Case Report

Nephrocalcinosis Associated with Continuous Enamel Hypoplasia and Severe Alveolar Bone Loss: A Case Report and Literature Review

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Abstract: *Enamel-renal syndrome (ERS) is a rare manifestation of nephrocalcinosis that has been associated with generalized enamel hypoplasia. The purpose of this paper was to describe, for the first time, the association of enamel-renal syndrome with severe localized periodontal bone loss. A 13-year-old boy presented with: generalized hypoplastic enamel; intrapulpal calcifications; retention of primary teeth; delayed eruption of permanent teeth; enlarged dental-follicles; misshaped roots of permanent teeth; gingival overgrowth; severe localized alveolar bone loss; and severe malocclusion. His parents were first cousins, suggesting autosomal recessive inheritance. Further studies are necessary to clarify whether the etiology of the oral disturbances relates to the genetic defect in the dental tissue or to the continuous metabolic distress associated with renal dysfunction. Nevertheless, since nephrocalcinosis is often asymptomatic, dentists should refer children with generalized enamel hypoplasia or/and multiple intrapulpal calcifications to nephrologists. (Pediatr Dent 2014;36:250-3) Received December 14, 2012 / Last Revision January 15, 2013 / Accepted January 21, 2013*

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Nephrocalcinosis is a genetic disease characterized by deposition of calcium salts in the renal tissue as a result of low levels of citrate in the urine. Nephrocalcinosis may be comorbid also with other metabolic diseases and some forms of Bartter syndrome.[1,2] Diagnosis of nephrocalcinosis is usually accidental and delayed.[3-12]

Enamel-renal syndrome (**ERS**) is a rare manifestation of nephrocalcinosis that has been associated with generalized enamel hypoplasia or amelogenesis imperfecta (**AI**).[4-12] This syndrome was first reported in two brothers by MacGibbon in 1972.[3] Ten articles in the English language have since documented 14 case reports.[3-11,13] Pedigree analysis is compatible with ERS as autosomal recessively inherited.

The purpose of this paper was to describe, for the first time, a phenotype of enamel-renal syndrome in conjunction with severe localized periodontal disease, review the literature, and discuss possible pathogenesis.

Case report

A 13-year-old boy was referred to the pediatric dental clinic at Tel Aviv University, Tel Aviv, Israel, with a presumptive diagnosis of autosomal recessive AI (Figures 1-5). His main complaints were: small ugly yellow teeth; high dental sensitivity to cold drinks and air; difficulty in mastication; and nocturnal gingival bleeding. He was the sixth child of healthy consanguineous parents (first degree cousins, suggesting autosomal recessive inheritance), born at 32 gestational weeks (birth weight=2,100 g). During pregnancy, his mother consumed, without medical consultation, several types of antibiotics (she did not remember the names) due to an acute dentoalveolar abscess.

The patient was diagnosed as suffering from medullary nephrocalcinosis at eight years old following macroscopic hematuria. Computed tomography and ultrasound examinations revealed calcifications between the cortex and the medulla of the kidney (Figure 4). The patient's height and weight were in



Figure 1. Intraoral view of a patient with nephrocalcinosis. Note generalized gingival overgrowth.



Figure 2. Intraoral view of the maxillary arch of a patient with nephrocalcinosis. Note the unerupted premolars and deep palate.

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the tenth and third percentiles of the growth curve, respectively. Plasma calcium and phosphate levels were in the normal range (calcium=9.8 mg/dl, phosphate=4.9 mg/dl). Urine citrate levels were low (1.07 mg/dl; normal range=1.5-6.0). His parents and five siblings had no clinical abnormalities.



Figure 3. Periapical radiograph of a patient with nephrocalcinosis and unerupted right and left second molars with fully developed roots. Note the increased size of the dental sac and calcifications in the pulp chambers of the first and second molars.

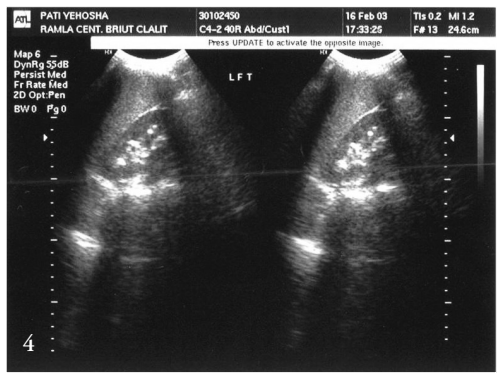


Figure 4. Ultrasound image of a patient with nephrocalcinosis revealed multiple calcifications in the kidney.



Figure 5. Periapical radiograph showing severe localized periodontitis associated with the maxillary right and left premolars in a patient with nephrocalcinosis.



Figure 6. Clinical view of periodontal defects in the maxillary right premolars during periodontal surgery in a patient with nephrocalcinosis.

The patient's dental history included only one visit to a dentist due to dental pain at 6.5 years old; one of his primary teeth was extracted. The patient placed his thumb on his teeth throughout the day. He slept with his mouth open and drank sugared carbonated drinks during the days and night. His speaking was disturbed by a tongue trust habit.

Intraoral examination. Intraoral examination revealed a mixed dentition with retained primary teeth and partially erupted permanent teeth. The enamel alterations were generalized, affecting both the mandibular and maxillary teeth. Teeth were small, with yellow/brown discoloration and thin or absent enamel. The buccal cusps of mandibular premolars were tapered, and marked attrition was present in the first permanent molars (Figures 1-3 and 5). Nevertheless, the dental tissue resisted explorer penetration.

The patient had poor oral hygiene habits; plaque presented throughout the tooth surfaces, and sub- and supragingival calculus and external staining on some of the teeth were observed. He had gingival overgrowth and a wide maxillary frenum attached to the free gingiva of the maxillary central incisors. Periodontal pockets at a depth of five to six mm were observed in the maxillary right and left premolars, and spontaneous bleeding was present in some areas of the mouth. His parents and siblings underwent periodontal examinations to disclose a possible family history of periodontitis, but none of them was found to suffer from the same periodontal disease.

The patient presented with skeletal Angle class II malocclusion associated with anterior and posterior open bite and cross bite. The palate was deep.

Radiographic examination (Figures 3 and 5). No difference in density was observed between enamel and dentin. Intrapulpal calcifications in both erupted and unerupted molars were evident. The alveolar bone seemed to be normal overall, except adjacent to the maxillary premolars where a profound bone loss was evident. Impaction of maxillary permanent canines, primary failure of eruption of mandibular second permanent molars associated with enlarged dental follicles, and partially erupted permanent teeth were also observed. The roots of the maxillary right premolar, left premolar, and mandibular second molars appeared dilacerated distally. Nevertheless, the dental age was in accordance with the patient's chronological age.

Treatment. Initial treatment included oral hygiene instruction and decreasing sensitivity of teeth. The latter was achieved by administration of high concentrations of fluoride supplements (such as Elmex Gel, 12,500 ppm F, Gaba, Lörrach, Germany) at home and periodic application of fluoride lacquer (Duraphat, 22,500 ppm F, Colgate-Palmolive AB, Danderyd, Sweden) at the dental office.

Retained primary teeth were extracted, and scaling and root planing were performed. To decrease the sensitivity of the posterior teeth and to prevent their further erosion, stainless crown coverage was performed. Fissure-sealants were applied to deep fissures, and composite restorations were applied to occlusal caries.

Two months following initial phase therapy, the patient suffered from three episodes of acute periodontal abscesses next to the maxillary first and second premolars accompanied by secretion of pus, cellulitis, and severe pain. A periapical radiograph revealed severe localized periodontitis associated with the maxillary right and left premolars (Figure 5).

Following one of these episodes, the maxillary left second premolar was extracted in the hospital as first aid treatment. Clinical examination revealed a periodontal pocket of a depth of up to 10 mm and a mean plaque index score of 4.75, according to Turesky et al.[14] The patient was treated during these episodes by curettage, rinsing with 0.12 percent chlorhexidine, and antibiotic supplementation (tetracycline 500 mg twice a day for seven days for each course). Finally, open flap periodontal debridement surgery was performed, followed by gingivectomy and frenectomy at the maxillary anterior area (Figure 6).

Eighteen months later, deterioration was observed in his general health condition, including a considerable increase in renal calcifications and obstructions in the renal transmission canaliculi. Deterioration was so severe that future dialysis treatment or renal transplantation seemed possible.

Two years following the periodontal surgery, the depth of the periodontal pockets decreased significantly from 10 to four mm in the maxillary premolars and the mean plaque index score decreased to 1.88 without presence of sub- or supragingival calculus. The patient remained under regular dental and medical follow-up.

Discussion

The association of generalized enamel hypoplasia and nephrocalcinosis, although rare, has been reported in 14 patients mentioned in 10 articles published in the English language literature[3-11,13] under the name of enamel-renal syndrome. All patients had thin or absent enamel and one or more additional dental disturbances, such as: eruption disturbances, as mentioned in 71 percent of the patients[4,5,7,8,10,11,13]; exfoliation disturbances (64 percent); intrapulpal calcifications (80 percent)[3,4-8,11,13]; and gingival overgrowth (40 percent)[5,7-8,13] (Table 1).

Table 1. DISTRIBUTION OF VARIABLES ASSOCIATED WITH PREVIOUS PUBLICATIONS DESCRIBING ENAMEL-RENAL SYNDROME (ERS)

Variables associated with previous publications describing ERS	Number of described patients	Reference(s)
Generalized enamel hypoplasia	14	2-10, 16
Intrapulpal calcifications	8	2-7, 10, 16
Growth disturbances	2	4, 8
Gingival enlargement	5	4, 6, 7, 16
Root dilacerations	2	3
Enlargement of dental sac	4	3, 4, 6, 7
Intra-alveolar resorption of crowns	4	2, 3, 6, 5
Open bite	2	4, 9
TMJ sensitivity	1	6
Delayed eruption of permanent teeth	10	2-4, 6, 7, 9, 10, 16
Delayed exfoliation of primary teeth	9	2-4, 6, 7, 10, 16
Age (ys) at diagnosis of patients described in published case reports	14	Ref no. 3: 12 and 10 Ref no. 4: 10.5 and 14.5 Ref no. 5: 32 and 40 Ref no. 6: 15 Ref no. 7: 13 Ref no. 8: 14 Ref no. 9: 20 and 23 Ref no. 10: 13.9 Ref no. 16: 9

The etiology of the association of generalized enamel hypoplasia with ERS is not completely clear.[8,11] One possibility is that the same genetic disorder induces a disturbance in proteins that are associated with dental enamel and kidney function. To date, mutations in five genes have been described in association with AI: (1) amelogenin; (2) enamelin; (3) family with sequence similarity member H; (4) kallikrein 4; and (5) matrix metalloproteinase 20.[15,16] Expression of mutations of these genes has not been described in the kidneys.[9,13]

Further research is necessary to determine whether proteins coded by genes found to associate with AI play a pivotal role in calcium and phosphate metabolism or renal tubular disorders.[9] Involvement of two separate but closely linked genes has also been suggested as an explanation for the association between generalized enamel hypoplasia and ERS.[5] Finally, some authors have suggested that albumin and osteopontin could be involved in both renal and dental defects, since they are involved in renal and dental calcium metabolism.[6]

Another possible explanation for the enamel hypoplasia observed in ERS is that the enamel disturbances result from continuous metabolic distress induced by nephrocalcinosis during the entire crown development period, not from a genetic disorder per se. Oliver et al.[17] reported a high incidence of hypoplastic enamel in the permanent teeth of 40 children suffering from the nephritic syndrome. They demonstrated a correlation between the timing of the severe renal disorder and the estimated timing at which the hypoplastic enamel was developed.[17] In ERS patients, the disturbances are continuous during the entire crown development period as consequent to delayed diagnosis and treatment, which did not occur before late childhood or early adulthood in all previous reports (Table 1). Accordingly, "continuous enamel hypoplasia" seems to best describe "enamel hypoplasia" associated with ERS.

The fact that most of the other dental disturbances in ERS (such as intrapulpal calcification, gingival overgrowth, and even periodontal disease) are as prevalent in patients with chronic renal failure and are not specific to ectodermal tissue[18,19] supports this proposition. Failure of tooth eruption and/or resorption of unerupted teeth within the alveolus is a manifestation often seen not only in the hypoplastic types of AI[20] but also in syndromes associated with hypoplasia of enamel, such as tricho-onychodental syndrome, trichodento-osseous syndrome, and the amelo-onychohypohidrotic syndrome.[16] Nevertheless, since no genetic mutation associated with ERS has been identified, further research is needed to clarify the pathogenesis of enamel hypoplasia and nephrocalcinosis.[9]

The current article describes, for the first time, association of ERS with severe localized periodontal bone loss. Gingival overgrowth was previously reported in conjunction with nephrocalcinosis syndrome and chronic renal failure.[3,13] Periodontal disease has been reported in conjunction with chronic renal failure[21-23] but not with nephrocalcinosis. In our patient, bone loss was observed adjacent to the maxillary premolars. The presented periodontal bone loss might be classified, therefore, as severe localized periodontitis associated with systemic disease (nephrocalcinosis syndrome).

This report supports previous publications that found an association between chronic renal failure and a tendency

for chronic marginal gingivitis, which was usually accompanied by hyperplasia of the gingiva[18,24] and higher prevalence of periodontitis.[21-23] The fact that periodontal involvement was not reported in previous publications of ERS might be related to the duration or severity of the disease or to better oral hygiene. The presentation of symptoms of periodontal bone loss 18 months before symptoms of nephrocalcinosis supports this proposition.

The relationship between alveolar bone loss and ERS is not completely clear; it can be induced by impairments in polymorphonuclear leukocyte function[23] and/or deposition of calcium oxalate in the periodontium.[22] These deposits can act as foreign bodies and intensify the inflammatory response, resulting in extensive alveolar bone loss and external tooth resorption.[25] It should be also noted that the high plaque index and poor oral hygiene might also contribute to the bone loss presented in reported patients. Nevertheless, this case report emphasizes the need to carefully evaluate the periodontal condition of all ERS patients.

Our patient received emergency dental treatment at 6.5 years old. Despite the generalized enamel hypoplasia that presented, the child was not referred for medical consultation to exclude nephrocalcinosis and the diagnosis of nephrocalcinosis was delayed until he was eight years old, following appearance of clinical hematuria. This chain of events is similar to that reported in almost all of the previous documentations of ERS. Early detection of nephrocalcinosis is especially important in light of previous publications[3-11,13] that showed unrecognized and untreated nephrocalcinosis to be associated with increased risk of morbidity and mortality.

In summary, ERS may be complicated with severe periodontal bone loss at an early age. Since intrapulpal calcification is a fundamental finding in patients with nephrocalcinosis, we recommend referring patients with autosomal recessive hypoplastic enamel and intrapulpal calcifications to nephrologists to exclude nephrocalcinosis.

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