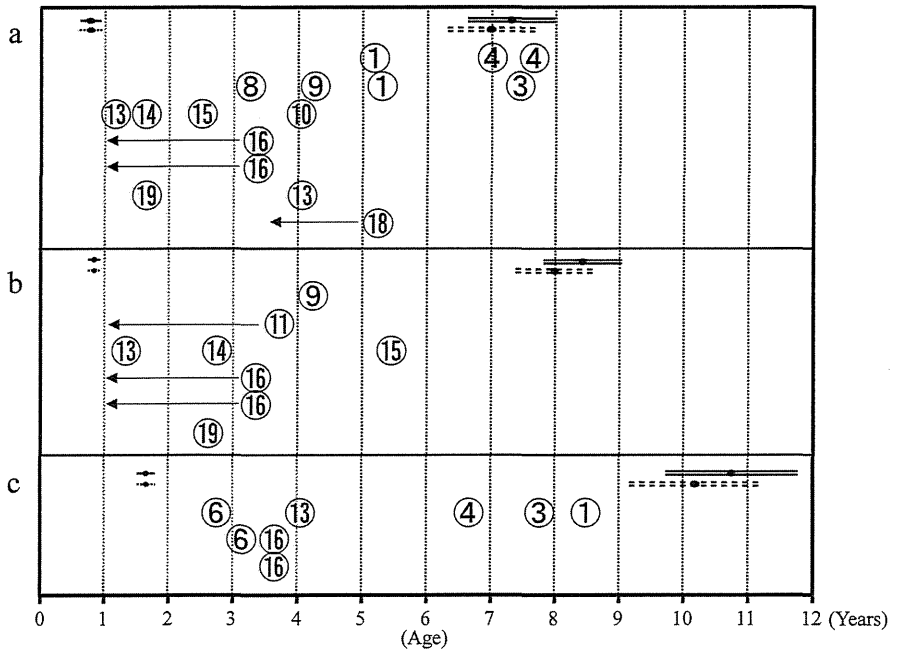

Fig. 2 Time of spontaneous exfoliation of right and left maxillary primary incisors and canines

Numbers in circles indicate case numbers. Arrows indicate estimated periods of exfoliation. Bold line indicates the mean time (center dot) of emergence of mandibular primary incisors and canines in boys, with an SD of 1. The double bold line indicate the same for the permanent successors and the center dot indicates the mean. Bold dotted and double-dotted lines indicate results for girl patients. Shadow indicates the term within 3 years after eruption of the primary tooth.
a: Central incisors, b: Lateral incisors, c: Canines.

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.

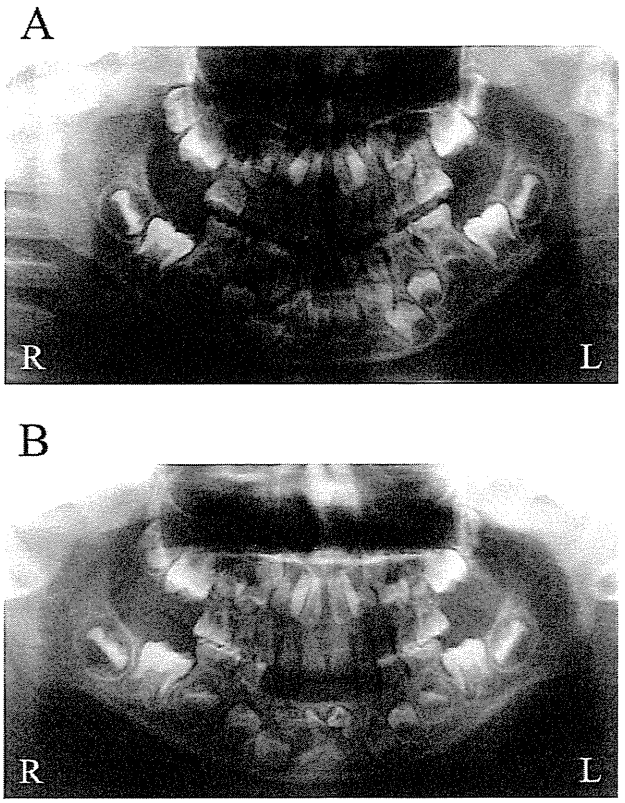

Fig. 3 Orthopantomograph of fraternal twins obtained at 6 years 3 months of age
(A) Case 3, (B) Case 4.

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[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[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 recommend 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[31], administration of parotoid hormone[32,33], transplantation of bone fragments and cultured osteoblasts[34], and allogenic mesenchymal stem cell transplantation[35]. Furthermore, animal experiments using *TNALP* knockout mice, a model of infantile hypophosphatasia[36], showed that enzyme replacement therapy with a deca-aspartate-tagged enzyme was successful[37]. That therapy also prevented hypomineralization of alveolar bone, dentin, and cementum[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[5]. Gene therapy by means of a single injection may prove to be a better treatment. In previous studies, *TNALP* knockout mice were treated with lentivirus gene therapy[39] and adeno-associated virus serotype 8 mediated gene therapy[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 *ALPL* (F301L and T1559delT) are reported to be associated with relatively mild and lethal forms, respectively, of hypophosphatasia in Japanese patients[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[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[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.

Acknowledgments

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骨系統疾患患児における歯科的問題点とその対応

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はじめに

平成24年度より厚生労働省科学研究費補助金難治性疾患克服事業「重症骨系統疾患の予後改善に向けての集学的研究（研究代表者：大阪大学医学系研究科小児科学　大薗恵一教授）」の研究分担者として、「骨系統疾患患児における歯科的問題点とその対応」というテーマの研究に従事している。本稿では、骨系統疾患患児における歯科的問題点とその対応についてまとめていきたい。

骨系統疾患とは、骨格に異常をきたす遺伝性疾患である。骨系統疾患を有する患児では歯科的な問題点を有することが多いが、日常臨床で遭遇する頻度が少なく、また臨床症状が多彩である。大阪大学歯学部附属病院小児歯科の現在の登録患者約2,000人から骨系統疾患を有する患児を抽出し、病名、歯科的症状およびそれらへの対応について調査した。その結果、36名の骨系統疾患患児の存在が確認された。内訳としては、骨形成不全症が18名と最も多く、次いで低フォスファターゼ症11名、X連鎖性低リン血症性ビタミンD抵抗性くる病4名と続き、その他は鎖骨頭蓋異形成症、脊椎骨端異形成症、軟骨無形成症が各1名であった（図1）。

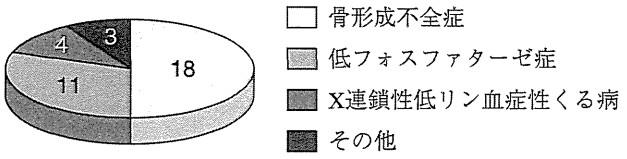


図1　本院小児歯科における骨系統疾患患児の内訳

今回は骨形成不全症、低フォスファターゼ症の歯科的問題点とその対応について述べたい。

骨形成不全症

骨形成不全症とは、Ⅰ型コラーゲンの形成異常によって骨の脆弱性をきたす疾患である。易骨折性、成長障害、青色強膜および聴力障害などの臨床症状を呈する。多くは常染色体優性遺伝であり、頻度は10万出生あたり4～6人だが、重症度は様々である[1)2)]。

歯科的症状としては象牙質形成不全が挙げられる。透過度の高いエナメル質を介して、形成不全の象牙質が見えるため、歯冠は半透明の琥珀色を呈する。また象牙質とエナメル質との接着が悪いため、エナメル質の剥離、著しい咬耗を認める（図2）。萌出前、直後の歯髄腔は広いが、象牙質が露出され、歯髄内

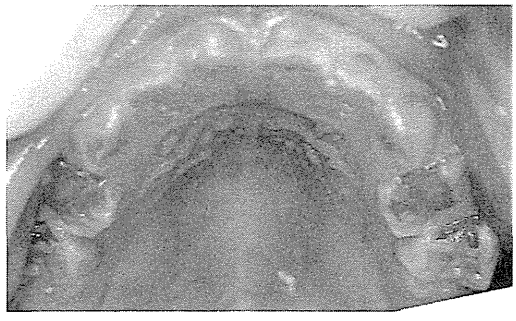


図2　骨形成不全症患児の口腔内写真（4歳3か月女児）

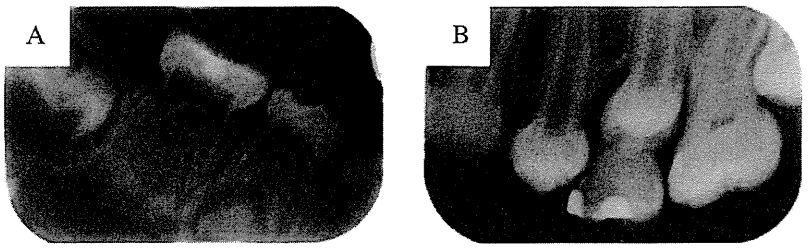


図3　骨形成不全症患児のデンタルエックス線像
A：下顎右側乳臼歯部（3歳4か月女児）、B：上顎左側臼歯部（12歳9か月男児）

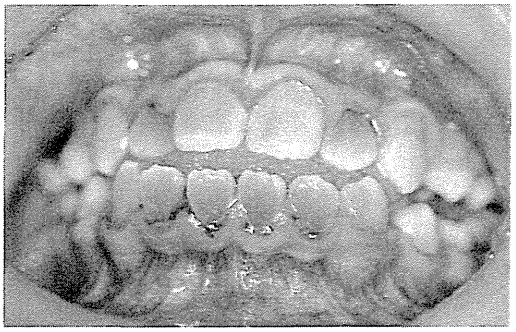


図4　骨形成不全症患児の口腔内写真（14歳7か月男児）

での象牙質の形成が起こり、歯髄腔の早期狭窄が起こる（図3）。この象牙質形成不全は、乳歯時と比較して永久歯での症状は軽度である（図4）。

乳歯において、エナメル質の剥離や咬耗が著しい場合、咬合高径を回復するために乳歯冠の装着を考慮する（図5）[3]。また、歯髄腔の狭窄は歯髄処置が困難となるため、う蝕の予防が重要である[4]。

骨吸収抑制剤であるビスフォスフォネート製剤の投与を受けている可能性がある場合、抜歯の際は医科への問い合わせが必要であるが、乳歯の交換期の抜歯で骨髄炎を誘発したという報告はない[4]。また、緊急性が高いものの低年齢であるなどの理由によって抑制下での治療が必要となった場合、易骨折性への配慮が重要である。

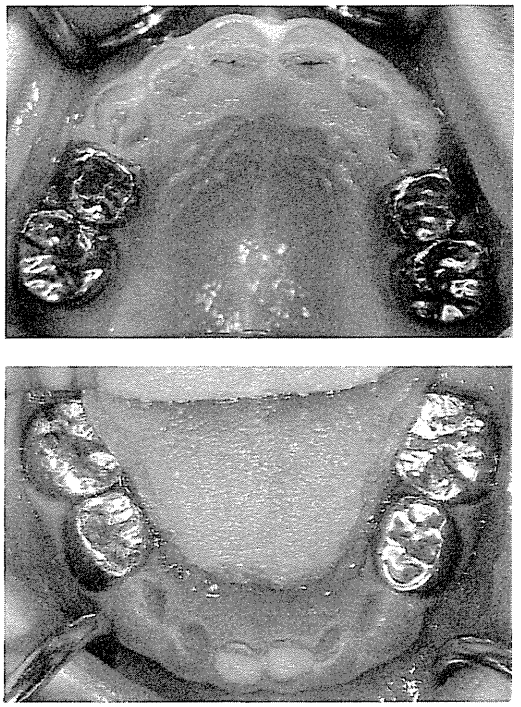


図5　骨形成不全症患児における乳歯冠による咬合の回復（5歳0か月女児）

低フォスファターゼ症

低フォスファターゼ症は組織非特異的アルカリフォスファターゼ（Alkaline phosphatase：ALP）遺伝子の異常により引き起こされる疾患である[5]。15万人に一人程度の発症といわれ、通常は常染色体劣性遺伝であるが、まれに常染色体優性遺伝もある[6]。ALPは

骨の石灰化に必要な酵素であるため、血清ALP値が低くなり、骨の石灰化が低下する。発生頻度は発症時期と症状によって、周産期型、良性周産期型、乳児型、小児型、成人型、歯限局型に分類されるが[7][8]、一般的に発症時期が早いほど重症である[9]。現在のところ、確立された治療法はない。

歯科的症状としては、セメント質の形成不全による乳歯の早期脱落がある（図6）[10]。永久歯の脱落に関する報告は極めて少ない。セメント質の形成不全のため歯根膜を介してのセメント質と歯槽骨との結合が弱く、咬合力に耐えることができずに乳歯が脱落するものと考えられる[10]。通常の歯周炎とは異なり炎症症状は軽度で、歯周病原性細菌の検出頻度も低い[11]。

平成21年度に全国29の大学歯学部および歯科大学の小児歯科学教室に本疾患罹患患児の有無を問い合わせ、該当者が存在する場合、病型、早期脱落乳歯および永久歯の有無とその時期について情報提供を依頼したところ、男児11名、女児8名の19症例の情報が得られた（表1）[10]。病型は小児型9名、歯限局型6名、良性周産期型3名、乳児型1名であった。乳歯の早期脱落は15名（約80％）において認めたが、永久歯の早期脱落を認めたケースはなかった。乳歯の早期脱落の好発部位は前歯部、とくに下顎前歯部であり、乳臼歯部では脱落を認めなかった。早期脱落の時期については、1歳から4歳にかけて集中していた（表2）。

早期脱落部への対応に関する報告はほとんどなく、歯周治療によって可及的な乳歯の保存を試みることが一般的な治療であろうと思われる。当科では、4歳5か月の時点で8本の乳前歯が早期脱落した良性周産期型の女児において、小児義歯の装着を試みた（図7）。以後、数回の義歯調整を行ったものの、残存乳歯の動揺や脱落はなく、経過は良好である。小児義歯の装着によって、咀嚼機能、発音機能および審美性の回復だけではなく、咬合力を分散させることによって残存歯の早期脱落を予防できるのではないかと考

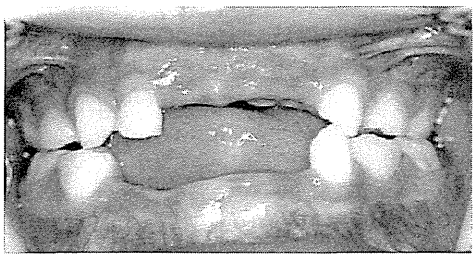


図6　低フォスファターゼ症患児の口腔内写真（4歳11か月女児）

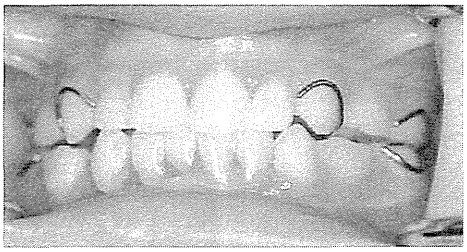
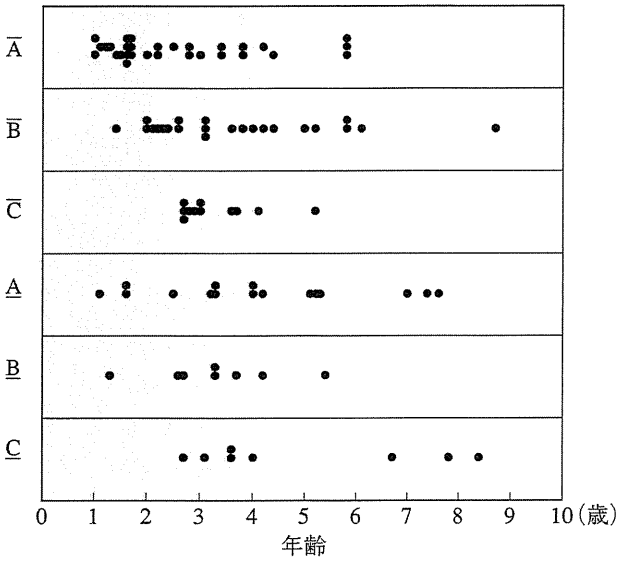


図7　低フォスファターゼ症患児における義歯の装着（4歳11か月女児）

表1　低フォスファターゼ症各分類における早期脱落歯の有無[10]

病型	性別	初診～最終診察時年齢	早期脱落乳歯	早期脱落永久歯
周産期型（良性）	女	2Y7M-14Y3M	2本	なし
周産期型（良性）	男	8Y8M-12Y4M	なし	なし
周産期型（良性）	女	1Y9M-4Y4M	3本	なし
乳児型	男	7Y8M-12Y8M	なし	なし
小児型	女	7Y0M-18Y0M	なし	なし
小児型	男	3Y0M-8Y9M	5本	なし
小児型	男	2Y2M-3Y9M	8本	なし
小児型	男	3Y10M-4Y8M	4本	なし
小児型	男	1Y5M-7Y	5本	なし
小児型	女	1Y7M-10Y2M	7本	なし
小児型	男	3Y5M-11Y	8本	なし
小児型	男	3Y2M-7Y3M	3本	なし
小児型	女	2Y7M-	6本	なし
歯限局型	男	3Y0M-8Y9M	2本	なし
歯限局型	男	2Y2M-3Y7M	4本	なし
歯限局型	女	4Y5M	1本	なし
歯限局型	女	2Y8M-15Y6M	6本	なし
歯限局型	男	5Y2M-23Y11M	なし	なし
歯限局型	女	4Y0M-8Y10M	7本	なし

表2　低フォスファターゼ症各症例における乳歯の脱落時期



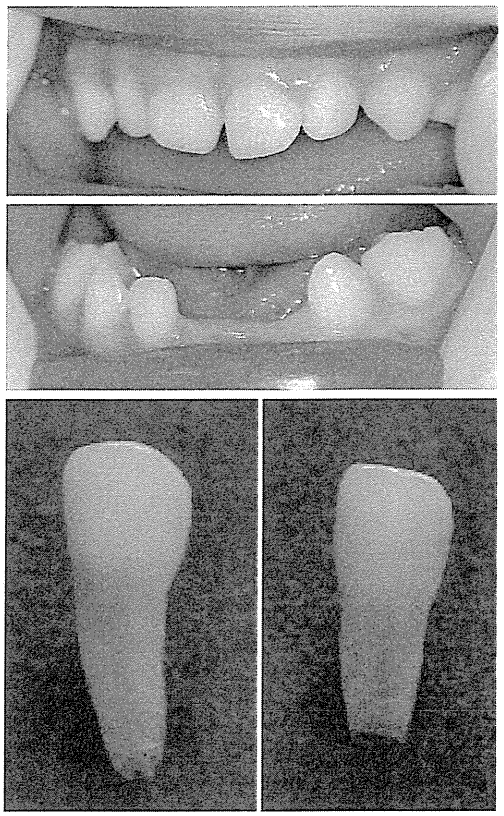


図8　低フォスファターゼ症患児の口腔内写真と持参された脱落歯（2歳3か月男児）

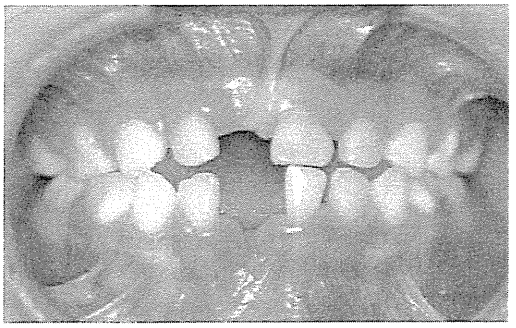


図9　低フォスファターゼ症患児の口腔内写真（4歳5か月女児）

えている。本疾患が平成20年度から小児義歯の保険適応に加わったことで、本症例への小児義歯の応用が普及することが期待される。

全身的な症状が軽度な場合、乳歯の早期脱落のため歯科を受診したことを機に、医科へと紹介され、低フォスファターゼ症と診断を受けることがある。当科においても初診時年齢1歳7か月の男児（図8）と4歳5か月の女児（図9）の2名が乳前歯の早期脱落のため当科を受診し、本学医学部附属病院へ紹介となり、歯限局型低フォスファターゼ症との診断を受けた。歯科領域における脱落歯を認める所見から医科領域へ紹介することで、低フォスファターゼ症の早期診断につながる可能性が上昇すると思われる。

おわりに

骨系統疾患の歯科的症状は様々であり、重症度も異なるために対応が困難である。また、骨系統疾患における歯科的問題に対応するためには小児科領域との連携が重要である。今後さらに症例を蓄積し、骨系統疾患を有する患児へのよりよい臨床的アプローチをエビデンスに基づいて構築していきたい。

なお、本研究班のホームページ（http://www.bone.med.osaka-u.ac.jp/skeleton/）を随時参照していただきたい。

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難治性疾患克服事業における研究班の一員としてご指名いただき、重症骨系統疾患における歯科的問題点とその対処法に関する研究を行う機会を与えていただいた大阪大学医学系研究科小児科学　大薗恵一教授に厚くお礼申し上げます。また、研究の遂行にあたり、多くの症例提示や臨床的な助言をいただいた各大学小児歯科学教室の先生方に深く感謝申し上げます。本研究は、厚生労働省科学研究費補助金難治性疾患克服事業「重症骨系統疾患の予後改善に向けての集学的研究」に対する補助金を用いて行われました。

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ORIGINAL ARTICLE

Development of an integrated support system for hereditary cancer and its impact on gynecologic services

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Abstract
Objective Patients with hereditary cancer need an integrated support system. A recently launched project was evaluated in terms of its efficacy in screening patients with hereditary cancer at the gynecologic service.
Methods The project team comprised gynecologists, surgeons, medical geneticists, and certified genetic counselors (CGCs) in our hospital. At the gynecologic service, a newly developed self-administered family history questionnaire (SAFHQ) was given to patients with ovarian, endometrial, or breast cancer as well as a history of multiple cancers. After an interview, a CGC constructed a pedigree and evaluated the risk for hereditary cancer. Patients at risk were recommended by a gynecologist to receive further genetic counseling at the Department of Genetics according to the modified Bethesda criteria, Amsterdam II criteria, and National Comprehensive Cancer Network (NCCN) guidelines 2012 for breast–ovarian cancer syndrome (HBOC). The numbers of newly screened patients were compared before and after the project launch.
Results The SAFHQ was administered to 131 patients and 106 (81 %) pedigrees were constructed between August 2012 and July 2013. The number of newly screened patients according to the Bethesda criteria was 4 and 8 at 10 years before and 1 year after the project launch, respectively. Two and 31 patients met the NCCN criteria for HBOC excluding ovarian cancer alone, respectively, at these 2 time points. Of 54 patients who were recommended to undergo further counseling, 10 (19 %) visited the Department of Genetics.
Conclusion After the launch of an integrated support system, the number of patients with hereditary cancers who were screened increased. The gynecologic service played a pivotal role in patient and family care.

Keywords Gynecology · Lynch syndrome · Hereditary breast and ovarian cancer · Genetic counseling · PDSA cycle

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Introduction

Recently, a prominent celebrity underwent a preemptive double mastectomy because of a high familial propensity for breast cancer. This news garnered global media attention and heightened general population awareness of the importance of genetic screening based on family medical history. Approximately 2–5 % of uterine and 5–10 % of ovarian cancers are hereditary [1–4]. Lynch syndrome/hereditary non-polyposis colorectal cancer syndrome and breast–ovarian cancer syndrome (HBOC) are the main

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hereditary gynecologic cancers. The incidences of Lynch syndrome and HBOC are similar in the Japanese population [5, 6]. However, the social and medical systems for caring for patients with hereditary cancer and their families are not widely accessible [7]. In 2011, the Japanese Clinical Practice Guideline of Breast Cancer announced that salpingo-oophorectomy reduces the risk of breast cancer, while the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2012 for the Clinical Practice of Hereditary Colorectal Cancer were published in 2012. In addition, a guide to risk, prevention, and management of gynecologic cancers was translated into Japanese in 2011 [8].

In 2012, a project to support patients with hereditary cancers and their family members was launched at the teaching hospital of Hyogo College of Medicine. This report discusses the promotion and development of an integrated support system, from a gynecologic perspective, for the benefit of screening patients with hereditary cancer.

Methods

The project team comprised gynecologists, surgeons, medical geneticists, and certified genetic counselors (CGC) in our hospital. A self-administered family history questionnaire (SAFHQ) was developed (Table 1), and the manner in which pedigrees were drawn was made consistent. Genetic and clinical data were disseminated. Development of a support system was planned and conducted according to the Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences and the Guidelines of the Japanese Society for Familial Tumors.

Table 1 Self-administered family history questionnaire (Department of Obstetrics and Gynecology) (English version)

Self-administered Family History Questionnaire (Department of Obstetrics and Gynecology)

ID:	Name (Last, First):	Date of Birth:	Age:

Please answer the following questions.

【A】 About yourself

A-1	What is your current disease called? ( )	
A-2	Have you undergone any surgery in the past?	Yes No
	If yes, please mention the disease for which surgery was performed. ( )	
A-3	Please encircle the conditions below, for which you have a history. For encircled conditions, indicate the age at diagnosis.	
	Breast cancer (Age:) Ovarian cancer (Age:) Fallopian cancer (Age:) Endometrial cancer (Age:) Colorectal cancer (Age:) Gastric cancer (Age:)	
A-4	Do you have other types of cancer?	Yes No
	If yes, indicate the disease and the age at diagnosis.	( ) (Age:)
A-5	Did you receive/do you plan to receive hormone therapy for breast cancer?	Yes No
A-6	Did you undergo a genetic test for hereditary cancer?	Yes No
A-7	Do you wish to talk about the genetic disease or test, if you have a risk of hereditary cancer?	Yes No
A-8	We can provide integrated support with other doctors and co-medical professionals in our hospital if you have a risk of hereditary cancer. Do you wish to be introduced to other doctors at the related department?	Yes No

Please complete the reverse side of this form.

Table 1 continued

【B】About your family

B-1	Do you have a family history of any cancer or polyp on your maternal or paternal side?	Yes No Unknown
B-2	If yes, please list the relationship of the patientto you, the individual diagnosis, and the age at diagnosis. Consider cancers as such colorectal cancer, gastric cancer, endometrial cancer, ovarian cancer, breast cancer, fallopian cancer, and brain cancer Consider relationships as such father, mother, brother, grandparent, uncle, aunt, and niece 【Example】 Father, colorectal cancer, 55 years old Paternal cousin, gastric cancer, 40 years old Maternal aunt, breast cancer and ovarian cancer, 35 and 42 years old	
B-3	Is there a male breast cancer patient in your family?	Yes No Unknown
B-4	Has any person in your family undergone genetic testing for hereditary cancer?	Yes No Unknown

Relationship	Cancer type	Age at diagnosis

Please hand over the completed form at the reception desk.

At the gynecologic service, a checklist was developed to guide recommendations for further genetic counseling including genetic testing. The revised Bethesda criteria as well as the Amsterdam criteria II were used for Lynch syndrome screening [9, 10]. Gastric cancer, atypical endometrial hyperplasia, and epithelial ovarian cancer were considered as Lynch-syndrome-related cancers. Non-obese women [body mass index (BMI) <25] <50 years old with regular menses who had endometrial cancer were included in the checklist [11]. For HBOC screening, a history of ovarian cancer alone was excluded from the criteria for further genetic risk evaluation by the National Comprehensive Cancer Network guidelines (NCCN) 2012 [12]. The checklist included patients with a history of two or more cancers except for cervical or hepatic cancer associated with viral infection.

After launching the project, inpatients and outpatients with ovarian, endometrial, or breast cancer as well as a history of multiple cancers were given the SAFHQ. After obtaining informed consent, the CGC interviewed the patients and constructed pedigrees. The gynecologist informed patients about hereditary cancers and recommended further genetic counseling on the basis of the checklist and pedigree results.

Cases of hereditary cancer have been recorded by gynecologists since 2001. The numbers of newly screened patients 10 years before and 1 year after the launch of the project were compared. After the project launch, the timing of information provision about hereditary cancer was recorded based on what treatment regimen or plan was administered to patients. The number of patients who visited the Department of Genetics was also recorded. The project was approved by our institutional review board, and written informed consent was obtained from patients to access their information recorded by the physicians or CGCs. Statistical analyses were performed using the software XLSTAT 2012 (Addinsoft, Paris, France) and P values were calculated using the χ^2 test.