CASE REPORT

Amelogenesis imperfecta: Report of a case and review of literature

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ABSTRACT
Amelogenesis imperfecta (AI) is a diverse collection of inherited diseases that exhibit quantitative or qualitative tooth enamel defects in the absence of systemic manifestations. Also known by varied names such as Hereditary enamel dysplasia, Hereditary brown enamel, Hereditary brown opalescent teeth, this defect is entirely ectodermal, since mesodermal components of the teeth are basically normal. The AI trait can be transmitted by either autosomal dominant, autosomal recessive, or X-linked modes of inheritance. Genes implicated in autosomal forms are genes encoding enamel matrix proteins, namely: enamelin and ameloblastin, tuftelin, MMP-20 and kallikrein – 4. This article presents a case reported to Dr. D. Y. Patil, Dental College and Hospital, Pune, India, along with a review of this often seen clinical entity.
Key words: Amelogenesis imperfecta, enamel, dental, genetic, inherited

INTRODUCTION

Tooth enamel is the most highly mineralized structure in the human body, with 85% of its volume occupied by hydroxyapatite crystals.[1,2] The physical properties and physiological function of enamel are directly related to the composition, orientation, disposition, and morphology of the mineral components within the tissue.[3] During organogenesis, the enamel transitions from a soft and pliable tissue to its final form, which is almost entirely devoid of protein.[4] The final composition of enamel is a reflection of the unique molecular and cellular activities that take place during its genesis. Deviation from this pattern may lead to amelogenesis imperfecta.

Review of Literature

Amelogenesis imperfecta (AI) encompasses a complicated group of conditions that demonstrate developmental alterations in the structure of the enamel in the absence of a systemic disorder.[5]

The prevalence of this condition has been expected to range from 1 in 718 to 1 in 14,000, depending on the population studied. Hypoplastic AI represents 60 – 73% of all cases, hypomaturation AI represents 20 – 40%, and hypocalcification AI represents 7%.[6]

Weinmann *et al.*, 1945, subdivided amelogenesis imperfecta into hypoplastic and hypocalcified types.[7] Several classifications have evolved since then, with at least ten subtypes, characterized by clinical features and mode of inheritance. Two X-linked phenotypic variants of amelogenesis imperfecta have been included in these classifications — a hypoplastic form and a hypomaturation form.

Witkop and Sauk listed the varieties of AI, divided according to whether the abnormality lay in a reduced amount of enamel (hypoplasia), deficient calcification (hypocalcification), or imperfect maturation of the enamel (hypomaturation), and also recognized the combined defects [Table 1].[8]

The inheritance pattern of X-linked disorders dictates that male-to-male transmission cannot occur. Conversely, all female offsprings of an affected male must be affected. Affected females have a 50% probability of passing on the trait to the offspring of either sex.

The most striking feature of both these conditions is that there are different manifestations between affected females and affected males. In the hypoplastic form, females show vertical ridging of the enamel, whereas, in males there is uniform hypoplasia.[9] In the hypomaturation form,[10,11] males have teeth of normal size and shape, but with irregular, pigmented mottling. Females display vertical bands of mottling, often inconspicuous under normal lighting conditions. In both types, this phenomenon in females represents Lyonization,[12,13] where alternating groups of ameloblasts are under the control of either the abnormal or the normal gene.

Many authors have ascribed to Haldane,[14] the recognition of amelogenesis imperfecta as the first X-linked "dominant"

Table 1: Classification of amelogenesis imperfecta (Witkop and Sauk)

Type I hypoplastic	
IA	hypoplastic, pitted autosomal dominant
IB	hypoplastic, local autosomal dominant
IC	hypoplastic, local autosomal recessive
ID	hypoplastic, smooth autosomal dominant
IE	hypoplastic, smooth X-linked dominant
IF	hypoplastic, rough autosomal dominant
IG	enamel agenesis, autosomal recessive
Type II hypomaturation	
IIA	hypomaturation, pigmented autosomal recessive
IIB	hypomaturation
IIC	snow capped teeth, X-linked
IID	autosomal dominant?
Type III hypocalcification	
IIA	autosomal dominant
IIB	autosomal recessive
Type IV hypomaturation — hypoplastic with taurodontism	
IVA	hypomaturation — hypoplastic with taurodontism, autosomal dominant
IVB	hypoplastic — hypomaturation with taurodontism, autosomal dominant

condition in man. His proposition was based on one of the pedigrees presented in an earlier report by Bampton[15] on "hereditary dental pigmentation." The oldest reported case of vertically wrinkled dental enamel is that found in the skeletal remains of an American Indian child, thought to date from AD 1100.[16]

The first clear descriptions of X-linked hypoplastic AI were those of Schulze and Lenz[9] and Schulze,[17] who recognized the different manifestations in affected males and females. This was confirmed and expanded upon by Schulze[18] in a monograph, detailing families from a geographically discrete area in Germany.

Witkop[10] included an X-linked recessive hypomaturation form in his early classification of AI, in which the affected males showed mottling of the enamel. He observed that clinical enamel involvement could be recognized in (carrier) females under specific examination conditions.[11] Winter and Brook described "X-linked recessive hypomaturation amelogenesis imperfecta," and reported the enamel to be of normal thickness and relatively soft, so that the surface could be penetrated with a sharp probe.[19] Severe attrition was a feature, especially on premolars and molars and the palatal aspects of the upper anterior teeth of males. A kindred with "X-linked recessive hypomaturation amelogenesis imperfecta" was presented by Haug and Ferguson.[20] However, the clinical description of teeth in females mentioned "vertical striations in every crown, consisting of voids and wrinkles interspersed between areas of normal enamel." This enamel was also softer than normal with marked abrasion, discolored, yellow to brown, with the cervical enamel of the posterior teeth less involved than the enamel of the incisors.

Witkop and Stewart[21] noted that (in the hypomaturation form) the mottled yellow-white color of the permanent teeth could darken with absorption of stains. In severely affected boys, the enamel of permanent teeth was slightly thinner than normal, with the cervical enamel tending to be better formed, whereas, in girls both primary and permanent teeth showed alternating bands of white opaque, and normal translucent enamel.

Witkop[22] observed that the inheritance pattern of the variant of AI referred to as snowcapped teeth was not clear. Escobar *et al.*,[23] suggested that this form was X-linked in its inheritance, and in his article, Witkop[24] seemed to accept snowcapped teeth as an X-linked trait. He also raised the possibility of an autosomal dominant form.[24] In a pedigree with snowcapped teeth, seen by Crawford and Aldred, 1992,[25] the inheritance is ostensibly autosomal dominant, with male-to-male transmission. Furthermore, the phenotype in males and females is identical.

Histopathological examination confirms that when enamel hypoplasia is the predominant clinical finding, the enamel is reduced in thickness. The enamel-dentin junction may show some exaggerated scalloping. Areas of homogeneous aprismatic enamel[26] or fused indistinct prisms are seen, with "a reduction in the distance between enamel rod incremental lines," where any enamel rod can be identified.[27] The histology of the phenotype described by Witkop[10,11] and Sauk *et al.*,[28] showed that the most marked defects in the enamel were seen in the outer half. The enamel rod sheaths were lacking and filled with "pigmented debris" or with "eosinophilic-staining material." Ground sections showed voids within the enamel, obliterating several rods (prisms). In the deeper enamel and the surface enamel, the structure was more normal. Microradiography[29-31] has shown varying degrees of radiographic defects of the enamel. Darling[29] described a zone of "markedly hypocalcified enamel" (with no mention of discrete channels) adjacent to the enamel-dentin junction in two teeth from a female with X-linked hypoplastic AI. Except for the ridged hypoplasia, the outer enamel had appeared entirely normal clinically and microradiographically. Microradiographs of deciduous molar teeth presented by Backman *et al.*,[30,31] from an affected male (categorized as X-linked recessive hypoplastic) showed marked "demineralization" of the enamel close to the enamel-dentin junction, with channels of demineralization extending to the enamel surface. Although demineralization is a term usually applied to a posteruptive pathological change, this was not suggested to be the case here. Under light microscopy, McLarty *et al.*.[32] found irregular spaces running from the enamel-dentin junction outward in a male considered to have X-linked hypomaturation amelogenesis imperfecta. Some of these consisted of tube-like structures that ended in a peripheral expansion. Although the descriptions of the enamel in the reports of McLarty *et al.*,[32] and Haug and Ferguson[20]

are consistent with a hypomineralization defect, the additional finding of enamel wrinkling in the females indicates some degree of hypoplasia. The observations of Darling[29] suggest that although the wrinkled surface enamel corresponding to the hypoplastic form of X-linked amelogenesis imperfecta may appear to be normally hard, there might be poorly mineralized enamel in the deeper portions. Schulze [33] recorded that the teeth could be yellow, yellow-red, or yellow-brown. It may be that the discoloration, evident in the enamel of some families reported as hypoplastic X-linked amelogenesis imperfecta, also indicates some degree of hypomineralization. It is difficult otherwise to explain the abnormal color and / or lucency of this tissue.

We present a case showing the clinical and histopathological features of this entity.

CASE REPORT

An 11-year-old girl reported to the Department of Pedodontics and Preventive Dentistry, Dr. D.Y. Patil Dental College and Hospital, Pune, with the chief complaint of discolored teeth since childhood.

This little girl's parents did not seek any treatment previously, thinking that since the condition was not resulting in any other systemic manifestations and since she had inherited the condition from her father, there was little they could really do about it and accepted it as part of her appearance. It was only now, when they realized that the girl avoided hard food substances, they got her to a dentist.

On enquiry, it was revealed that her deciduous teeth were also similarly discolored, and her father, younger brother of eight years, and younger sister of six years, also suffered from the same condition. The pedigree chart could be constructed as in Figure 1.

Apart from this, her past medical history was noncontributory. The history did not reveal any eruption disturbances. From a functional point of view, she had been avoiding hard food substances; at the same time, remaining caries free, except for a sole proximal carious lesion in 36, involving the enamel and dentin.

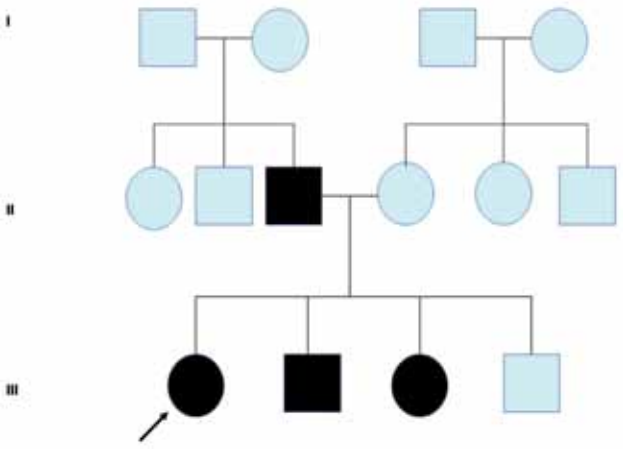

Figure 1: Pedigree chart for the case

On intraoral examination, it was found that she had a normal complement of teeth. The thickness of enamel was reduced on the teeth and was completely chipped off from some teeth exposing the dentin. The surfaces of the teeth were rough. The teeth, in general, exhibited a yellowish brown discoloration, with diffuse pitting present on the exposed tooth surfaces, more prominent on the labial and buccal aspects. The emergence pattern and timing of teeth seemed to be within the normal range. No open bite was present. Examination of the periodontium revealed the presence of chronic, generalized, marginal, and papillary gingivitis, with calculus deposition and unsatisfactory oral hygiene [Figures 2-4].

A provisional diagnosis of hypoplastic, rough autosomal dominant AI was proposed along with a differential diagnosis of environmental enamel hypoplasia, dentinogenesis imperfecta, dentin dysplasia, regional odontodysplasia, and the tricho-dento-osseous syndrome.

Radiographic investigations included an orthopantomogram (OPG) and full mouth intraoral periapical (IOPA) radiographs. The OPG showed the presence of all unerupted third molars, as well as a seemingly normal pattern and timing of eruption of teeth [Figure 5]. Examination of the IOPA radiographs revealed a normal pulp chamber and root canal spaces with no signs of obliteration. The enamel was almost half its expected thickness, but was more radiodense than the dentin.

The ground section of an over-retained deciduous molar extracted from the girl showed that the enamel was thin and was composed of laminations of irregularly arranged enamel prisms. No abnormality was apparent in the dentin [Figure 6]. Figure 7 shows a ground section of a normal tooth, where regularly arranged enamel prisms along with the normal thickness of enamel can be appreciated [Figure 7].

The diagnosis of hypoplastic, rough, autosomal dominant AI was confirmed on the basis of typical, clinical, radiographic, and histopathological features.

Esthetics along with functional limitations were the reason the patient's parents brought her to the hospital for treatment. The treatment proposed for her ranged from bonded veneer restorations to tooth preparations for the placement of a full crown. Restoration of the carious lesion in 36 would be accompanied by a full coverage restoration. The coronal pulp in these children tends to recede faster than in normal teeth and hence crown preparations for full coverage crowns can often be done for relatively young patients.

Attrition of teeth is a major problem in cases of AI. Therefore, the use of stainless steel crowns as a preventive measure is

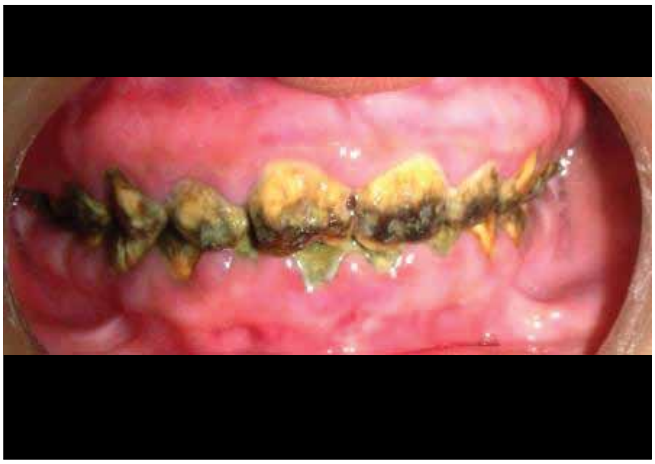

Figure 2: View of the labial surfaces of teeth

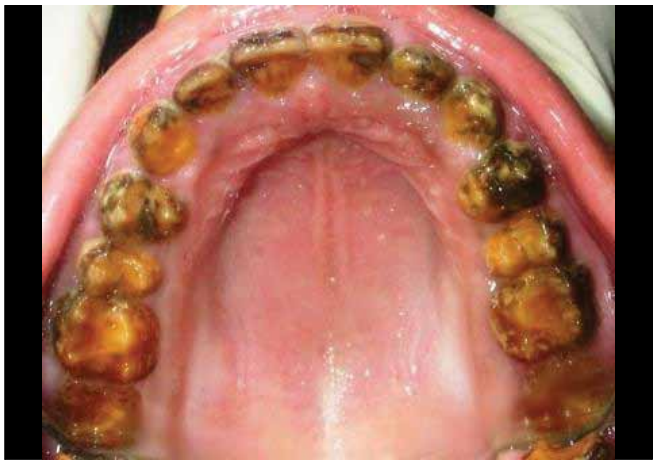

Figure 3: Maxillary occlusal view

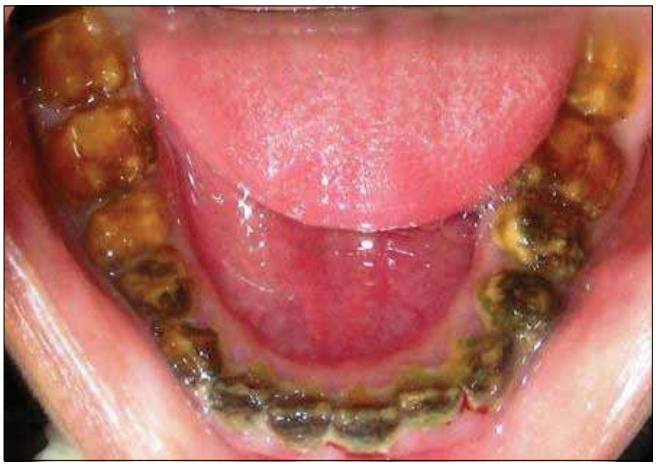

Figure 4: Mandibular occlusal view

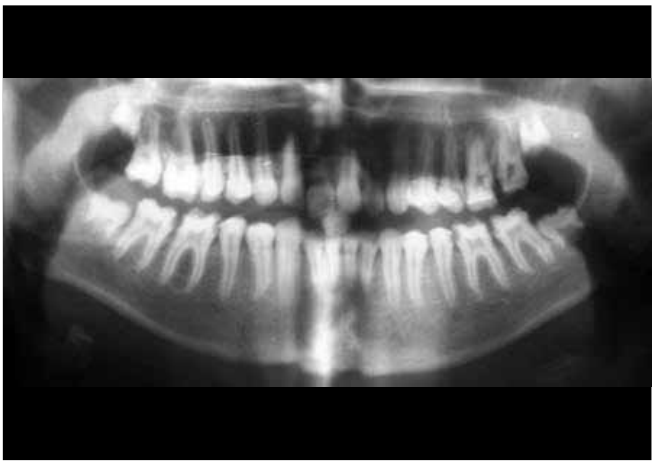

Figure 5: Orthopantomogram

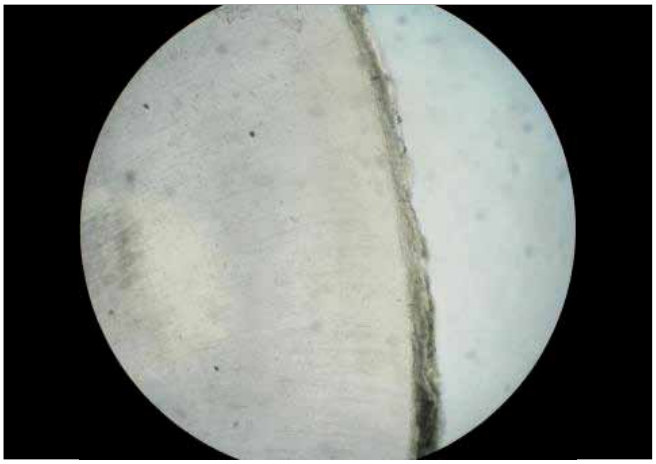

Figure 6: Ground section of affected tooth

Figure 7: Ground section of normal tooth

advocated. Hand scaling was advocated and oral hygiene instructions were given to the patient. Regular brushing of the teeth using the modified Bass technique was taught to the patient to be practiced twice a day (morning and at night before going to bed) using a soft toothbrush and a fluoridated toothpaste (containing 1000 ppm of available fluoride) followed by rinsing with 2% w/v of chlorhexidine gluconate for 15 days.

DISCUSSION

Amelogenesis imperfecta is a developmental, often inherited

disorder, affecting dental enamel. It usually occurs in the absence of systemic features and comprises of diverse phenotypic entities.[4]

The predominant clinical manifestations of affected individuals are enamel hypoplasia (enamel is seemingly correctly mineralized, but thin), hypomineralization (subdivided into hypomaturation and hypocalcification), or a combined phenotype, which is seen in most cases.[8,34,35]

The trait of AI can be transmitted by an autosomal-dominant, autosomal-recessive, or X-linked mode of inheritance.[36,37]

The distribution of AI types is known to vary among different populations. In a study in Sweden, 63% of the cases were inherited as autosomal-dominant. In contrast, in a study in the Middle East, the most common prevalent type of AI was found to be autosomal-recessive.[8,38]

Witkop[10] originally noted that hypomaturation amelogenesis imperfecta in two families affected only males. The use of "recessive," in his terminology "X-linked recessive amelogenesis imperfecta," could be because the females were thought to be unaffected. Prompted by the presentation of a third proband, he was subsequently able to re-examine the females of one of the two initial families under adequate lighting conditions that revealed "alternating vertical bands of mottled white hypomature enamel separated by normal-appearing enamel".[11]

This appearance does have similarities to the cases reported by McLarty *et al.*[32] and Haug and Ferguson,[20] that is, an apparent hypomineralization together with vertical hypoplasia of the enamel. Weinmann *et al.*,[7] subdivided AI into hypoplastic and hypocalcified types, a distinction that has persisted into most subsequent classifications.

Such a differentiation may have a greater basis in clinical judgment, with its emphasis on perceived phenotype, than in the histological fact, and may account for some of the apparent discrepancies in terminology in the literature relating to X-linked amelogenesis imperfecta.

Linkage studies[39] have hitherto placed the disease on the distal short arm of the X chromosome, and further recombinant DNA investigations will enable us to distinguish between an apparent simple hypoplastic form,[9] a hypoplastic and hypomineralized form,[20,32,40] and a pure hypomaturation form.[10,11]

Some of the genes encoding the specific enamel proteins have been indicated as candidate genes for AI. Mutational analyses within the studied families have supported this hypothesis.[41]

The *amelogenin* gene is a tooth-specific gene expressed in pre-ameloblasts, ameloblasts, and in the epithelial root sheath remnants; while a low-expression of amelogenin mRNAs has been recently shown in odontoblasts.[42,43] To date, there are 14 *AMELX*-associated AI mutations.[44]

The *enamelin* (*ENAM*) gene is a tooth-specific gene expressed predominantly by the enamel organ, and, at a low level, in odontoblasts. The human *ENAM* gene is localized on chromosome 4 (4q13.3). One autosomal-inherited form of AI, namely, autosomal-dominant amelogenesis imperfecta (ADAI), was linked to a 4Mb region on 4q21. The *ENAM* gene has been mapped within this locus by radiation hybrid analysis (RHA) and fluorescent *in situ* hybridization (FISH), and was therefore considered a candidate gene for this type of AI.[45] The work of Kim *et al.* further relates phenotype to genotype and identifies a mid-crown, horizontal form of genetically determined hypoplasia.[46]

Enamel phenotypes of *ENAM* mutations may be dose-dependent, with generalized hypoplastic AI segregating as a recessive trait and localized enamel pitting segregating as a dominant trait.[47]

The *ameloblastin* (*AMBN*) gene is expressed at high levels by ameloblasts and at low levels by odontoblasts and pre-odontoblasts, while moderate expression is also observed in Hertwig's epithelial root sheath, and in odontogenic tumors, such as in ameloblastomas.[48] The human *AMBN* is localized on chromosome 4 at locus 4q21, near other genes associated with the mineralized tissues: osteopontin, bone sialoprotein, and bone morphogenetic protein 3. *AMBN* maps within the critical region for autosomal-dominant AI, and is therefore considered as a candidate gene. However, it was excluded from a causative role by mutational analyses within the families studied by Mårdh-Kärrman C *et al*.[49]

The *amelotin* gene (AMELOTIN 4q13) has been reported by Iwasaki *et al.*, 2005,[50] to play a role in the molecular interaction during amelogenesis. However, so far no mutation of the amelotin gene has been related to AI.[51]

The *KLK4* gene is located near the telomere of chromosome 19 (19q13.3 – 19q13.4) downstream of the *KLK2* gene, and is considered a member of the human tissue kallikrein gene family.[52] *KLK4* is expressed by both ameloblasts and odontoblasts.

On account of the abnormal enzymic activity, the crystallites of the enamel grow to the normal length, but not completely in thickness.

The *MMP-20* gene codes for a calcium-dependent proteinase that is a member of the matrix metallopeptidases family (MMPs). Additionally, no other intact, physiologically normal, tissue has been demonstrated to express *MMP-20*, apart from ameloblasts, pre-ameloblasts, and odontoblasts, whereas, the expression of *MMP-20* in human odontogenic tumors and

carcinoma cell lines originating from the tongue has recently been described.[53] Mutation in the matrix metalloproteinase 20 gene (*MMP-20*) in the region 11q22.3 – q23, has been described as being associated with autosomal recessive pigmented hypomaturation amelogenesis imperfecta.[54,55]

The *DLX3* gene is a member of the family of homeobox genes that are homologous to the *distalless* (Dll) gene of *Drosophila*, known to be expressed during development of the chondrocranium, dermatocranium, sensory organs, brain, limbs, and appendages, and in the processes of osteogenesis and hematopoiesis.[56] Mutation within the human *DLX3* gene homeodomain is associated with AI (hypoplastic–hypomaturation type), with taurodontism (AIHHT). Dong *et al.*, 2005, suggest that the tricho-dento-osseous syndrome (TDO) and amelogenesis imperfecta hypoplastic–hypomaturation with taurodontism (AIHHT) are allelic for *DLX3*.[57]

An additional locus for autosomal dominant AI has been found recently on chromosome 8q24.3.[58]

However, *AMELX*, *AMBN*, *ENAM*, *KLK4*, and *MMP-20* were excluded from a causative role in two families with autosomal-dominant hypocalcified AI, suggesting that this type of AI is caused by the mutation of a gene that is either not known or not considered to be a major contributor to enamel formation.[59]

Mutations in the amelogenin gene (*AMELX*) cause X-linked amelogenesis imperfecta, while mutations in the enamelin gene (*ENAM*) cause autosomal-inherited forms of amelogenesis imperfecta. Recent reports involve kallikrein-4 (*KLK4*), *MMP-20*, and *DLX3* genes in the etiologies of some cases.[60]

As in all genetic diseases, the final classification will be based on genetic mutation and the resulting biochemical abnormality in each family. Several investigators have suggested a classification system based on the phenotype and pedigree, combined with a scanning electron microscopic examination, biochemical methods, and molecular genetics.

Histologically, a ground section of the teeth involved showed very thin enamel, composed of laminations of irregularly arranged enamel prisms.[61] The SEM studies of the extracted deciduous teeth, in a case of autosomal recessive rough hypoplastic amelogenesis imperfecta, showed an exposed outer enamel surface, with irregularly shaped globular protrusions. At the cervical region of the crown, a series of wavy, parallel ridges was seen in the enamel regions. The cementum area was clearly distinguishable from the more coronal region by its mottled and fibrillar pattern, and the tendency for the cementum to overlap the ridged coronal structure along the cervical line. The enamel had a high organic content with some abnormal prism formation. The dentinoenamel junction was sharply defined and easily identifiable because of the more homogenous appearance of the enamel matrix, as compared with that of the dentin, with its array of collagen fibrils.[62]

The histology of autosomal dominant hypomaturation–hypoplasia type of AI with taurodontism, definitively described by Winter *et al.*, comprised of areas of severe hypomineralization with a pore volume of between 1 and 25%. They described a normal prismatic structure to the enamel, but with considerable post-calcification organic content and occasional bands of globular defects. The dentin was also reported as being defective, with a decreased number of tubules, an increased amount of intertubular dentin, dilatations, and cellular inclusions. All these findings were more marked in the radicular dentin. The pulp was normal, but enlarged in size.[63]

The varying etiology of AI conjures a wide array of clinical features whose restorative management poses a challenge for dentists. As both esthetics and function are compromised in these patients, their management usually involves complete oral rehabilitation by way of full coverage crowns, direct and indirect veneers, and bonded esthetic restorations, depending on the condition of the individual tooth and the age of the patient. Types ID, IE, IG, IIA, IIIA, IIIB, and IVB demonstrate very thin enamel or highly defective enamel, which leads to rapid attrition. These variants require full coverage as soon as is practical. If the treatment is delayed, a loss of usable crown length occurs. In those patients without sufficient crown lengths, full dentures (overdentures in some cases); often become the only satisfactory approach.

The other types of AI demonstrate less rapid tooth loss, and the esthetic appearance is the prime consideration. In some cases a lack of good enamel bonding of veneers occurs and does not result in a durable restoration. The use of glass ionomer cements with dentinal adhesives often overcomes this weakness.

CONCLUSION

Several investigators have suggested a classification system for amelogenesis imperfecta, based on the phenotype and pedigree combined with scanning electron microscopic examination, biochemical methods, and molecular genetics.

Thus the dentist has to diagnose the condition as early as possible to offer early intervention and balance the decision for early intervention and long-term survival of the restorations. Dental practitioners should consider the social implications for these patients and intervene to relieve their suffering. Thus, this article is an attempt to improve the clinician's knowledge about the clinical diagnosis as well as intervention required for such a condition.

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