Case Report

Dental Anomalies in a Child With Craniometaphysial Dysplasia

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Abstract: *Craniometaphysial dysplasia (CMD) is a rare disorder that mainly affects craniofacial bones. It is caused by mutations within a region of human homolog (Ankh) of the mouse progressive ankylosis (Ank) gene. ANK, together with other factors, regulates intracellular and extracellular levels of pyrophosphate/inorganic phosphate critical for maintaining mineral homeostasis. The systemic manifestations noted in CMD patients have been reported previously. The dental anomalies in CMD patients, however, have been minimally described in the dental literature. The purpose of this case report was to describe both systemic and dental manifestations of a 3½-year-old child with craniometaphysial dysplasia. At the gross level, enamel discoloration and tooth malformations were observed in multiple primary teeth without obvious defects in the roots. Radiographic evidence of excess mineralization was noted on the primary maxillary second molars, limited to the mesial region of the crowns. The genetic and molecular effects of Ank/Ankh mutations are also discussed. (Pediatr Dent 2007;29:415-9) Received August 31, 2006 / Revision Accepted December 31, 2006.*

KEYWORDS: CRANIOMETAPHYSIAL DYSPLASIA, ANKH GENE, ENAMEL, PHOSPHATE

Craniometaphysial dysplasia (**CMD**) is a rare congenital disorder characterized by marked sclerosis of the craniofacial bones, often with neurological defects, such as blindness, facial paralysis, and deafness, due to increased intracranial pressure. Metaphyses of long bones are widened, but the extracranial skeleton and joints are otherwise not affected.[1,2] An autosomal recessive condition with similar craniofacial features, craniodiaphysial dysplasia (**CDD**) affects the diaphyses of long bones and is associated with mental retardation.[3] There are autosomal dominant (**AD**) and autosomal recessive forms, with the latter showing more severe complications.[4,5] The AD form is caused by mutations of the human homolog (**Ankh**) of the mouse progressive ankylosis (***Ank***) gene on human chromosome 5. The molecular basis of CDD is not yet known.

ANK, as well as its human homolog (ANKH), are putative transporters of inorganic pyrophosphate ($\mathbf{PP_i}$) from the intracellular compartment to the extracellular space.[6] Combined with other factors—such as the PP_i-generating nucleoside triphosphate pyrophosphohydrolase plasma cell membrane glycoprotein-1 (**PC-1**, also known as **NPP1**)[7] and tissue nonspecific alkaline phosphatase (**TNAP**), an enzyme proposed to cleave PP_i substrate to its inorganic phosphate ($\mathbf{P_i}$) constituents[8]—ANK regulates intracellular and extracellular levels of PP_i/P_i, which are important for maintaining mineralized tissues, including mineral homeostasis of bones and teeth.

Although there have been clinical reports of CMD patients in the literature, to our knowledge reports on dental features are limited to 1 case which that showed delayed eruption of permanent teeth in a child with CMD.[9] The purpose of this case report was to describe both systemic and dental manifestations in a patient with craniometaphysial dysplasia. The genetic and molecular mechanisms on how Ankh mutation affects tooth/root development are also discussed.

Case report

Past medical history. The patient was born to a 29-year-old, gravida 1, para 0-1 mother at 39 weeks gestation via normal spontaneous vaginal delivery, with a birth weight of 3.4 kg. He was discharged home shortly after delivery. Soon after birth, his family noticed a difference in his facial appearance. At approximately 6 months of age, he was evaluated in a local emergency room for concerns related to upper airway compromise. At that time, the family was told that the child had a "genetic

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disorder." Subsequent evaluations led to the diagnosis of CMD. The patient experienced chronic nasal stuffiness, snoring, a mild nasal discharge, and mouth breathing with upper respiratory tract infections, but no other medical problems.

Family history. Family history was negative for any skeletal or dental anomalies. The patient has a healthy 2-month-old sister. Neither his parents nor his sister have features of CMD, suggesting that his represents a new spontaneous mutation.

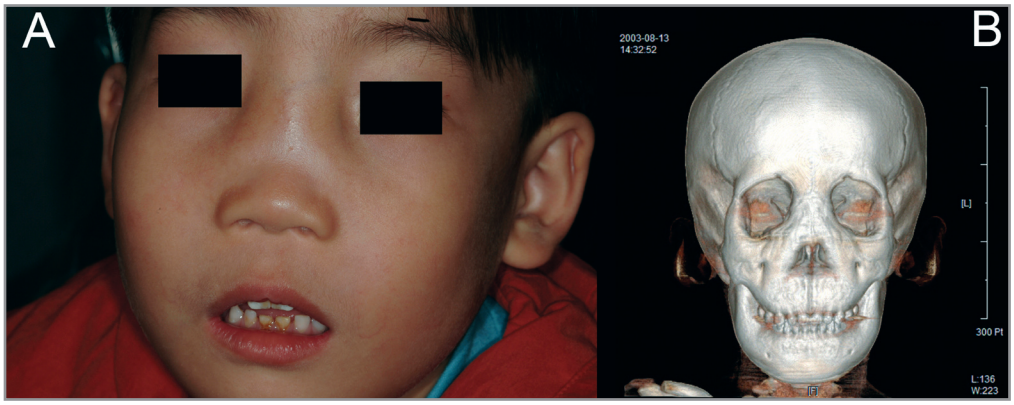

Figure 1. (A) A facial photo and (B) a 3-D CT scan image of the skull, both demonstrating the classic facial features of craniometaphysial dysplasia with dramatic thickening of the nasal bones and the nasal glabellar region.

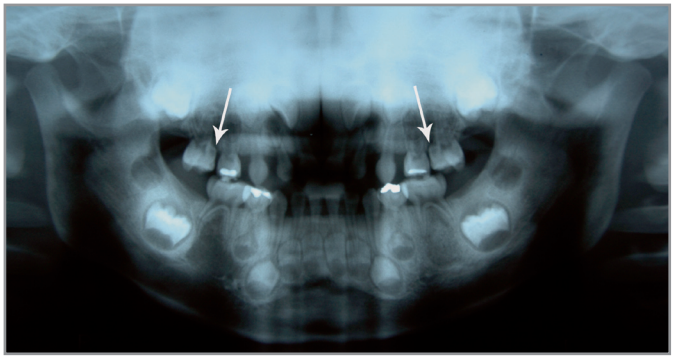

Figure 2. A panoramic radiograph of the patient's orofacial tissues: Thick bones were present in mid-facial area. The radiographic appearance of all primary teeth as well as development of the permanent dentition appeared to be normal. The arrows indicate the "enamel pearl"-like excess mineralization of the primary maxillary second molars.

Physical examination. At 3½ years old, the patient was referred to the Children's Craniofacial Center, Children's Hospital and Medical Center, Seattle, Wash, for evaluation. His height, weight, and occipital frontal circumference were all between the 75th and 90th percentile. He had classic facial features of the autosomal dominant form of craniometaphysial dysplasia, with dramatic thickening of the nasal bones and the nasal glabellar region, resulting in leonine facies (Figure 1a). Nasal endoscopy revealed normal nostrils but severe intranasal stenosis due to medialization of the turbinates. The patient had significant thickening of the zygoma, zygomatic arches, and particularly the mandibular ramus and body. He had the appearance of hypertelorism due to lateral displacement of the lateral canthi and the breadth of his nose. The intracanthal distance (37 mm) and the interpupillary distance (53 mm) were normal. His visual acuity was 20/25 on the right and 20/20 on the left by Allen picture testing. Cranial nerves II-XII were intact, and funduscopic examination was without evidence of papilledema or nystagmus. His tone and reflexes were symmetric. The external ears were normally formed. Oropharyngeal examination revealed broadening of the alveoli, but otherwise no overt mucosal disease or palatal malformations. His axial and appendicular skeleton was normal without evidence of metaphysial flaring. The remainder of his general physical exam was not significant.

Radiographic findings. CT scans revealed classic features of craniometaphysial dysplasia, with dramatic thickening of all of the facial bones, vomer, nasal turbinates, medial pterygoids, middle ear ossicles, calvaria, skull base, and narrowed optic foramina (Figure 1b). Neither CT nor MRI scans demonstrated evidence of ventriculomegaly or increased intracranial pressure. The panoramic radiograph showed some identifiable anomalies of the developing permanent dentition (Figure 2). In the maxillary arch, the permanent maxillary central incisors appeared to be abnormally shaped and were rotated. Developing tooth buds for remaining permanent teeth were observed, except for the mandibular second premolars. The tooth buds superimposed over the maxillary lateral incisors might be supernumerary teeth, although we were not able to confirm presently since maxillary occlusal radiographs were not available.

Oral examination. Upon presentation for clinical oral examination, the soft tissues, dentition, and occlusion were examined. The intraoral soft tissues were within normal limits. The marginal gingiva was mildly inflamed—consistent with gingivitis due to local factors. A full complement of 20 primary teeth in occlusion was noted. The sizes of all teeth were within the normal clinical range. Thus, the radiographic appearance of macrodontia molars is likely due to distortion of the panoramic radiograph. The primary canines exhibited a Class I relationship. Overbite was 20% and overjet was 3 mm. The patient had a telescopic bite with the mandibular trans-

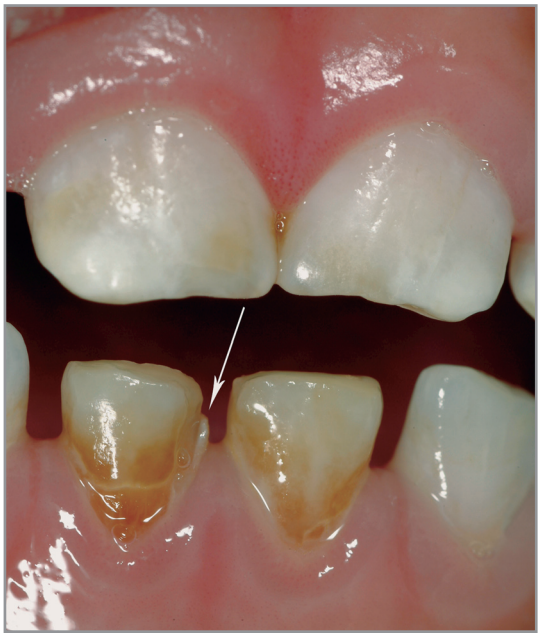

Figure 3. A frontal view of the upper and lower anterior teeth showing discoloration of the tooth surfaces. The arrow indicates the malformation or excess mineralization of the mandibular central incisor.

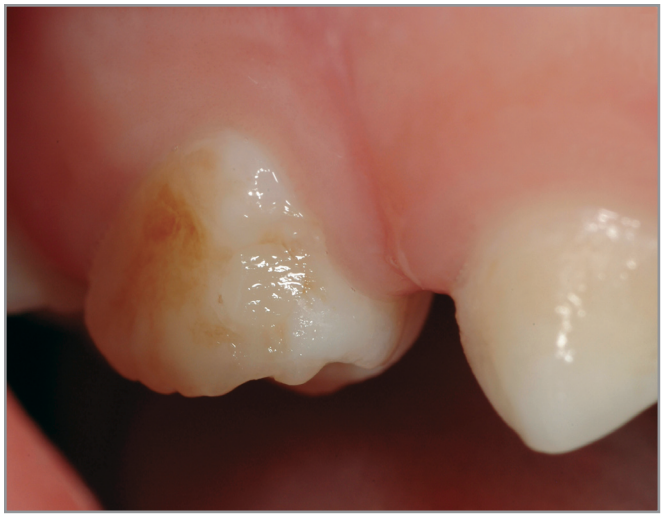

Figure 4. A lateral view of the primary maxillary right first molar showing the discoloration and defects on tooth surface.

verse dimension narrower than the maxillary transverse dimension and, upon occluding, his mandibular posterior teeth were palatal to the maxillary posterior teeth. In orthodontic terminology, this is known as a Brodie bite. It was felt that this was related to the thickness of maxillary bone development which, in turn, affected dental relationships. The thickness of the bone will complicate future treatment approaches. There was no evidence of active dental caries, although some restorative treatment had previously been performed on 4 primary teeth. Many of the teeth exhibited dysmorphic and discolored surfaces. This was particularly true of the primary mandibular central incisors (Figure 3) and the primary maxillary first molars (Figure 4). The labial surface of the primary mandibular central incisors exhibited a brownish-orange discoloration consistent with enamel dysplasia and/or enamel hypoplasia. The primary maxillary second molars showed a similar malformation, with the addition of what appeared to be an enamel pearl on the buccal surface, near the mesiobuccal line angle, bilaterally (Figure 2). Rubber cup pumice prophylaxis did not affect any of the visual findings other than the removal of plaque.

Discussion

Tooth development involves complicated gene induction and regulation between multiple types of cells in different stages, with many similarities to bone formation.[10-13] It has been well documented that epithelial-mesenchymal interactions play critical roles in the initiation of tooth formation.[14-16] The majority of inorganic mineral content associated with bone, cementum, dentin, and enamel is in the form of hydroxyapatite, which is mainly composed of calcium and phosphate. Therefore, mineral metabolism, especially calcium and phosphate homeostasis, play critical roles in the development and regeneration of hard tissues. Regulation of phosphate is critical for development and maintenance of tissue homeostasis.[6,17,18] Mineralized tissues, depending on location, respond differently to regulators of phosphate homeostasis.[19-21] The mechanisms involved in phosphate regulating tooth development and homeostasis are just beginning to be understood.[22,23] The dental phenotype reported in this case highlights the need for careful oral and dental examination in patients reporting craniofacial-skeletal anomalies, especially those associated with phosphate metabolism.

Regulators of phosphate metabolism have received considerable attention within recent years, with convincing evidence that inorganic phosphate (P_i), beyond its known role as an important component of hydroxyapatite mineralization, may also function as a signaling molecule and regulate cell behavior and subsequent mineralization. Conversely, pyrophosphate (PP_i) has been identified as a natural inhibitor of crystal formation in interstitial fluids and is used therapeutically, in the form of bisphosphonate, to control crystal growth.[24-27] Systemic factors—such as fibroblast growth factor-23 (FGF-23),[28] phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX),[29] and KLOTHO[30]—are also implicated as important regulators of phosphate homeostasis. Results from studies to date suggest that local control of PP_i/P_i is critical for normal root/periodontal tissue development and, further, that cementum may be uniquely sensitive to PP_i and P_i in the local area.[19-21] As

mentioned in the introduction, ANK, PC-1, and TNAP are the major regulators on PPi/Pi homeostasis. In cases of TNAP deficiency (Tnap mutation or KO, the condition hypophosphatasia in humans), bones are osteopenic and root cementum is disrupted, generally with a lack of acellular cementum and severely disrupted cellular cementum.[31] Absence of cementum prevents insertion of periodontal ligament (**PDL**) (Sharpey's) fibers, leading to lack of attachment and exfoliation of teeth. By contrast, humans and animals with loss of function of PC-1 (NPP1) or *ANK* exhibit low levels of PP_i in the local extracellular environment, resulting in ectopic calcifications in joints—with mice exhibiting an arthritis-like condition.[6,27] Further evidence for the remarkable sensitivity of oral hard tissues to phosphates includes the accumulating reports that individuals using bisphosphonates, especially intravenously, are at risk of developing osteonecrosis of the jaw.[32-34]

It has been demonstrated that CMD patients have a mutation that affects ANK. In mouse models, an unexpected and intriguing tooth phenotype has been reported with mutations in either Enpp1 (encodes NPP1 or PC-1) or *Ank*. Rather than observing ectopic calcification in the PDL—as noted in other ligaments (joints) in mice with these mutations—a marked increase in cementum formation was observed, while PDL, enamel, dentin, and alveolar bone appeared unaffected.[20] In the case examined here, we noted enamel discoloration and malformation of crowns. The human counterpart of mouse *Ank* and Enpp1 mutations do not parallel the defects noted in rodents. In both situations, however, a dramatic disruption of the normal mineralization process can be observed. Although this is the only CMD case that has so far included enamel defects in the literature, it might imply the involvement of P_i/PP_i regulation in the development of the crown portion of a tooth (enamel and/or dentin). Other factors may also cause similar enamel defects, however, such as prenatal and postnatal infectious diseases, malnutrition, fluorosis, etc. Further investigations—including histological examination of roots (including PDL) and crowns, when available—will help better define the tooth phenotype associated with CMD.

The dental phenotype in this case does not warrant management clinically at this time. The identification of defects in tooth development in CMD, however, may be important in the long-term management of children with this debilitating condition. Although no standard therapy for the extensive thickening of the craniofacial skeleton exists, debulking procedures to decompress increased intracranial pressure, entrapped cranial nerves, and compression of the brain stem are frequently temporizing.[35-38] The addition of excessive tooth mineralization to the phenotype of CMD may help to develop pharmacologic therapies to abrogate the effects of loss of function due to Ankh mutations.

The findings reported here underscore the need to characterize the oral-tooth phenotype in disorders linked with craniofacial anomalies. Continued characterization of the orodental phenotype observed in patients with genetic disorders associated with phosphate metabolism should assist in understanding the role of these genes/proteins in modulating mineral formation. Additionally, it will provide valuable information for improving therapies targeted at controlling the abnormal mineralization present in these disorders.

References

1. Nurnberg P, Thiele H, Chandler D, et al. Heterozygous mutations in ANKH, the human ortholog of the mouse progressive ankylosis gene, result in craniometaphysial dysplasia. Nat Genet 2001;28:37-41.
2. Reichenberger E, Tiziani V, Watanabe S, et al. Autosomal dominant craniometaphysial dysplasia is caused by mutations in the transmembrane protein ANK. Am J Hum Genet 2001;68:1321-6.
3. Richards A, Brain C, Dillon MJ, Bailey CM. Craniometaphysial and craniodiaphyseal dysplasia, head and neck manifestations, and management. J Laryngol Otol 1996;110:328-38.
4. Kim YH, Roh DH, Choi BY, Oh SH. Craniometaphysial dysplasia. Acta Otolaryngol 2005;125:797-800.
5. Mintz S, Velez I. Craniometaphysial dysplasia associated with obstructive sleep apnea syndrome. Dentomaxillofac Radiol 2004;33:262-6.
6. Ho AM, Johnson MD, Kingsley DM. Role of the mouse ank gene in control of tissue calcification and arthritis. Science 2000;289:265-70.
7. Goding JW, Terkeltaub R, Maurice M, Deterre P, Sali A, Belli SI. Ecto-phosphodiesterase/pyrophosphatase of lymphocytes and non-lymphoid cells: Structure and function of the PC-1 family. Immunol Rev 1998;161:11-26.
8. Whyte MP, Landt M, Ryan LM, et al. Alkaline phosphatase: Placental and tissue-nonspecific isoenzymes hydrolyze phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5'-phosphate. Substrate accumulation in carriers of hypophosphatasia corrects during pregnancy. J Clin Invest 1995;95:1440-5.
9. Hayashibara T, Komura T, Sobue S, Ooshima T. Tooth eruption in a patient with craniometaphysial dysplasia: Case report. J Oral Pathol Med 2000;29:460-2.
10. Mitsiadis TA, Rahiotis C. Parallels between tooth development and repair: Conserved molecular mechanisms following carious and dental injury. J Dent Res 2004;83:896-902.
11. Thesleff I. Genetic basis of tooth development and dental defects. Acta Odontol Scand 2000;58:191-4.
12. Jung HS, Hitoshi Y, Kim HJ. Study on tooth development: Past, present, and future. Microsc Res Tech 2003;60:480-2.

13. Thesleff I, Mikkola M. The role of growth factors in tooth development. Int Rev Cytol 2002;217:93-135.
14. Papagerakis P, MacDougall M, Berdal A. Differential epithelial and mesenchymal regulation of tooth-specific matrix proteins expression by 1.25-dihydroxyvitamin D3 in vivo. Connect Tissue Res 2002;43:372-5.
15. Zeichner-David M, Oishi K, Su Z, et al. Role of Hertwig's epithelial root sheath cells in tooth root development. Dev Dyn 2003;228:651-63.
16. Thesleff I, Vaahtokari A, Kettunen P, Aberg T. Epithelial-mesenchymal signaling during tooth development. Connect Tissue Res 1995;32:9-15.
17. Gurley KA, Chen H, Guenther C, et al. Mineral formation in joints caused by complete or joint-specific loss of ANK function. J Bone Miner Res 2006;21:1238-47.
18. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004;19:429-35.
19. Anderson HC, Harmey D, Camacho NP, et al. Sustained osteomalacia of long bones despite major improvement in other hypophosphatasia-related mineral deficits in tissue nonspecific alkaline phosphatase/nucleotide pyrophosphatase phosphodiesterase 1 double-deficient mice. Am J Pathol 2005;166:1711-20.
20. Nociti FH Jr, Berry JE, Foster BL, et al. Cementum: A phosphate-sensitive tissue. J Dent Res 2002;81:817-21.
21. van den Bos T, Handoko G, Niehof A, et al. Cementum and dentin in hypophosphatasia. J Dent Res 2005;84:1021-5.
22. Lorenz-Depiereux B, Bastepe M, Benet-Pages A, Amyere M, Wagenstaller J, Muller-Barth U, et al. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. Nat Genet 2006;38:1248-50.
23. Pereira CM, de Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA. Dental alterations associated with X-linked hypophosphatemic rickets. J Endod 2004;30:241-5.
24. Fleisch H. Diphosphonates: History and mechanisms of action. Metab Bone Dis Relat Res 1981;3:279-87.
25. Rodan GA. Mechanisms of action of bisphosphonates. Annu Rev Pharmacol Toxicol 1998;38:375-88.
26. Terkeltaub R, Lotz M, Johnson K, et al. Parathyroid hormone-related proteins is abundant in osteoarthritic cartilage, and the parathyroid hormone-related protein 1-173 isoform is selectively induced by transforming growth factor beta in articular chondrocytes and suppresses generation of extracellular inorganic pyrophosphate. Arthritis Rheum 1998;41:2152-64.
27. Terkeltaub RA. Inorganic pyrophosphate generation and disposition in pathophysiology. Am J Physiol Cell Physiol 2001;281:C1-11.
28. Sitara D, Razzaque MS, Hesse M, et al. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. Matrix Biol 2004;23:421-32.
29. Miao D, Bai X, Panda DK, Karaplis AC, Goltzman D, McKee MD. Cartilage abnormalities are associated with abnormal Phex expression and with altered matrix protein and MMP-9 localization in Hyp mice. Bone 2004;34:638-47.
30. Prie D, Beck L, Urena P, Friedlander G. Recent findings in phosphate homeostasis. Curr Opin Nephrol Hypertens 2005;14:318-24.
31. Beertsen W, VandenBos T, Everts V. Root development in mice lacking functional tissue non-specific alkaline phosphatase gene: Inhibition of acellular cementum formation. J Dent Res 1999;78:1221-9.
32. Badros A, Weikel D, Salama A, et al. Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors. J Clin Oncol 2006;24:945-52.
33. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: A long-term complication of bisphosphonate treatment. Lancet Oncol 2006;7:508-14.
34. Woo SB, Hellstein JW, Kalmar JR. Narrative review: Bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144:753-61.
35. Ahmad FU, Mahapatra AK, Mahajan H. Craniofacial surgery for craniometaphysial dysplasia. Neurol India 2006;54:97-9.
36. Day RA, Park TS, Ojemann JG, Kaufman BA. Foramen magnum decompression for cervicomedullary encroachment in craniometaphysial dysplasia: Case report. Neurosurgery 1997;41:960-4.
37. Puri P, Chan J. Craniometaphysial dysplasia: Ophthalmic features and management. J Pediatr Ophthalmol Strabismus 2003;40:228-31.
38. Sheppard WM, Shprintzen RJ, Tatum SA, Woods CI. Craniometaphysial dysplasia: A case report and review of medical and surgical management. Int J Pediatr Otorhinolaryngol 2003;67:687-93.