Case Report

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Amelogenesis Imperfecta and Nephrocalcinosis Syndrome: A Case Report and Review of the Literature

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Key Words
Amelogenesis imperfecta · Nephrocalcinosis syndrome · Dental enamel · Impaired renal function · Autosomal recessive trait

Abstract
Amelogenesis imperfecta (AI) is a group of hereditary disorders that affect the quality and/or quantity of dental enamel. This paper describes the clinicopathological features of a patient who was born of consanguineous parents and who presented with oral alterations, including yellow and misshapen teeth, intrapulpal calcifications, delayed tooth eruption, and gum enlargement. Scanning electron microscopy of the teeth revealed hypoplastic enamel, and a renal ultrasound detected bilateral nephrocalcinosis, leading to a diagnosis of AI and nephrocalcinosis syndrome. Since nephrocalcinosis is often asymptomatic and can be associated with impaired renal function, dentists who see children with generalized and thin hypoplastic AI should consider a renal ultrasound scan and referral to a nephrologist, if appropriate. Children with nephrocalcinosis should also be considered for a dental check.

Introduction

Amelogenesis imperfecta (AI) is a heterogeneous group of hereditary disorders that affect dental enamel [1]. It can affect some or all of the teeth in the deciduous and/or permanent dentition. AI has frequently been reported as an isolated finding with autosomal dominant, autosomal recessive or X-linked modes of inheritance [2]. Occasionally, AI occurs with other features as part of a syndrome in, for example, amelo-onycho-hypohidrotic syndrome, Morquio syndrome, Kohlschutter syndrome, tricho-dento-osseous syndrome, AI with taurodontism syndrome, oculo-dento-osseous dysplasia, epidermolysis bullosa hereditaria, AI and nephrocalcinosis syndrome.

Nephrocalcinosis is deposition of calcium in renal tissue, and may be predominantly cortical or, more commonly, medullary found in conditions such as primary hyperparathyroidism, distal renal tubular acidosis, medullary sponge kidney, hypervitaminosis D, oxalosis, and some forms of Bartter's syndrome [3]. The rare syndrome of AI with nephrocalcinosis, also called the enamel-renal syndrome (OMIM 204690), was first reported by MacGibbon in 1972 [4]; since this report, only another 9 cas-

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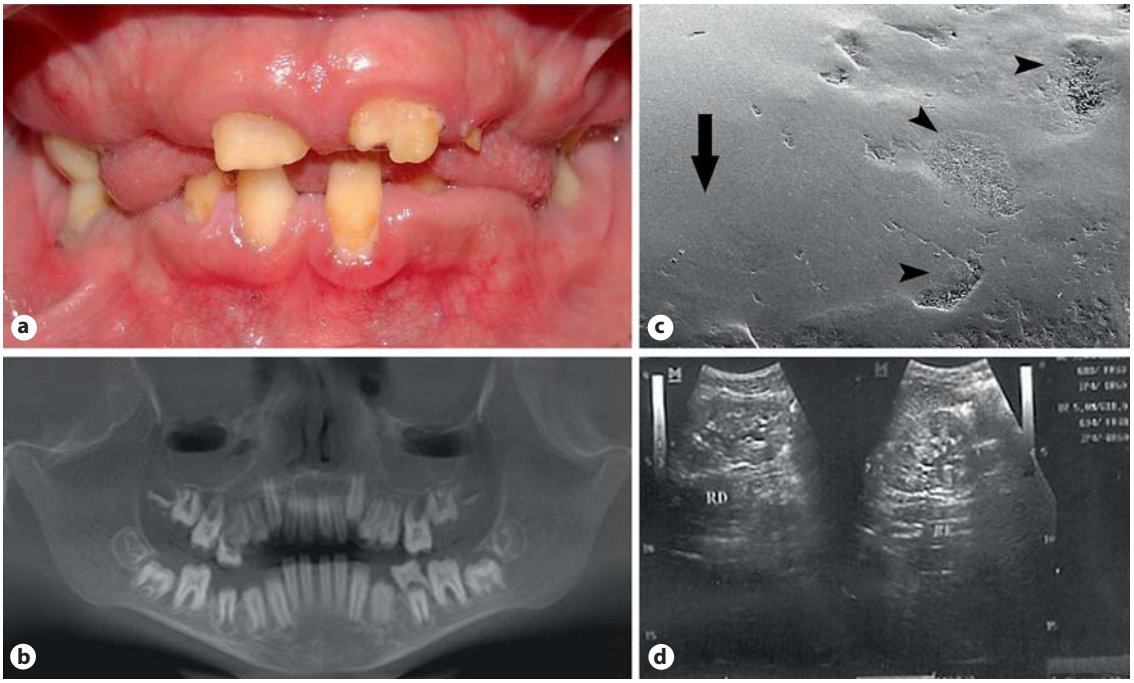

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Fig. 1. a Dental examination revealed teeth with yellow discoloration, altered shape and reduced thickness of enamel. The gums showed generalized enlargement associated with plaque and calculus accumulation. **b** Panoramic reconstruction of CT showed several impacted teeth. Intrapulpal calcifications in molars and lack of contrast between enamel and dentin in erupted and unerupted teeth were noted. **c** Scanning electron microscopy micrograph of a primary tooth affected by AI. Enamel ultrastructure revealed a thin irregular enamel layer with normal structure (arrow), but with rough and porous areas, and irregularly shaped empty spaces (arrowheads). **d** Renal USS showing bilateral nephrocalcinosis.

es have been described in the English-language literature [5–13].

The purpose of the present study is to describe a patient showing the typical features of AI and nephrocalcinosis syndrome, and to highlight the important role for dentists and pediatricians in recognizing this uncommon syndrome.

Case Report

The proposita, a 9-year-old girl, was the 4th child born to healthy consanguineous (first degree cousins) parents. The family history was otherwise unremarkable. She was born normally at term after an uneventful pregnancy. Intraoral examination revealed yellow to yellowish-brown teeth with rough surfaces, conspicuous and irregular defects, and a lack of contact points (fig. 1a). The enamel alterations were generalized affecting both lower and upper sets of teeth. The gums were enlarged and inflamed (fig. 1a), and the patient's mother informed us that the gums became enlarged just after the eruption of the first teeth. Radiographic examination showed deciduous teeth and incomplete permanent dentition with the delayed eruption of several teeth (fig. 1b). No density difference between enamel and dentin was observed. Intrapulpar calcifications in both erupted and unerupted molars were evident (fig. 1b). A diagnosis of hypoplastic AI was made, and the patient was investigated further. A renal ultrasound showed bilateral nephrocalcinosis (fig. 1d), and laboratory findings, including serum electrolytes, calcium, phosphate, urea, creatinine and alkaline phosphatase, and parathormone level, were all normal; blood pressure was also normal. The parents and 3 healthy siblings had no clinical abnormalities.

Initial treatment was good oral hygiene and supragingival scaling. Plaque control reduced the gum enlargement. The primary maxillary right second molar and mandibular left second molar were both decayed and extracted. They were examined by scanning electron microscopy, which confirmed the diagnosis of thin hypoplastic AI. The teeth showed a thin enamel layer with normal structure, interrupted with rough and porous areas, and irregularly shaped empty spaces (fig. 1c). The parents were given some genetic counseling, and the patient remained under regular dental and medical follow-up. Corrective dental treatment of the permanent dentition is being planned.

Discussion

The association of AI and nephrocalcinosis is rare, and we have found only 10 reports in the English-language literature [5–13]. This association has been described in

nonconsanguineous and consanguineous families, and with no family history, suggesting that the syndrome is inherited as an autosomal recessive trait [4–6, 8, 11–13].

Nephrocalcinosis can be found in a variety of inherited and acquired diseases affecting calcium metabolism and excretion, oxalate metabolism, and impaired renal acid excretion, with calcium deposition mainly in the renal interstitium [14]. Nephrocalcinosis may be the cause of renal impairment, but only rarely end-stage renal failure, unless complicated by renal stones and recurrent infections [14]. Since nephrocalcinosis has no single cause, it should always be investigated further [15].

Patients with AI and nephrocalcinosis syndrome may have no renal complications until late childhood or early adulthood, with perhaps recurrent urinary infections, pyelonephritis, or renal colic and the passage of a renal stone. In our case, nephrocalcinosis was only detected when the diagnosis of autosomal recessive hypoplastic AI was made and prompted a renal ultrasound scan (USS). The patient had no urinary symptoms to suggest renal stones, and serum urea, creatinine and electrolytes were within normal limits. However, nephrocalcinosis can progress, and it will be important to keep her under regular medical follow-up.

MacGibbon [4] in 1972 first reported 2 siblings with a combination of AI, nephrocalcinosis, and apparently normal calcium metabolism. Both were diagnosed in the first decade of life with defects in their dental enamel, but nephrocalcinosis was only diagnosed in early adulthood. Indeed, the sister was diagnosed in early adulthood with AI and nephrocalcinosis syndrome when her older brother died at the age of 26 years, after he had developed renal failure and hypertension. Later, the sister developed similar complications, including multiple urinary infections, hypertension and renal failure. The second pedigree described contains 2 subjects who presented with AI, enuresis and intermittent urinary infections [5]. Their dental enamel defects were classified as autosomal recessive hypoplastic AI with pulp calcification; both developed nephrocalcinosis, but had normal serum electrolytes, pH, bicarbonate, parathormone, calcitonin, 25(OH) vitamin D, calcium, phosphate, and alkaline phosphatase levels. Hall et al. [6] described another sister and brother pair with AI and nephrocalcinosis syndrome. Although both patients have had their AI clinically diagnosed, nephrocalcinosis, and subsequently AI and nephrocalcinosis syndrome, was identified later after the girl developed acute pyelonephritis at the age of 10 years. In another study, Dellow et al. [7] described one large family containing one consanguineous marriage with 2 out of 4 children affected by AI and nephrocalcinosis syndrome. As often occurs in this syndrome, the renal involvement was not recognized until they were adults. Apart from previously reported cases, Fu et al. [10] described one 14-year-old girl affected by AI and nephrocalcinosis syndrome, which was complicated by impaired renal concentration and hypokalemic metabolic alkalosis (Bartter-like syndrome).

In previous reports, it has been recommended that children with autosomal recessive hypoplastic AI should have a renal examination [6–8], such as kidney-ureter-bladder X-ray (KUB), USS or computed tomography (CT). It is important to keep in mind that both KUB and USS do not always reliably detect nephrocalcinosis, and USS may even overdiagnose it, whereas CT is the gold standard method, but it delivers a larger dose of radiation than a KUB. More recent studies suggesting significant potential morbidity and mortality associated with unrecognized and untreated nephrocalcinosis have recommended that all patients with AI should have a renal evaluation, including renal USS and renal function tests [9, 11, 12]. Kirzioglu et al. [13] analyzed the prevalence of nephrocalcinosis in AI patients by renal USS, revealing suspicious radiopacities in 1 out of 5 patients with a diagnosis of AI. Interestingly, all patients with evidence of nephrocalcinosis were classified as the hypoplastic type of AI. Since AI and nephrocalcinosis syndrome is very uncommon, we agree with previous reports and recommend a kidney USS examination in children with the hypoplastic type of AI in which there is an autosomal recessive pattern of inheritance [6–8].

To date, mutations in five genes have been described in association with AI, including amelogenin (AMELX), enamelin (ENAM), family with sequence similarity member H (FAM83H), kallikrein 4 (KLK4), and matrix metalloproteinase 20 (MMP20), improving the classification of AI and increasing our understanding of enamel development in health and disease [16]. None of the mutated proteins identified in AI patients has been found to be expressed in the kidney, suggesting that some of the dental proteins that are thought to be dental-specific may be expressed in other organs, or that there are as yet unrecognized proteins associated with both dental enamel and kidney development [10]. Besides tricho-dento-osseous syndrome, which is caused by mutations in the homeobox gene DLX3, there has been no other genetic characterization of syndromes containing AI as a feature [17]. Recently, mutation in the homeobox gene MSX2 was identified in a patient with AI combined with cleft lip and palate, and polycystic kidney disease [18]. Thus, it is clear

that genetic investigations are essential to clarify the defect underlying AI and nephrocalcinosis syndrome, and that homeobox genes, which encode transcription factors that play vital roles in specifying cell fate, identity and function during embryogenesis, may be good gene candidates [19].

In summary, we have described a patient with AI and nephrocalcinosis syndrome with plaque-induced gum enlargement. Although the patient had normal renal function, the presence of nephrocalcinosis is a risk factor for renal impairment. Since nephrocalcinosis is frequently identified in early adulthood, whereas AI is diagnosed in the first decade of life, it is important to alert pediatric dentists to consider referring children with autosomal recessive generalized thin hypoplastic AI for a renal examination. Similarly, oral examination is recommended in patients with a diagnosis of pediatric nephrocalcinosis.

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