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Case report of a rare syndrome associating amelogenesis imperfecta and nephrocalcinosis in a consanguineous family

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KEYWORDS
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Summary A rare syndrome associating amelogenesis imperfecta (AI) with nephrocalcinosis has been reported. The purpose of this study is to characterise the phenotype of a consanguineous family presenting amelogenesis imperfecta, delayed permanent teeth eruption and nephrocalcinosis. Six family members were examined. Ground sections of the case index deciduous teeth and biopsies of enlarged dental follicles were analysed. The patients's parents were first cousins. The case index had yellow discoloration and altered teeth shapes, retention of deciduous teeth, and delayed eruption. Panoramic radiographs revealed multiple enlarged pericoronal follicles in unerupted teeth and generalised intrapulpal calcifications. Renal ultrasound showed the presence of nephrocalcinosis. No other family members presented enamel defects or nephrocalcinosis. Histologically, the enamel appeared hypoplastic, and dental follicles indicated pericoronal hamartoma. The consanguineous marriage suggests an autosomal recessive mode of inheritance. Further studies are necessary to clarify the genetic defect behind this syndrome that associates AI, nephrocalcinosis and impaired tooth eruption.

Introduction

Amelogenesis imperfecta (AI) is a diverse group of hereditary conditions that affects the quality and quantity of dental enamel.[1] It may affect all or some teeth in the deciduous and/or permanent dentition. X-linked and autosomal dominant and recessive

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modes of inheritance have been reported, and the molecular basis of this condition is not fully understood. However, in the past decade, several mutations in the amelogenin (AMEL X) gene and enamelin gene have been identified in X-linked and autosomal forms of AI.[2–4]

A rare syndrome associating amelogenesis imperfecta with nephrocalcinosis (OMIM 204690),[5] precipitation of calcium salts in the kidney, has been reported in very few families.[6–10] The purpose of the present study is to characterise the phenotype in a consanguineous family presenting amelogenesis imperfecta, delayed permanent teeth eruption and nephrocalcinosis.

Materials and methods

Family and phenotype analysis

The Ethics Board of the Brazilian Ministry of Health-CONEP approved this study and informed consent approval was obtained from all participants. A complete dental and medical examination was performed on six family members to determine the affection status. In the case index, incisional biopsies of the pericoronal tissues of two unerupted upper cuspids were performed; specimens were embedded in paraffin, stained with H—E, and examined with light microscopy. Ground sections of two deciduous teeth were also examined with light microscopy (Axiophot, Zeiss).

Results

Family phenotype

A 13-year-old male patient was referred to the Dental Anomalies Clinic of the University of Brasilia, Brazil, with a presumptive diagnosis of autosomal recessive AI. The patient's parents were first cousins in the first degree (Fig. 1). The medical history and general physical condition of the case index were unremarkable. None of the family members examined had dental anomalies or nephrocalcinosis.

Intraoral examination of the case index revealed the retention of deciduous teeth (molars and cuspids), enlargement of gingival tissue, and eruption of the upper permanent central incisors, lower incisors and all first molars. The deciduous and permanent erupted teeth showed a yellow discoloration with thin enamel. Anatomy of the erupted upper left incisor presented a semi-lunar shaped defect (Figs. 2 and 3). The radiographic examination showed complete permanent dentition with well-developed roots and delayed eruption. No density difference between enamel and dentin was observed. All permanent and deciduous teeth, erupted and unerupted, presented coronal intrapulpal calcifications, needle-shaped in the incisors and round-shaped in the posterior teeth. In all quadrants, the third and second molars, premolars and canines were unerupted. The unerupted teeth had large well-defined pericoronal radiolucencies, except for the third molars. The roots of the upper lateral incisors appeared dilacerated, and the lower lateral incisors were dislocated distally. The second molars showed distorted and poorly developed roots, mainly in the lower arch (Fig. 4).

Renal ultrasound showed bilateral nephrocalcinosis. Plasma calcium and phosphate levels appeared normal, but the phosphatase alkaline was slightly increased (Figs. 5 and 6).

Histological analysis

No enamel was observed in the ground sections (Fig. 7). The histopathological analysis of the pericoronal follicles showed hyperplastic odontogenic

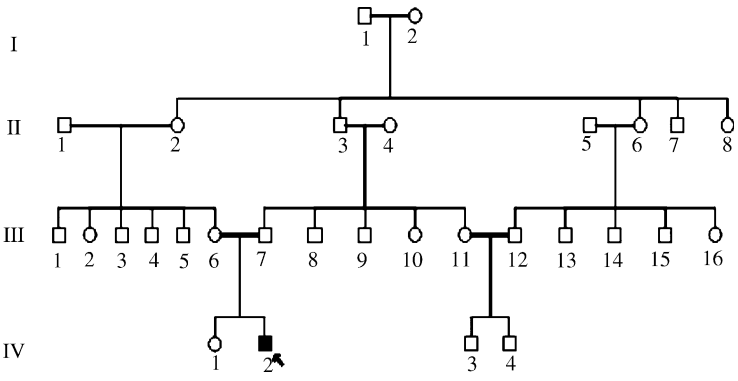
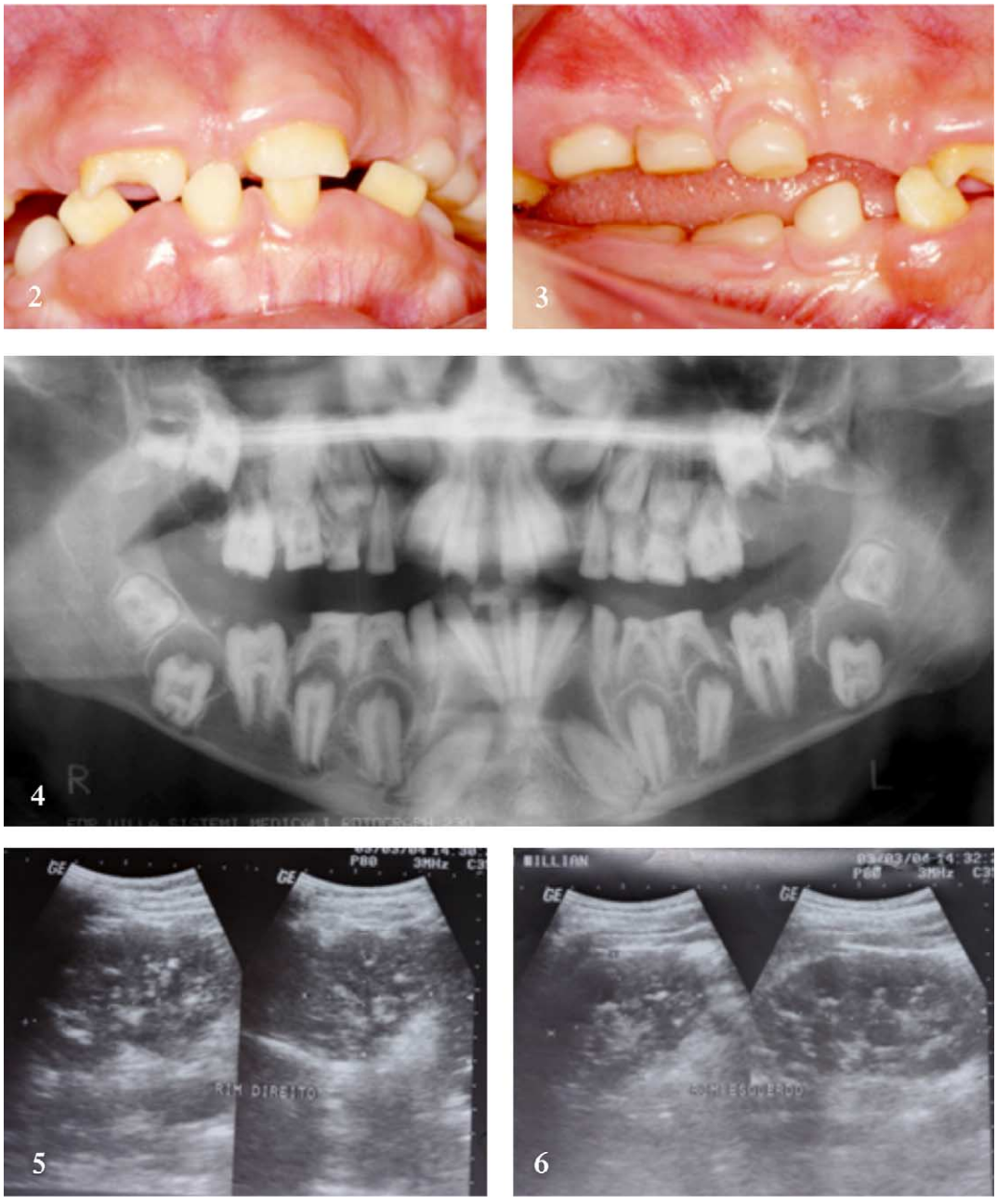


Figure 1 Pedigree of the family that suggests an autosomal recessive mode of inheritance.

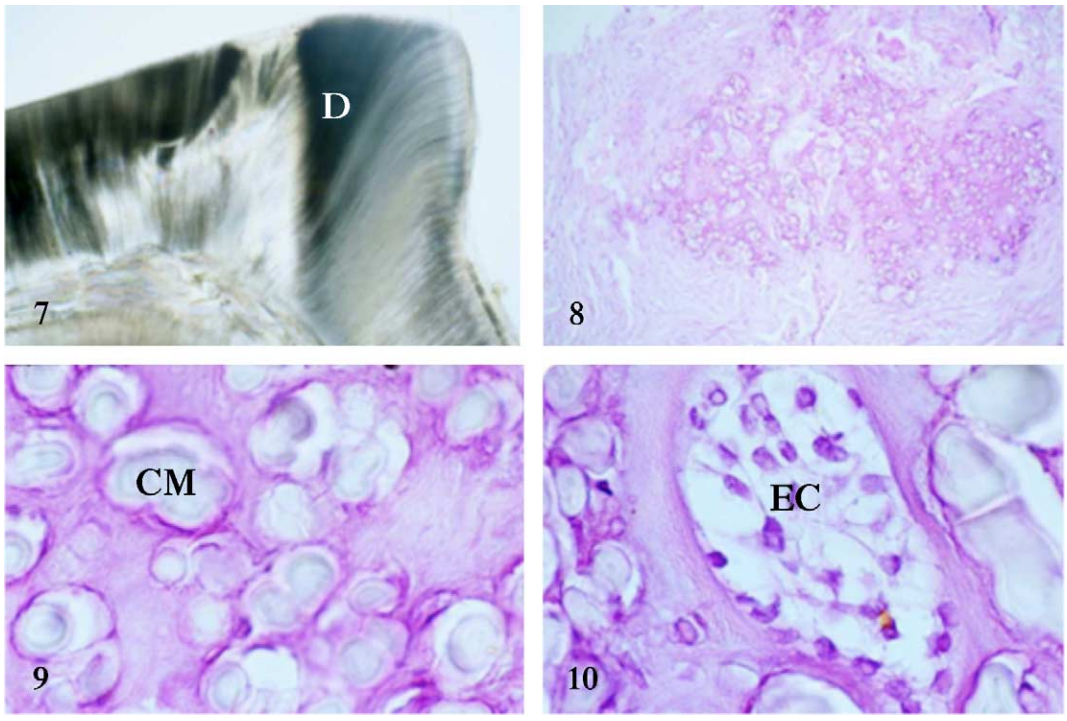


Figures 2—6 Patient (IV-2). (2) Clinical photograph of the case index permanent and deciduous dentition showing alterations in the tooth shape, reduction of the enamel thickness and yellow discolorate. Note the semi-lunar enamel defect in the central incisor. (3) Clinical photograph showing a lateral view where deciduous teeth show abrasions tooth shape alterations and yellow discoloration. (4) Panoramic radiographs showing all permanent and deciduous teeth, erupted and unerupted with coronal intrapulpal calcifications, needle-shaped in the incisors and round-shaped in the posterior teeth. The unerupted teeth had large well-defined pericoronal radiolucencies, except for the third molars. The roots of the upper lateral incisors appeared dilacerated, and the lower lateral incisors were dislocated distally. Lower second molars showed distorted and poorly developed roots. (5 and 6) Renal ultrasound presenting nephrocalcinosis.

ectomesenchyme with several round dysplastic calcifications (Figs. 8 and 9). Various odontogenic epithelial islands, consisting mainly of clear cells, were scattered in a myxofibrous background (Fig. 10). A diagnosis of the pericoronal hamartoma was made.

Discussion

The consanguineous of the patient's parent suggests an autosomal recessive inheritance in this condition. In the present case, nephrocalcinosis was detected after the diagnosis of AI. Its importance



Figures 7—10 Patient (IV-2). (7) Ground section of an exfoliated deciduous molar showing the absence of enamel (×40). (8) Hyperplastic myxofibrous pericoronal follicle of the case index (IV-2) with round calcifications (H—E, ×100). (9) Higher magnification of the calcified masses surrounded by a hyperplastic myxofibrous pericoronal follicle (H—E, ×440). (10) Higher magnification of odontogenic epithelial islands with clear cells in the pericoronal follicle tissue (H—E, ×440).

is due to the morbidity associated with unrecognised and untreated nephrocalcinosis. The AI and nephrocalcinosis syndrome has been previously reported in consanguineous and non-consanguineous families. The common characteristics are the presence of thin or absent enamel, presence of intrapulpal calcifications, delayed tooth eruption bilateral, nephrocalcinosis and normal plasma calcium.[6—10]

The enlargement of the pericoronal follicles was observed in this case, as well as the complex histological appearance with mineralised structures and epithelial islands suggest hamartomatous pericoronal proliferation. AI patients with similar enlarged pericoronal follicles have been reported[11,12]; however, no nephrocalcinosis was detected in these cases. In addition, similar pericoronal enlargements in non-AI patients have been also described.[13,14] Whether or not the presence of the pericoronal hamartoma is the cause of the delayed eruption needs to be clarified. Yonemochi et al.[15] studied pericoronal hamartomas in non-AI patients and suggested that the presence of hamartomatous lesions in the pericoronal areas might induce active tissue remodelling and result in fibrosis in their surrounding, which may impede tooth eruption.

The presence of tooth shape abnormalities and generalised intrapulpal calcifications suggest that the tooth morphogenesis and dentinogenesis are also affected in this syndrome. These findings suggest that some of the features associated with amelogenesis imperfecta result from abnormal enamel formation, whereas abnormal eruption and pulp calcification may occur as a result of the expression of the genetic mutation in tooth cells other than ameloblasts. Recent studies have shown that many of the dental proteins that were believed to be tissue specific may be expressed in more than one dental tissue and also in non-dental tissues.[16—18] Further research concerning these proteins is necessary to determine if they play a role in the calcium and phosphate metabolism and renal function.

Much research has been done over the last years to define the molecular basis of AI. The X-linked forms have been studied most extensively, however, genetic defects have been also identified in autosomal forms.[4,19,20] Only mutations in the amelogenin (AMEL X) gene have been associated with the various X-linked AI forms.[3] The first enamelin mutation associated with autosomal forms of amelogenesis imperfecta (ADAI) was recently identified in a family with smooth hypoplastic form of ADAI.[21] Since, additional ENAM mutations have been identified.[22—24] More recently, a mutation in the kallikrein (KLK4) gene causing autosomal recessive

hypomaturation AI was reported.[20] At present, no mutations have been identified in AI and nephrocalcinosis syndrome. Further studies evaluating the presence of nephrocalcinosis in isolated forms of AI would be useful, since no data concerning renal alterations in these patients has been reported.

Tissue non-specific phosphatase alkaline (TNSALP), the calcium sensing receptor (CaSR) and calbindin 28 kDa are proteins involved in the calcium and phosphate metabolism and are expressed in both teeth and kidney cells. Mutations in the TNSALP gene result in hypophosphatasia (OMIM 146300, 241500, 241510),[5] an inherited disease characterised by defective bone and teeth mineralisation and deficiency of serum and bone alkaline phosphatase activity.[25–32] Premature exfoliation of fully rooted teeth and enamel defects have been reported in patients with hypophosphatasia.[33,34] The physiologic importance of the calcium sensing receptor has been documented by the characterisation of human syndromes resulting from gain or loss of function in the CaSR gene. Loss of function mutation cause familial hypocalciuric hypercalcaemia (OMIM 145980)[5] and neonatal severe hyperparathyroidism (OMIM 239200).[5] In contrast, gain of function mutations are responsible for a form of autosomal dominant hypocalcaemia (OMIM 146200).[5] No dental alterations have been described on these conditions.

Recently, the matrix extracellular phosphoglycoprotein MEPE, a member of the SIBLING (Small Integrin-Binding Ligand, N-linked Glycoprotein) family, primarily expressed in osteoblasts, osteocytes and odontoblasts has been proposed as a phosphaturic factor important in bone–renal metabolism and bone mineralisation.[35–37]

Nephrocalcinosis is a common feature in other inherited conditions, such as primary hypomagnesaemia (OMIM 248250),[5] dent disease (OMIM 300009),[5] renal tubular acidosis (OMIM 179800, 267200),[5] and X-linked recessive hypophosphataemia (OMIM 307800),[5] however, no dental or tooth eruption abnormalities have been reported in these conditions. X-linked hypophosphataemia results from mutations in PHEX, an endopeptidase, predominantly expressed in bone and teeth, but not in the kidney.[38–41]

Due to the importance of a renal involvement, kidney ultrasound should be performed in all AI patients in order to exclude nephrocalcinosis and to determine if this alteration is exclusive of this rare syndrome or can be found in other AI forms. Finally, further research is necessary to clarify the genetic defect behind this syndrome, which combines two uncommon conditions, such as AI and nephrocalcinosis.

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