

Review Article

Amelogenesis Imperfecta- A Review

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ABSTRACT:

Dental enamel is the epithelial derived hard tissue covering the crowns of teeth it is most highly mineralized and hardest tissue of the body. Dental enamel is acellular and has no physiological means of repair outside of that provided by saliva. Amelogenesis imperfect (AI) is a disorder which affects the enamel structurally as well as clinically of all or nearly all the teeth in a more or less equal manner. The enamel may be hypoplastic, hypomineralized or both. AI is a group of inherited defects of dental enamel formation that show both clinical and genetic heterogeneity. Enamel findings in AI are highly variable, ranging from deficient enamel formation to defects in the mineral and protein content. AI exists in isolation or associated with other abnormalities in syndromes. It may show autosomal dominant, autosomal recessive, sex-linked and sporadic inheritance patterns. In families with an X-linked form it has been shown that the disorder may result from mutations in the amelogenin gene, *AMELX*. The enamelin gene, *ENAM*, is implicated in the pathogenesis of the dominant forms of AI. Autosomal recessive AI has been reported in families with known consanguinity. Diagnosis is based on the family history, pedigree plotting and meticulous clinical observation.

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INTRODUCTION

Amelogenesis Imperfecta (AI) is a developmental disorder of genomic origin, associated with abnormal enamel formation. Although AI is considered as a single disease entity, it actually represents a group of heterogeneous conditions, with diverse structural defects of enamel resulting in a range of clinical phenotypes.¹ It is characterized by clinical and genetic heterogeneity in the absence of systemic abnormalities or diseases. AI is also known by varied names such as hereditary enamel

dysplasia, hereditary brown enamel, and hereditary brown opalescent teeth.² The prevalence varies from 1:700 to 1:14 000, according to the populations studied.³ During the secretory stage of enamel formation, enamel matrix proteins amelogenin, enamelin and ameloblastin secreted by ameloblasts play key roles in the growth of enamel crystal. Reports have shown that mutations in the amelogenin gene (*AMELX*), and enamelin gene (*ENAM*), is implicated in the pathogenesis of the dominant forms of AI. In

AI because of poor differentiation of ameloblast it results in poor development or complete absence of enamel of the teeth.⁴ There are three subtypes of AI hypoplastic, hypocalcified and hypomaturation. Hypoplastic AI has absence of normal enamel morphology, which results in reduced occlusal function and reduced esthetics and an increased chance of caries development.⁴ Radiographic examination usually show a full complement of teeth, but the crowns of the teeth either have very thin enamel or lack enamel completely. Other dental features associated with AI include quantitative and qualitative enamel deficiency, pulpal calcifications, taurodontism and root malformations, impaction of permanent teeth, progressive root and crown resorption,

congenitally missing teeth and anterior and posterior open bite occlusion.² This article aims to review the classification, clinical features, genetic association, histopathology, methods of diagnosis, differential diagnosis and treatment planning of Amelogenesis Imperfecta.

CLASSIFICATION

Many classifications of AI have evolved since the original division into hypoplastic and hypocalcified types in 1945 (See Table 1). Some have been exclusively based on the phenotype (appearance), others have used the phenotype as the primary discriminant and the mode of inheritance as a secondary factor in diagnosis.

Table 1: Classification Systems Applied to Amelogenesis Imperfecta

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| Weinman et al., 1945 | Two types based on phenotype: hypoplastic and hypocalcified |
| Darling, 1956 | Five phenotypes based on clinical microradiographic and histopathological findings, hypoplastic Group 1: generalised pitting Group 2: vertical grooves Group 3: generalised hypoplasia Hypocalcified Type 4a: chalky, yellow brown enamel Type 4b: marked enamel discolouration and softness with post eruptive loss of enamel Type 5: generalised or localised discolouration and chipping of enamel |
| Witkop, 1957 | Classification based primarily on phenotype 5 types: Hypoplastic Hypocalcification Hypomaturation Pigmented hypomaturation Local hypoplasia |
| Schulze, 1970 | Classification based on phenotype and mode of inheritance |
| Witkop and Rao, 1971 | Classification based on phenotype and mode of inheritance . three broad categories hypoplastic, hypocalcified hypomaturation. Hypoplastic: Autosomal dominant hypoplastic – hypomaturation with taurodontism. Autosomal dominant smooth hypoplastic with eruption defect and resorption of teeth. Autosomal dominant rough hypoplastic Autosomal dominant pitted hypoplastic Autosomal dominant local hypoplastic X-linked dominant rough hypoplastic |

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|-------------------------------|---|
| | <p>Hypocalcified: Autosomal dominant hypocalcified</p> <p>Hypomaturation: X-linked recessive hypomaturation Autosomal recessive pigmented hypomaturation Autosomal dominant snow capped teeth White hypomature spots</p> |
| Winter and Brook, 1975 | <p>Classification based on primarily on phenotype . four main categories hypoplasia, hypocalcification, hypomaturation, hypomaturation –hypoplasia with taurodontism,with mode of inheritance as a secondary means of sub-classification</p> <p>Hypoplasia: Type 1 – autosomal dominant thin and smooth hypoplasia with eruption defect and resorbtion of teeth. Type 2 – autosomal dominant thin and rough hypoplasia Type 3 – autosomal dominant randomly pitted hypoplasia Type 4 – autosomal dominant localised hypoplasia Type 5 – X – linked dominant rough hypoplasia</p> <p>Hypocalcification: Autosomal dominant hypocalcification</p> <p>Hypomaturation: Type 1 – X – linked recessive hypomaturation Type 2 – autosomal recessive pigmented hypomaturation Type 3 – snow capped teeth</p> <p>Hypomaturation – hypoplasia with taurodontism: Type1 – autosomal dominant smooth hypomaturation with occasional hypoplastic pits and taurodontism Type 2 – autosomal dominant smooth hypomaturation with thin hypoplasia and taurodontism</p> |
| Witkop and Sauk, 1976 | <p>Classification based on phenotype and mode of inheritance, similar to classification of witkop and Rao</p> |
| Sundell&Koch,1985 | <p>Classification based solely on phenotype</p> |
| Witkop, 1988 | <p>Four major categories based primarily on phenotype (hypoplastic, hypomaturation, hypocalcified, hypomaturation – hypoplastic with taurodontism) subdivided into 15 subtypes by phenotype and secondarily by mode of inheritance.</p> <p>Type 1 – hypoplastic Type 1a- hypoplastic,pitted autosomal dominant Type 1b – hypoplastic, local autosomal dominant Type 1c – hypoplastic, local autosomal recessive Type 1d - hypoplastic, smooth autosomal dominant Type 1e – hypoplastic, smooth X – linked dominant Type 1f - hypoplastic, rough autosomal dominant Type 1g – enamel agenesis, autosomal recessive</p> <p>Type 2 – hypomaturation Type 2a – hypomaturation, pigmented autosomal recessive Type 2b – hypomaturation, X –linked recessive Type 2c – hypomaturation, snowcapped teeth, X- linked Type 2d – hypomaturation, snow capped teeth autosomal dominant</p> <p>Type 3a – autosomal dominant,</p> |

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|----------------------------------|--|
| | Type 3b – autosomal recessive Type 4 – hypomaturation hypoplastic with taurodontism Type 4a – hypomaturation, hypoplastic with taurodontism Autosomal dominant Type 4b – hypoplastic- hypomaturation with taurodontism, autosomal Dominant |
| Aldred and Crawford, 1995 | Classification based on: Molecular defect (when known) Biochemical result (when known) Mode of inheritance Phenotype |
| Hart et al.,2002 | Proposed a molecular defect subclassification of the AMELX conditions genomic DNA sequence cDNA sequence amino acid sequence nucleotide and amino acid sequences AMELX mutations described to date |
| Aldred et al, 2003 | Classification based on Mode of inheritance Phenotype – clinical and radiographic Molecular defect (when known) Biochemical result (when known) |

CLINICAL FEATURES

Hypoplastic AI: Hypoplastic form on AI is characterized by thin enamel with yellowish - brown color, rough or smooth and glossy, square-shaped crown, lack of contact between adjacent teeth, flat occlusal surfaces of the posterior teeth due to attrition, and with/without grooves and pitting. Radiographically, in hypoplastic type, there is a presence of thin radiopaque layer of enamel with normal radiodensity. Histologically, in hypoplastic type, defect is in enamel matrix formation.

Hypocalcified AI: Hypocalcified form of AI is the most common type and is characterized by normal size and shape of crown, softer enamel which wears down rapidly and can be removed by a prophylaxis instrument, and become pigmented-dark brown colored. Radiographically, in hypocalcified form, thickness of enamel is normal but radiodensity of enamel is less than that of dentin. Histologically, in hypocalcification

type, defects of matrix structure and mineralization is seen.

Hypomaturation AI: Hypomaturation form of AI is characterized by normal thickness of enamel but softer than normal but harder than hypocalcified type and may crack away from the crown, mottled-colored cloudy white/yellow/brown/ snow capped. Radiographically, radiodensity of enamel is similar to that of dentin. Histologically, in hypomaturation type, alterations in enamel rod and rod sheath structures had been noted in various studies.

In hypoplastic-hypomaturation with taurodontism, the enamel is thin, mottled yellow to brown, and pitted. Molar teeth exhibit taurodontism and other teeth have enlarged pulp chambers.

GENETIC INVOLVEMENT IN AMELOGENESIS IMPERFECTA

Amelogenin: Amelogenin, the protein product of the AMELX Xq22 and AMELY Yp11 genes, is considered to be critical for

normal enamel thickness and structure. Amelogenin is the most abundant, accounting for more than 90% of total enamel protein. Amelogenin is thought to form a scaffold for enamel crystallites and to control their growth, but its exact functions are not fully known. The 9bp deletion in exon 2 coding for the signal sequence resulted in hypoplastic enamel that is normally mineralized, but of reduced thickness. This phenotype is compatible with a mutation affecting the transport of a protein, required of the formation of enamel. Deletions of a C-nucleotide in different codons cause a premature stop codon and loss of the C-terminus of the protein, leading to the production of hypoplastic and/or hypomineralization AI, and the symptoms can vary among affected members of same family.¹⁸

Ameloblastin: Ameloblastin, also known as amelin, is expressed by the enamel-producing ameloblast cells. It is a tooth-specific glycoprotein, which represents the most abundant nonamelogenin enamel matrix protein. The protein is found inside rounded structures at the distal end of the cell body and near the secretion pole of ameloblasts. It was also present near the dentin-enamel junction. Ameloblastin binds specifically to ameloblasts and inhibits cell proliferation of mutant ameloblasts. In mutant teeth, ameloblasts regain some early phenotypes of undifferentiated dental epithelial cells, and the abnormalities occur when the cells detach. This results indicate that ameloblastin is a key adhesion molecule for enamel formation and suggest that ameloblastin plays an important role by binding to, and maintaining the differentiated phenotype of secretory ameloblasts.¹⁸

Enamelin: Enamelin, the largest enamel extracellular matrix protein, was initially identified by Fukae, et al.(1993).¹⁹ It is produced by ameloblasts, initially during the secretory stage concentrating near the Tomes

processes. Much lower levels of enamel expression have been observed in dental pulp, presumably secreted by odontoblasts, and along the forming root. Enamelin is present in small amounts and undergoes a series of proteolytic cleavages to generate several polypeptides that are thought to participate in enamel crystal nucleation and extension, and the regulation of crystal habit.¹⁸

A substitution in exon 4, introduced a premature stop codon, was described in Swedish families. This milder form of AI, known clinically as autosomal-dominant local hypoplastic AI, accounts for 27% of the autosomally inherited cases in Northern Sweden. Most recently, a splice donor site mutation after enamel codon 196 was shown to cause autosomal-dominant hypoplastic AI.¹⁸

Proteinases: Different proteinases, serving different functions, are expressed during stages of amelogenesis. These proteinases are believed to regulate the enamel matrix protein processing that ultimately defines the structure and composition of enamel. The predominant proteinases are matrix metalloproteinase-20 in secretory enamel matrix and kallikrein-4 in the mature stage.¹⁸

Enamelysin: MMP-20, also known as enamelysin, was originally identified by Bartlett, et al.²⁰ This enzyme is expressed by ameloblasts and the odontoblasts of the dental papilla. Low levels of MMP-20 expression were observed in the pulpal organ. No other intact physiologically normal tissue is known to express MMP-20. Therefore, MMP-20 is considered a tooth-specific metalloproteinase. MMP-20 expression was observed in pathologic tissues such as in calcifying odontogenic cysts, odontogenic tumors and tongue carcinoma. Enamelysin is secreted into the enamel matrix in its developmental stages - secretory and transition. This enzymes accounts for most of the proteolytic activity

of the enamel matrix. Because enamelysin is present in the mineralizing front, it is thought to initiate the hydrolysis of the enamel matrix proteins allowing the crystals to grow in length but not in width or thickness. A solitary point mutation in exon 6 of the amelogenin gene has been reported to cause hypomineralized AI. This mutation is related to the MMP-20 cleavage site and is known to impair the efficiency of its hydrolysis, reducing the formation of TRAP.¹⁸

Kallikrein-4: KLK-4 is expressed from a gene on chromosome 19. Recent studies have shown that kallikrein mutation in association with autosomal recessive hypomaturation AI, indicating that the normal KLK-4 function is critical for enamel mineralization. The loss of KLK-4 function primarily affects the maturation stage of enamel development inhibiting the growth of enamel crystallites affecting the final deposition of an additional 15-20% mineral.¹⁸

HISTOPATHOLOGY

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 or fused indistinct prisms are seen, with “a reduction in the distance between enamel rod incremental lines,” where any enamel rod can be identified.²¹ The histology of the phenotype described by Witkop and Sauk *et al.*, 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).²¹ In the deeper enamel and the surface enamel, the structure was more normal. Microradiography has shown varying degrees of radiographic defects of the enamel. Darling described a zone of

“markedly hypocalcified enamel” (with no mention of discrete channels) adjacent to the enameldentin junction in two teeth from a female with X-linked hypoplastic AI.⁶ Except for the ridged hypoplasia, the outer enamel had appeared entirely normal clinically and microradiographically.²¹ Microradiographs of deciduous molar teeth presented by Backman *et al.*, 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.^{22,23} Although demineralization is a term usually applied to a post-eruptive pathological change, this was not suggested to be the case here. Under light microscopy, McLarty *et al.* 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.²⁴ The observations of Darling 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.⁶

DIAGNOSTIC METHODS

Clinical: The family history, pedigree plotting, clinical observation and meticulous recording form the backbone of diagnosis in this, as in any potentially inherited condition. Extraoral radiographs may reveal the presence of unerupted and sometimes spontaneously resorbing teeth. Intra-oral radiographs will reveal the relative contrast between enamel and dentine in cases where mineralisation may have been affected. The same films in conjunction with clinical observation will provide information on the degree of any enamel hypoplasia.³

Genetic Diagnosis: Laboratory genetic diagnosis is presently only a research tool.³

DIFFERENTIAL DIAGNOSIS

Extrinsic disorders of tooth formation, chronological disorders of tooth formation and localised disorders of tooth formation should be considered in the differential diagnosis. The commonest differential diagnosis is dental fluorosis. The variability of this condition, from mild white "flecking" of the enamel to profoundly dense white colouration with random, disfiguring areas of staining and hypoplasia, requires careful questioning to distinguish from AI. Fluorosis may present with areas of horizontal white banding corresponding to periods of more intense fluoride intake and may show the premolars or second permanent molars to be spared (chronological distribution). In the latter case, the history will often reveal excessive fluoride intake either in terms of a habit such as eating toothpaste in childhood, or related to a local water supply. A similar distribution of findings – chronological enamel hypoplasia – can arise from one of many causes during the time of tooth formation. Ranging from gastrointestinal upset of a prolonged nature, such as coeliac disease (a diagnosis which may not be confirmed until later life), to anti-leukaemic therapy; these causes may be identified from the history and from the chronological distribution of the markings seen.³

TREATMENT PLANNING

Amelogenesis imperfecta presents with problems of socialization, function and discomfort which may be managed by early vigorous intervention, both preventively and restoratively. In adult, the permanent dentition may be protected by use of full cast crowns on posterior teeth and veneers on anterior teeth. Root canal treatment and esthetic crown replacement for decayed teeth should be done to achieve the Jackson's triad of esthetic harmony, structural balance and

functional efficiency. Treatment of hypoplastic and hypocalcified type AI is comparatively different. Sundell reported that teeth were treated with prosthetic restoration in hypocalcified AI, while hypoplastic type teeth were treated with composite restoration. A multidisciplinary approach consisting of an orthodontist, prosthodontist and endodontist should be planned.² Treatment planning must focus on early diagnosis, pain management, prevention, stabilization, restoration of defects, and regular long-term management. The treatment plan should also accommodate factors including the patient's age, socio-economic status, disease type and severity, and overall oral condition. Affected patients are typically treated with hard porcelain crowns, composite restorations, stainless steel crowns, laminate applications, or overdenture applications. The therapeutic goals for these patients should focus on recovering aesthetic appearance and functional phonation, as well as preserving gingival health.²⁵

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