Amelogenesis Imperfecta: Clinical and Consanguinity Study

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Authors’ contributions

This work was carried out in collaboration between all authors. Author TFS designed the study. Authors ACN, ELS, LKMS, ADV and SESM worked on the data acquisition. Authors TFS, CCOS and RGVA analyzed the data and drafted the manuscript. All authors read and approved the final version of the manuscript.

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ABSTRACT

Background: Amelogenesis imperfecta is a complex group of hereditary conditions characterized by malformation of the dental enamel. Although to be well described in literature, this condition may be related to others local and systemic disorders and present a peculiar hereditary character.

Objectives: The aim of this study was to describe a family with several members affected by amelogenesis imperfecta.

Materials and Methods: This descriptive cross-sectional study was performed to show a family with several members affected by amelogenesis imperfecta. A sample of 39 individuals related to

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one family residing in a city of southern Ceará State – Brazil. Each member was subjected to clinical and radiological examination and the family pedigree was built.

**Results:** Of the 39 members, 28 were consanguineous and the amelogenesis imperfecta was detected in 20 subjects (71.42% of consanguineous members). All affected individuals presented a defect in the crystal structure of enamel leads to a mottled enamel with white to brown to yellow colors besides wear of the occlusal or incisal surfaces suggesting the hypomature type of amelogenesis. Radiographically, radiopaque areas inside the pulp (suggesting pulp calcifications) were observed in 20.0% of affected individuals. Additionally, some subjects showed cysts and stones at kidney (25.0%).

**Conclusions:** The amelogenesis imperfecta, in the studied family, has a dominant genetic character and may be related with kidney changes such as nephrocalcinosis.

**Keywords:** Amelogenesis imperfect; dental; tooth enamel.

1. **INTRODUCTION**

Amelogenesis imperfecta (AI) is a rare hereditary disorder that cause developmental alterations in the structure of dental enamel resulting in defect in tooth mineralization [1]. In general, both the primary and permanent dentitions may be diffusely affected [2]. The frequency of AI has been estimated to range from 1/700 and 1/14000 individuals depending upon the population studied [3,4].

AI can be classified according the clinical features and mode of inheritance [5]. The classification proposed in 1988 by Witkop is the most commonly used [2,5,6]. Based on enamel appearance and developmental defects, AI is classified in 4 patterns: hypoplastic, hypomaturational, hypocalcified, and hypomaturational-hypoplastic [5-7] and may present in isolation form or may be a component of syndromic disease [8]. Autosomal recessive, dominant and X-linked forms of non-syndromic AI already have been described [5]. In addition, when associated with syndromes, AI was related as findings of amelo-onycho-hypohidrotic syndrome, Morquio syndrome, Kohlschutter syndrome, tricho-dento-osseous syndrome, AI with taurodontism syndrome, oculo-dento-osseous dysplasia, epidermolysis bullosa hereditaritaria, AI and nephrocalcinosis syndrome [9].

Several authors suggest that cause for AI may be mutations in many genes such as ITGB6, SLC24A4, AMELX, FAM83H, MMP-20, WDR72, KLK4, LAMB3, LAMA3, DLX3, AMBN and AMTN [10-20]. However, the current list of candidate genes related to AI may be insufficient to identify the pattern of genetic abnormalities associated with familial form of this disorder.

The literature presents many studies on AI and its treatment, however, the knowledge about hereditary characteristics of the familial AI, as well as the genes associated with this condition have not been fully clarified. The purpose of this study was to present a family that showed the typical features of AI, emphasizing the phenotype of the familial heredity, as well as the clinical and radiographic characteristics of the individuals affected.

2. **MATERIALS AND METHODS**

This was a descriptive cross-sectional study performed with a sample of 39 individuals related to one family residing in a city of southern Ceará State – Brazil. From 4 patients with AI of the same family initially identified in the School of Dentistry at Centro Universitário Doutor Leão Sampaio – UNILEÃO, the pedigree to check the inheritance pattern of condition was built.

To make the pedigree, intraoral examination was performed in all family. All patients were examined sitting in a dental chair under lighting. Before the clinical analysis, all teeth were cleaned with prophylactic paste and bristle brushes. The edentulous individuals (two subjects of the first generation) were analyzed through the reports of the characteristics of the lost teeth. Additionally, the medical history of all subjects was investigated by anamnesis.

After clinical examination, all subjects identified with AI features underwent to radiographic evaluation (panoramic and periapical radiographs) and a renal ultrasound. Rx analyzes were performed by the same examiner, a dentistry specialist (TFS). The diagnosis of renal condition was made by a nephrologist. Renal ultrasonography was performed in two-
dimensional mode with dynamic equipment convex scanning in frequency 3.5 Mhz.

The data were tabulated and analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, SPSS Inc., Chicago, USA). Absolute and relative frequencies were determined for all variables studied.

3. RESULTS

3.1 Pedigree Results

Of the 39 individuals of the same family, 28 were consanguineous. Of total consanguineous members, 20 subjects were diagnosed with AI (10 females and 10 males). The mean age of sample was 16 years, ranging from 09 to 70 years old. The medical history of the individuals showed no significant information. The isolated analysis of the generations showed that descendants of the first generation presented 100% of the members affected. On second generation, the percentage of descendants affected was high: the individual 1.I-3 had 66.6% of affected offspring; the 1.I-6 had 100% of affected offspring; and the 1.I-5 presented 50% of the descendants affected. On third generation the members 1.II-2, 1.II-6, 1.II-15 and 1.II-17 had 100.0% of affected offspring. In addition, the individual 1.II-13 had 50.0% of affected offspring.

The family pedigree suggests that the AI has an autosomal dominant pattern, since all examined generations showed the phenotype of the condition (Fig. 1).

3.2 Clinical Features

Table 1 shows all the clinical features of patients diagnosed with AI. Oral examination of all affected individuals revealed that the teeth were of normal size and contour, however, were observed a mottled enamel with white to brown to yellow colors besides wear of the occlusal or incisal surfaces. Based in findings, the clinical diagnosis was made of hypomaturation amelogenesis imperfecta (Fig. 2).

3.3 Imaging Examination

Intraoral radiographs (panoramic and periapical) were performed in all individuals with AI. The radiographic analysis showed, in some cases, the hyperplastic pericoronal follicles, absence of contrast (density) between enamel and dentin, thin enamel layer, absence of regular anatomy in erupted teeth and pulp calcifications (Fig. 3).

Of the 28 consanguineous subjects studied, only 7 (25.0%) conducted the kidney examination. Renal abnormalities were observed in five of these patients. In 4 cases, the ultrasound examination of his kidneys demonstrated hyperechoic areas in the medulla tissue suggesting the presence of calcifications (subjects 1.I-3, 1.II-4, 1.II-15, 1.II-22). In the individual 1.II-13, the ultrasound revealed that the renal parenchyma showed a hypoechoic area suggesting the presence of cyst (Fig. 4).

![Fig. 1. Pedigree chart of the studied family. The affected individuals are represented by filled symbols (females are represented by circles and males by squares)]
Fig. 2. Clinical features of Al. Individual 1.III-3 in occlusion showing the Al in both primary and permanent teeth, as well as loss of enamel structure in the tooth 21; (A) Front view; (B and C) Side view

Fig. 3. Periapical radiographs of individuals 1.III-3 (A) and 1.II-10 (B) showing areas suggestive of pulp calcifications

Fig. 4. The ultrasound examination of kidneys. (A) Patient 1.II-22 showing calcification in the right kidney. (B) Patient 1.II-13 showing cystic area in the left kidney
Table 1. Clinical characteristics found on the familial members affected by Al

| Individuals* | 1.1-1 (M)-56 | 1.1-3 (M)-48 | 1.1-5 (M)-70 | 1.1-6 (M)-31 | 1.1-8 (F)-28 | 1.1-10 (M)-26 | 1.1-13 (F)-23 | 1.1-15 (M)-141 | 1.1-17 (F)-27 | 1.1-19 (M)-29 | 1.1-20 (F)-37 | 1.1-21 (F)-28 | 1.1-22 (M)-30 | 1.1-3 (M)-9 | 1.1-5 (M)-11 | 1.1-8 (F)-4 | Frequency (%) |
|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Clinical features | Microdontia | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0% |
| | Yellow teeth | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 100.0% |
| | Giroversion | - | - | - | - | - | - | - | + | - | + | + | - | + | - | + | 35.0% |
| | Incisal/occlusal abrasion | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 95.0% |
| | Retention of deciduous | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0% |
| | Gingival hyperplasy | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0% |
| | Permanent impacted | - | - | - | - | - | + | - | + | - | - | - | - | - | - | - | - | - | 15.0% |
| | Absence of contrast between enamel/dentin | - | - | - | - | + | + | - | + | - | + | + | - | + | + | - | - | - | 35.0% |
| | Pulp calcification | - | - | + | - | - | - | + | - | - | - | - | - | - | + | - | - | - | 20.0% |
| | Missing teeth | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - | - | 75.0% |
| | Kidney changes | NI | + | NI | NI | + | - | NI | NI | + | + | NI | NI | NI | NI | - | + | NI | NI | 25.0% |
| | Other alterations | - | - | - | - | - | - | - | - | - | - | - | - | - | - | AU | - | - | - | 5.0% |

* Individuals named according to the familial pedigree code. In parentheses are given sex (M: male, F: female) and age in years.; (+) Positive; (-) Negative; (AU) Autism; (NI) Non-Information
4. DISCUSSION

Amelogenesis imperfecta is considered a heterogeneous group of genetic disorders that cause developmental alterations in the structure of dental enamel [1]. The literature suggests that Al may be associated with biochemical and morphological abnormalities in others parts of the human body [5]. The prevalence of Al in the population is variable, with no racial predilection and rare when it involves a familial group [4,21,22]. Our results showed a family with several members affected by Al suggesting an important genetic condition associated with Al in this group.

According to McDonald et al. [23] the phenotype is presented in vertical inheritance, therefore, it appears in successive generations, transmitted from individual to individual in both male and female. In our study, the isolated analysis of generations showed that the descendants of the first generation presented 100% of the members affected. This suggests that Al on that familial group may had its genesis in this generation. On the second and third generations, the percentage of descendants affected also was high. These findings support that Al of this familial group had autosomal dominant genetic inheritance. The literature described that autosomal dominant inheritance of amelogenesis imperfecta is the most common form of Al in the general population [24,25]. This form has been associated with a mutation in the gene ENAM that codes for the protein enamelin [25]. Enamelin has an important role in mineralization during which it initiates the deposition of enamel through the external surface of the distal membrane of the ameloblast [24]. The literature highlights that mutation in genes such as AMELX, ENAM, AMBN, MMP20, KLK-4, FAM83H, WDR72, SLC24A4, C4orf26, ITGB6, and LAMB3 have been found to cause non-syndromic Al in human patients and that these abnormalities can be transmitted among the descendants [22,26-28].

Based on anamnesis and clinical and radiographic examination of the affected members, the diagnosis of Al hypomaturatation type was suggested. In hypomatured Al, the affected teeth exhibit mottled, opaque white-brown or yellow discolored enamel, which is softer than normal [29,30]. It is believed that the hypomaturatation Al is associated with abnormalities on the maturation phase of amelogenesis [27,31]. The prevalence data shows that hypomatured Al occurs among 20% to 40% of the cases [27]. In the studied family, in addition to opaque white-brown-yellow staining, the affected teeth also presented occlusal and incisal abraded, even in those recently erupted, as well as pulp calcifications in some teeth. The literature described that the dental enamel may present variations regarding its consistency and texture, the occlusal and incisal surfaces may present easily abraded and contact points are absent [32,33]. Furthermore, it is believed that the delay in the eruption of the teeth, pulp calcification, dental agenesis, hypercementosis, malformations on the root, dental dysplasias and taurodontism also are part of the Al characteristics [34-36].

Al, although usually isolated, can be associated with syndromes [37]. Al may be one of characteristics of Ameloneychohypohidrotic Syndrome (OMIM 104570), of Morquio Syndrome (OMIM 253000), of Kohlschutter-Tonz Syndrome (OMIM 226750), Trichodentoosseous Syndrome (OMIM 190320), of Amelogenesis Imperfecta, Type IV (OMIM 104510), of Epidermolysis Bullosa (OMIM 226650), Cone-Rod Dystrophy and Amelogenesis Imperfecta (MIM 217080) [37-41]. Amelogenesis Imperfecta and Nephrocalcinosis Syndrome (AINCS) is one of these conditions [28]. AINCS is a rare condition caused by diffuse depositions of calcium in the renal parenchyma; the biallelic mutation in the gene FAM20A was listed as etiological factor of this syndrome [42]. In the study of Martelli-Junior et al., 2011, was reported the main features of AINCS, among of them can list the loss of difference in radiographic density between enamel and dentin, retention of primary teeth, pulp calcification, nephrocalcinosis, absence of interproximal dental contact, hypoplastic Al and gingival enlargement [35]. We believe that some subjects in our study may be characterized with AINCS, however, the clinical and imaginological monitoring is very important and necessary to enable the definitive diagnosis of the syndrome.

5. CONCLUSION

This study describes a familial group with a large number of members affected by Al, wherein of the total of 28 consanguineous, 20 individuals are affected. Al on this familial group has genetic autosomal dominant penetrance. Additionally, pulp calcifications and renal abnormalities may be associated with Al.
CONSENT
All patients signed a formal informed consent.

ETHICAL APPROVAL
This study was approved by the Research Ethics Committee (protocol number 1.289.790).

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

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