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ABSTRACT

Cranio metaphyseal dysplasia (CMD) is a rare genetic disorder encompassing hyperostosis of craniofacial bones and metaphyseal widening of tubular bones. Dental abnormalities are features of CMD that have been little discussed in the literature. We performed dentofacial examination of patients with CMD and evaluated consequences of orthodontic movement in a mouse model carrying a CMD knock-in (KI) mutation (Phe377del) in the *Ank* gene. All patients have a history of delayed eruption of permanent teeth. Analysis of data obtained by cone-beam computed tomography showed significant bucco-lingual expansion of jawbones, more pronounced in mandibles than in maxillae. There was no measurable increase in bone density compared with that in unaffected individuals. Orthodontic cephalometric analysis showed that patients with CMD tend to have a short anterior cranial base, short upper facial height, and short maxillary length. Microcomputed tomography (micro-CT) analysis in homozygous *Ank*^{KI/KI} mice, a model for CMD, showed that molars can be moved by orthodontic force without ankylosis, however, at a slower rate compared with those in wild-type *Ank*^{+/+} mice ($p < .05$). Histological analysis of molars in *Ank*^{KI/KI} mice revealed decreased numbers of TRAP⁺ osteoclasts on the bone surface of pressure sides. Based on these findings, recommendations for the dental treatment of patients with CMD are provided.

KEY WORDS: tooth eruption, orthodontics, cone-beam computed tomography, craniofacial abnormalities, mouse model, ANKH.

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Dental Anomalies Associated with Cranio metaphyseal Dysplasia

INTRODUCTION

The term cranio metaphyseal dysplasia (CMD) was coined by Jackson and co-workers in 1954 for a rare disorder involving progressive life-long thickening of craniofacial bones and metaphyseal widening of tubular bones (Jackson *et al.*, 1954). CMD either occurs spontaneously or is transmitted in an autosomal-dominant (AD) or autosomal-recessive (AR) trait. Mutations for the AD form of CMD have been identified in the human *ANK* gene (*ANKH*) as in-frame point mutations or as single amino acid insertions or deletions (Nurnberg *et al.*, 2001; Reichenberger *et al.*, 2001). ANK is a transmembrane protein transporting pyrophosphate, an inhibitor of mineralization. CMD can be diagnosed early in infancy due to difficulties with feeding and breathing caused by obstruction of the nasal lumen (Ramseyer *et al.*, 1993; Haverkamp *et al.*, 1996; Cheung *et al.*, 1997). The spectrum of complaints of patients with CMD frequently includes hearing loss, visual disturbance or blindness, and facial palsy possibly due to neuronal compression (Beighton *et al.*, 1979; Franz *et al.*, 1996; Richards *et al.*, 1996). Dental abnormalities in patients with CMD were reported in a few case reports; however, it is not clear whether CMD has any characteristic dental phenotype because published results of individual patients vary (Hayashibara *et al.*, 2000; Mintz and Velez, 2004; Zhang *et al.*, 2007).

Most patients with CMD require orthodontic treatment. Orthodontic tooth movement involves a bone remodeling process where osteoclasts resorb bone on the pressure side while osteoblasts generate bone on the tension side. Decreased osteoclastogenesis in patients with CMD and in a CMD knock-in (KI) mouse model carrying a Phe377del in the ANK gene has been reported (Chen *et al.*, 2011). We hypothesized that CMD mutations in ANK lead to reduction of tooth movement upon application of orthodontic force. To test this hypothesis, we compared tissue responses to orthodontic treatment in wild-type *Ank*^{+/+} and homozygous *Ank*^{KI/KI} mice by microcomputed tomography (micro-CT) and histology.

Dental abnormalities for many rare genetic bone disorders have not been thoroughly investigated, and therefore dentists often lack guidelines for treating these patients. In response to requests from parents of young patients with CMD, and their dentists, we studied seven patients with different ANK mutations and for the first time describe dentofacial anomalies of patients with CMD by quantitative radiographic and cephalometric methods based on cone-beam computed tomography (CBCT) imaging. We also compiled dentofacial findings from patients with CMD and studied orthodontic tooth

Figure 1. Dentofacial examination of patients with craniometaphyseal dysplasia (CMD). **(A)** Summary of patient ages, genders, and ANKH mutations. **(B)** Facial features of a patient with CMD with hypertelorism and a flat nasal bridge. **(C)** Intra-oral photographs of upper and lower arches. Arrows indicate palatal and lingual tori of a 14-year-old patient with CMD. **(D)** Representative axial and coronal views of cone-beam computed tomography (CBCT) images from a patient with CMD. Expansion of maxillae and thickening of cranial bones are indicated by black arrows and white arrows, respectively. **(E)** Representative sagittal and axial views (left panel) and coronal view (right panel) showed hypoplastic/partial obliteration of paranasal sinuses. 1, sphenoid sinus; 2, ethmoid sinus; 3, maxillary sinus; 4, frontal sinus. **(F)** CBCT image showing an expanded mandible, indicated by black arrows, in a patient with CMD.

movement in a CMD mouse model to establish recommendations for the dental treatment of patients with CMD. This approach can be applied to similar craniofacial bone disorders with impact on dentitions.

MATERIALS & METHODS

Detailed descriptions can be found in the online Appendix.

RESULTS

Common facial features of patients with CMD are hypertelorism and a broad, flat nasal bridge (Fig. 1B). Intra-oral examination revealed overall healthy soft tissue and normal tooth morphology with the exception of case 2, who had enamel hypomineralization as shown by chalky white spots in permanent maxillary posterior teeth. Prominent palatal and lingual tori were seen in cases 1, 2, 3, and 7 (Fig. 1C). All patients have or had slower eruption of permanent teeth, with a delay of approximately 2 yr.

Reconstructed 3D CBCT images were used to analyze the dental and osseous structures, bone density, and possible obliteration of the sinuses and foramina (Table 1). Cranial bones in patients with CMD were generally hyperostotic (Fig. 1D). The most prominent bone deposition was found in the inner table of

the frontal and occipital bones. Pixel intensity values (PIVs) derived from CBCT volumes of these bones showed lower density compared with that of other bones. All patients with CMD had narrowed foramina in the skull base and smaller maxillary, ethmoid, sphenoid, and frontal sinuses (Fig. 1E). While the majority of maxillary and frontal sinuses were hypoplastic, some cases showed pneumatization in the ethmoid and sphenoid sinuses. Bucco-lingual dimensions of jawbones were increased, with expansion in mandibles more pronounced than in maxillae (Table 1, Figs. 1D, 1F). Although craniofacial and jaw bones were thickened in patients with CMD, PIVs did not indicate increased bone density compared with that in unaffected individuals. Temporomandibular joints appeared radiographically normal except for degenerative changes observed in case 7. None of the patients with CMD showed nasal septum deviation.

Cases 1, 2, and 7 had orthodontic treatment at the time of evaluation, and other cases had referrals for orthodontic consultation. We analyzed the dental and jawbone relationship with lateral cephalograms generated from CBCT scans of cases 3, 4, 5, and 6 who had not received orthodontic treatment. Individuals tended to have a small anterior cranial base (S-N), acute cranial base angle (Ar-S-N), short anterior facial height (N-ANS), small maxilla (ANS-PNS), obtuse gonial angle (Ar-Go-Gn), and increased maxillary vertical dento-alveolar heights (NF-U1,

Table 1. CBCT Measurements of Jawbone Thickness and PIVs of Cranial and Jaw Bones

Case	^a Ant. Max. (mm)	^b Post. Max. (mm)	^a Ant. Mand. (mm)	^b Post. Mand. (mm)	PIVs (cortical)	PIVs (trabecular)	Involved Sinus
1	11.8	14.7	9	13	500-700	-169 to 0	Max
2	15.2	13.9	11	14	100-1000	-230 to -61	Max, F
3	16.3	18	10.9	13	400-900	-225 to -90	Max
4	15.4	14	12.5	14	300-937	-247 to -80	Max, F
5	16.7	17	15.5	23	200-550	-200 to -50	Max, F, S, Eth
6	15.1	17	12.6	16	400-1000	-258 to -60	Max, F, S, Eth
7	15.5	13.7	9.7	12	400-700	-120 to 90	Max, F
Norms	11.5	13	6.5	11.5	>900	150-250	Unaffected

^aBucco-lingual dimensions of anterior maxillary or mandibular bones measured at midline.

^bBucco-lingual dimensions of posterior maxillary or mandibular bones presented as the average of the largest dimensions of right and left sides. CBCT, cone-beam computed tomography; PIVs, pixel intensity values; Max., maxillary bone or maxillary sinus; F, frontal sinus; S, sphenoid sinus; Eth, ethmoid sinus.

NF-U6). The relationship between maxillae and mandibles in the anterior-posterior axis was highly variable, from a moderate Class II to a moderate Class III (Table 2).

To study the effects of CMD *Ank* mutations on tissue response to orthodontic force, we next studied orthodontic tooth movement in our CMD mouse model. The dentition of *Ank*^{KI/KI} mice is affected by the thickening of jawbones, excessive cementum deposition, abnormal incisor development, and impaired osteoclastogenesis (Dutra *et al.*, 2013). We used 12-week-old *Ank*^{+/+} and *Ank*^{KI/KI} mice to place springs between upper incisors and first molars for 7 and 14 days and used micro-CT and histology to investigate changes in bone, periodontal ligament, and roots. Orthodontic force moves mouse molars mesially by resorbing alveolar bone on the pressure side, while new bone forms on the tension side. We measured the closest distance between the first and second maxillary molars in 3D micro-CT reconstructions. After 14 days of orthodontic force, the spacing between first and second molars of *Ank*^{KI/KI} mice was significantly smaller than that in *Ank*^{+/+} mice ($p < .05$) (Fig. 2A), suggesting that *Ank*^{KI/KI} molars can be orthodontically moved but at a slower rate.

To study histological changes in the periodontium, we measured the periodontal ligament (PDL) space on pressure and tension sides at disto-buccal (DB) roots of first molars. After 7 and 14 days of orthodontic force, the absolute PDL space on the pressure side was significantly smaller than that on the tension side in both *Ank*^{+/+} and *Ank*^{KI/KI} mice (Fig. 2B). When we compared the percentage increase or decrease of the PDL space of the mesial sides between the orthodontically treated molars and the contralateral untreated molars, the difference between *Ank*^{+/+} and *Ank*^{KI/KI} mice was much more pronounced. The PDL area on the pressure sides of treated molars of *Ank*^{+/+} mice was increased after the application of orthodontic force for 7 and 14 days compared with the contralateral control molars, while in *Ank*^{KI/KI} mice, the PDL space at the pressure side was smaller than in the contralateral control molars (negative percentage change) (Fig. 2C). This finding suggests that orthodontic force causes sufficient alveolar bone resorption in wild-type *Ank*^{+/+} molars, which leads to expansion of the PDL space compared with the untreated side, whereas in *Ank*^{KI/KI} mice, less resorption and remodeling occur, and thus the PDL space is compressed compared with the untreated side. The percentage change of PDL

space on the tension side continued to increase from 7 to 14 days in *Ank*^{+/+} mice, while it remained at a similar level in *Ank*^{KI/KI} mice (Fig. 2B, Appendix Fig. 3). This result corresponds to the micro-CT finding of reduced molar distance after tooth movement in *Ank*^{KI/KI} mice.

We next performed tartrate-resistant acid phosphatase (TRAP) staining on cross-sections of murine maxillary molars to study the presence of osteoclasts around DB roots of first molars. TRAP⁺ cells were located on alveolar bone or root surfaces on the pressure sides after orthodontic force for 7 and 14 days. Numbers of TRAP⁺ cells were decreased in *Ank*^{KI/KI} molars (Figs. 2D, 2E). Reduced numbers and size of osteoclasts were also seen in bone-marrow-derived macrophage cultures from *Ank*^{KI/KI} mice (Chen *et al.*, 2011). Interestingly, we observed mild root resorption in 2 out of 6 *Ank*^{+/+} molars, while all 6 *Ank*^{KI/KI} molars showed various degrees of resorption on the cementum (Fig. 2D), which suggests that it may be easier for osteoclasts to resorb the excessive cementum of *Ank*^{KI/KI} roots than to resorb bone. No excessive cementum was noted in CBCT images of patients with CMD, but cases 1 and 2, who had completed orthodontic treatment, showed blunt roots in anterior teeth, which is a sign of root resorption. No root resorption was identified in case 7, who had also undergone orthodontic treatment. We conclude that orthodontic tooth movement in patients with CMD is possible, albeit at a slower rate.

DISCUSSION

Cone-beam computed tomography is increasingly used for dental and craniofacial diagnoses because it provides high resolution, has 3D capability, and exposes patients to less radiation than multi-detector medical CTs (Scarfe *et al.*, 2006; Ludlow and Ivanovic, 2008; Scarfe and Farman, 2008). In this study, we showed that 12-inch field-of-view CBCT images can be used to study structures of dentition, craniofacial bones, and sinuses as well as bone density by measuring PIVs. Normal values of PIVs for this study came from a radiographic database at UCHC and were similar to the published PIVs of bone-equivalent materials (Reeves *et al.*, 2012). Analysis of our data showed that the bone density in our group of seven patients with CMD appeared to be normal in cortical bone but reduced in the trabecular compartment of cranial and jaw bones. We previously showed decreased

Table 2. Orthodontic Linear and Angular Measurements of Patients with Craniometaphyseal Dysplasia

Orthodontic Linear Measurements (mm)									
Case	S-N	N-Me	N-ANS	ANS-Me	Go-Gn	Ar-Go	Co-Gn	U1-NF	U6-NF
1	73/75	125/129	48/50	77/72	80/75	47/49	126/122	31/28	26/23
2	65/75	111/129	43/50	68/72	74/75	46/49	116/122	31/28	27/23
3	69/75	120/127	48/50	73/71	74/75	40/48	115/121	32/28	26/23
4	59/72	98/109	41/50	60/63	63/67	34/40	95/111	28/28	22/23
5	67/72	106/110	37/50	70/64	68/67	45/41	104/112	32/28	28/23
6	72/71	110/107	44/50	68/62	65/65	35/39	102/110	29/31	23/26
7	74/77	129/137	50/50	80/75	86/79	47/52	124/127	34/31	30/26
Orthodontic Angular Measurements (angle)									
Case	SNA	SNB	ANB	Ar-S-N	Ar-Go-Gn	ANS-PNS			
1	77/82	74/80	3/2	127/124	133/122	50/53			
2	85/82	84/80	1/2	117/124	132/122	45/53			
3	80/82	76/80	4/2	122/124	136/122	49/53			
4	86/82	79/80	7/2	120/124	139/122	42/53			
5	75/82	78/80	-3/2	117/124	125/122	41/53			
6	80/82	74/80	6/2	114/124	136/122	47/58			
7	82/82	82/80	0/2	113/124	134/119	45/58			

Data represent measurements from pts/norm values.

Bold face indicates: ≥ 1 standard deviation from the norm.

mineral density in the cortical bone of femurs by ash weight and Fourier-transform infrared spectroscopy in the CMD (*Ank^{KI/KI}*) mouse model (Chen *et al.*, 2009). Both human and mouse studies suggest that ANK mutations in CMD do not cause hypermineralization. Previous reports of hardened bones in patients with CMD were not substantiated by 3D imaging or quantitative measurements (Ramseyer *et al.*, 1993; Ahmad *et al.*, 2006).

To develop recommendations for the dental treatment of patients with CMD, we first performed thorough dental examinations and orthodontic cephalometric analyses. Patients with CMD in this study had no periodontal disease, normal pulp space but expanded jawbones, and palatal or lingual tori developed at very young ages. They tended to have a short anterior cranial base, short upper facial height, short maxillary length, and approximately two-year delayed eruption of permanent teeth. We recommend that tori should be considered in any treatment plan involving denture design. Because of expanded jawbones, if endodontic surgery is needed, a smaller field of view (FOV), such as a 6-inch FOV, should be useful for measuring distances between roots or lesions and buccal or lingual/palatal cortical bones, to avoid unnecessarily enlarged osteotomy during surgery. Most patients with CMD need orthodontic treatment. Because the eruption of teeth in patients with CMD was merely delayed, we believe that, in most cases, no surgical force eruption is required. Teeth can be moved by orthodontic force without ankylosis. Treatment plans for orthodontics can be considered 2 yr later than normal, and the required time for orthodontic treatment is likely to be longer.

Osteoclast resorption of alveolar bone at the pressure side is essential for tooth movement. Mutations in ANK leading to CMD result in reduced osteoclastogenesis in *Ank^{KI/KI}* mice and

in patients with CMD (Chen *et al.*, 2011). Therefore, orthodontic movement may be affected in patients with CMD. We studied tooth movement by orthodontic force in our CMD mouse model. This allowed us to analyze spatial changes and osteoclast numbers by micro-CT and histology, which for obvious reasons is not possible to do in patients with CMD. We chose horizontal rather than vertical root sections to count osteoclast numbers to minimize variability as suggested by Yoshimatsu and colleagues (Yoshimatsu *et al.*, 2006). All sections were collected from male mice of the same age and from similar levels in an apical-gingival direction. As expected, we found reduced numbers of osteoclasts and decreased tooth movement in *Ank^{KI/KI}* mice. Possible reasons for reduced osteoclast numbers include: (1) bone marrow space is markedly reduced, and thus fewer osteoclast progenitors reside in *Ank^{KI/KI}* mandibles; and (2) migration and function of *Ank^{KI/KI}* osteoclasts are reduced (Chen *et al.*, 2011). Chemokines such as CCL3, CCR1, and CCR5 have been shown to play a role in recruiting osteoclasts to the sites of pressure upon orthodontic force (Andrade *et al.*, 2009; Taddei *et al.*, 2013). Detailed studies will be needed to determine whether differences in chemokine expression affect bone remodeling in *Ank^{KI/KI}* mice during orthodontic movement. Other models of osteoclast deficiency unrelated to CMD showed similar deficiencies in orthodontic tooth movement, such as a mouse model with bisphosphonate treatment (Fujimura *et al.*, 2009). The data from our CMD mouse model may not fully represent tissue responses in patients with CMD because of species specificity and severity of disease phenotypes. However, we believe that the CMD mouse model is a useful tool to study how CMD mutations in ANK affect tooth movement on cellular and histological levels.

Figure 2. Orthodontic tooth movement in a craniometaphyseal dysplasia (CMD) mouse model. **(A)** microcomputed tomography (micro-CT) images (left panel) of maxillae from male 12-week-old *Ank*^{+/+} and *Ank*^{KI/KI} mice with or without orthodontic force for 14 days. Distances between first and second molars are indicated by red arrows. The histogram (right panel) shows that distances are significantly smaller in *Ank*^{KI/KI} mice (**p* < .05; Student's *t* test). **(B)** Histogram shows that the periodontal ligament area is significantly narrower on pressure sides compared with tension sides after 7 and 14 days of orthodontic tooth movement in *Ank*^{+/+} and *Ank*^{KI/KI} mice (**p* < .05; two-way analysis of variance [ANOVA]). Sections measured for each group: *Ank*^{+/+} day 7 (*n* = 11), *Ank*^{KI/KI} day 7 (*n* = 8), *Ank*^{+/+} day 14 (*n* = 12), and *Ank*^{KI/KI} day 14 (*n* = 8). **(C)** Histogram showing percentage increase or decrease of PDL area on pressure sides after 7 and 14 days of orthodontic tooth movement compared with that on mesial sides of contralateral control teeth without orthodontic force in *Ank*^{+/+} and *Ank*^{KI/KI} mice (**p* < .05; one-way ANOVA). Sections measured for each group: *Ank*^{+/+} day 7 (*n* = 11), and *Ank*^{KI/KI} day 7 (*n* = 8). **(D)** Tartrate-resistant acid phosphatase (TRAP) staining of paraffin sections show alveolar bone (B) and root (R) on the pressure sides of *Ank*^{+/+} and *Ank*^{KI/KI} mice after 7 and 14 days of orthodontic tooth movement. Yellow arrows indicate TRAP+ cells. Asterisk (*) shows root resorption. Double-ended white arrows indicate excessive cementum formation in *Ank*^{KI/KI} mice. Scale bar = 100 μ m. **(E)** Histogram showing decreased numbers of TRAP+ osteoclasts in *Ank*^{KI/KI} mice after 7 and 14 days of orthodontic tooth movement (N.Oc/ μ m = number of osteoclasts/length of bones and roots on the pressure sides, **p* < .05; one-way ANOVA).

It is known that osteoblasts deposit bone on tension sides (Uribe *et al.*, 2011) and that osteocyte ablation reduces osteoclastogenesis during orthodontic tooth movement (Matsumoto *et al.*, 2013). There is no direct experimental evidence for ANK mutations affecting osteoblast activity in patients with CMD. For *Ank*^{KI/KI} mice, we previously reported that: (1) bone formation rate and mineral apposition rate of femurs and calvariae were not significantly different from those in wild-type mice; (2) small but significantly reduced levels of osteoblast differentiation markers *Ocn*, *Runx2*, *Osx*, and *Phex* existed in *Ank*^{KI/KI}

calvarial cultures; (3) serum ALP was significantly increased but ALP expression measured in osteoblast cultures was normal; and (4) RNA levels of *Fgf23*, mainly expressed by osteocytes, were significantly increased. Deficiencies of osteoblasts or osteocytes in *Ank*^{KI/KI} mice are possibly secondary effects of reduced serum Pi and Ca levels and are not as strong and well-defined as in osteoclasts. To clarify whether mutant osteoblasts and osteocytes have any impact on tooth movement, we will study a mouse model expressing the CMD-causing ANK mutation only in an osteoblast- and osteocyte-specific manner. We

believe that this tool will shed more light on the role of mutant osteoblasts and osteocytes during orthodontic tooth movement.

In summary, here we characterized dentofacial anomalies of patients with CMD at different ages with radiographic and cephalometric quantitative measurements. Based on clinical findings and mouse data, we further provide recommendations for the dental treatment of patients with CMD. It is our goal to improve the quality of dental health for patients with CMD or similar disorders. We believe that the analytic methods of this study may serve as a model for other rare bone diseases that affect craniofacial bones and dentition.

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