Case Report

Dental Anomalies in a Child With Craniometaphysial Dysplasia

Hai Zhang, DMD, PhD¹ • Martha J Somerman, DDS, PhD² • Joel Berg, DDS, MS³ • Michael L Cunningham, MD, PhD⁴ • Bryan Williams, DDS, MSD⁵

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.

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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 (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 (P_i) constituents⁸—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

¹Dr. Zhang is an assistant professor, Department of Restorative Dentistry, ²Dr. Somerman is a professor and the Dean, Department of Periodontics, and ³Dr. Berg is a professor and the chair, Department of Pediatric Dentistry, all in the School of Dentistry, University of Washington, Seattle, Wash; ⁴Dr. Cunningham is a professor, Department of Pediatrics, and Chief, Division of Craniofacial Medicine, University of Washington and Children's Craniofacial Center, Children's Hospital and Regional Medical Center, Seattle; and ⁵Dr. Williams is the director, Department of Dental Medicine, Children's Hospital and Regional Medical Center, Seattle. Correspond with Dr. Zhang at haizhang@u.washington.edu

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.

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 20/25on 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



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.

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.



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 3¹/₂ 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

Radiographic findings. CT scans revealed classic fea-

tures 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 dentifiable anomalies of the developing 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 (Pi), 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 (PPi) 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^{3°}-are also implicated as important regulators of phosphate homeostasis. Results from studies to date suggest that local control of PPi/Pi is critical for normal root/periodontal tissue development and, further, that cementum may be uniquely sensitive to PPi and Pi 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 PPi 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.

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