

IS AMELOGENESIS IMPERFECTA A SIGNAL OF SYSTEMIC DISORDERS? A BRIEF REVIEW OF LITERATURE

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Abstract

Amelogenesis imperfecta (AI) is a clinically and aetiologically heterogeneous group of inheritable disorders characterised by qualitative or quantitative anomalies of enamel development.

AI has a high degree of clinical diversity. Affected individuals show either hypoplastic or hypomineralized enamel, while both of these signs is apparent in many cases. The prevalence of AI is reported at 1/700 births in northern Sweden and, 1/14,000 births in the US. The inheritance patterns include autosomal dominant, autosomal recessive, X-linked dominant or X-linked recessive modes of transmission.

Several kinds of AI have been reported with X-linked inheritance and the amelogenin genes are found on both X and Y chromosomes in humans.

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Definition and Prevalance

Amelogenesis imperfecta(AI) is a heterogenous group of hereditary disorders that primarily affects teeth enamel. While syndromic and non-syndromic forms of AI are reported, non-syndromic forms are most prevalent^{1,2}.

The estimated birth prevalence is 1:700 in northern Sweden to 1:14000 in the US. The condition is not a single entity; there is a number of subtypes and different appearances. Four major types were recognized based on phenotype (hypoplastic, hypomaturation, hypocalcified, and hypomaturation-hypoplastic) and then subdivided into 14 subtypes based primarily on phenotype and, secondarily, by mode of inheritance (Table 1).

The extent of the enamel defect is dependent upon three conditions: (1) the

intensity of the etiologic factor; (2) the duration of the factor's presence; and (3) the time at which the defect occurs during crown development. For systemic factors to have an effect on developing permanent teeth, they must generally occur after birth and before the age of 6 years. During this time the crowns of all permanent teeth (with the exception of the third molars) develop. Because most enamel defects affect anterior teeth and first molars, systemic factors will have occurred predominantly during the first and a half year of life. Primary teeth and possibly the tips of the first permanent molars and permanent central incisors may reflect ameloblast dysfunction occurring in utero, as these are the teeth undergoing enamel calcification during this period. Affected patients should be questioned about fluorosis, which could also cause generalised enamel hypoplasias.

It can be difficult to differentiate AI in patients with hypoplastic defects (thin pitted or grooved enamel) and/or hypomineralization where the enamel mineral content is decreased. However, hypomineralized areas are attributable to environmental factors, i.e. trauma, or to a certain stage in tooth development. While diverse

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aetiological factors including diet, stress, fever, injury, infection, and genetics have been proposed for localised enamel defects, most emphasis has been placed on non genetic factors.

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 Hypocalcified

IIIA-autosomal dominant
IIIB-autosomal recessive

Type IV Hypomaturation-hypoplastic with taurodontism

IIVA-hypomaturation-hypoplastic with taurodontism, autosomal dominant
IVB-hypoplastic-hypomaturation with taurodontism, autosomal dominant

Table 1: Classification of amelogenesis imperfecta proposed by Witkop (1988).

The development of teeth is a complex process that involves sequential and reciprocal interactions between dental epithelium and mesenchyme. It is characterized by events that determine the histodifferentiation of mesenchymal cells into dentin-secreting odontoblasts and of epithelial cells into enamel-secreting ameloblasts³. Very little is known concerning the transcriptional mechanism that regulates hard tissue formation in tooth⁴.

Although many studies indicate the importance of odontoblasts in the induction of epithelium into ameloblast cell fate, an epithelial-dependent, cell-autonomous control is also needed for ameloblasts to fully differentiate, mature, and deposit enamel matrix. Presecretory, secretory, and mature ameloblasts express several secreted proteins such as ameloblastin, amelogenin, enamelin, tuftelin, dentin

sialoprotein, apin, amelotin; enzymes such as kallikrein 4 and enamel proteinases such as matrix metalloproteinase 20; signalling molecules such as BMPs, TGF β 1, SHH, and WNTs; and transcription factors such as Msx2, Sp3, Sp6 and Dlx5. Studies using transgenic animals provide functional data showing that disruption of ameloblast signaling and its mediators results in aberrations of ameloblasts differentiation and enamel deposition³.

Although growth hormone (GH) has an important role in skeletal development, its effect on dentition is less clear. A number of studies have shown that GH is able to increase the formation of hard tissues *in vivo* (e.g. enamel). GH is able to induce the proliferation of epithelial stem cells in molar tooth buds, along with preameloblast differentiation and dentine matrix formation. According to the somatomedin hypothesis, it is believed that these actions on bone-forming cells are mediated by local or endocrine-insulin-like growth factor I (IGF-I). However, evidence is accumulating that GH may also use other mediators to sustain its action, e.g. hepatocyte growth factor (HGF) in the liver, fibroblast growth factor in chondrocytes, epidermal growth factor (EGF) in the kidney and liver, and estrogen in the uterus, through induction of either the growth factor or its receptor. It is known that GH, directly or indirectly through its modulation of gene products, increases the expression of insulin-like growth factors (IGFs) in cartilage, and influences skeletal growth primarily by stimulating the growth of cartilage in areas of endochondral ossification. GH deficiency and AI could be seen together in some AI patients of short stature⁵.

Clinical description

AI has a high degree of clinical diversity. Dental anomalies associated with AI include: quantitative and qualitative enamel deficiencies; pulpal calcification; tooth sensitivity; poor dental esthetics; decreased occlusal-vertical dimension; multiple impacted teeth; delayed eruption; congenitally missing teeth; hypercementosis; root malformations; taurodontism; gingivitis and periodontitis⁶. Four main forms of AI can be distinguished, three of which are related to a certain state in amelogenesis and the fourth connected with taurodontism. These main forms can be further divided into 14 subtypes based on predominant clinical manifestation and mode of

inheritance^{1,7}.

In pitted hypoplastic AI, the pinpoint-to pinhead-sized pits were generally randomly distributed in the dentition, rather than chronologically distributed, and can not be, therefore, attributed to a certain stage in tooth development. Dental radiographs show thin to visually absent enamel covering the entire dentition. In primary teeth, the extend of enamel was thinner than in corresponding non-affected teeth. The enamel was in some cases, so soft, that it was often lost soon after eruption. Radiographically the enamel fails to contrast with dentin⁵.

Teeth with rough hypoplastic amelogenesis imperfecta have an extremely thin enamel layer so that teeth do not meet at a contact point. Yellow-brown discoloration are observed in connection with the hypoplastic defects of teeth.

In teeth with hypomaturational AI, the enamel is mottled opaque white with a yellow-brown discoloration that becomes more severe with advancing age. The enamel is of normal extend and radiographically of almost the same density as dentin. Snow-capped teeth represent a manifestation of AI characterized by a lower degree of mineralization which look similar to fluorosis⁸. In X-linked hypomaturational AI the enamel is of normal thickness with approximately the same radiodensity as dentin. In men and women the colour is opaque, white to mottled yellow-brown.

The enamel in teeth with hypocalcification AI is characterized by a more severe degree of hypomineralization than that of teeth with hypomaturational AI. The enamel is lustreless, opaque white to yellow-brown, of normal extent but so soft that is often lost soon after eruption, leaving a tooth crown composed only of dentine. There was large organic (inclusions) as are seen in hypocalcified AI⁹.

In hypocalcification and hypomaturational-hypoplastic with taurodontism AI, permanent teeth exhibited excessive attrition or enamel fracture. Both primary and permanent teeth were affected, but primary teeth were affected to a less severe extent than permanent teeth.

An anterior openbite malocclusion, generally considered to be of skeletal origin, is a frequent associated finding in AI. While altered enamel is the major feature of AI, other craniofacial anomalies including an obtuse gonial

angle and cranial base changes have been reported^{10,11,12}. Anterior open bite was present in the primary and permanent dentitions of 50% of the patients with type I (hypoplastic), 30.8 % of the patients with type II AI (hypomaturational), and 60 % of the type III AI (hypocalcified)⁵. The relation of the underlying gene of major effect mutation to the observed malocclusion in AI is unclear, yet the association of openbite malocclusion with a large number of AI cases suggests an aetiological association⁹.

Etiology

Improved insight into the genetic causes of AI will aid future classification, which continues to be based primarily on dental phenotypes in isolation amelogenin (AMELX), kallikrein 4 (KLK 4), matrix metalloproteinase 20 (MMP20), FAM83H, distal-less homeobox 3 (DLX3) and enamelin (ENAM) genes have been previously associated with various forms of AI¹³. Mouse models have identified two additional genes, ameloblastin (AMBN; 4q21) and Tufelin (TUFT1;1q21) that cause phenotypes with enamel defects, when the gene is knocked-out or over-expressed, respectively^{14,15}. The different types of AI reflect differences in the timing during amelogenesis, when the disruption occurs and are inherited, either as X-linked, autosomal dominant, or autosomal recessive traits¹³. Of these, three (ENAM, KLK4 and MMP20) can cause autosomal recessive amelogenesis imperfecta (ARAI). While the recessive mutation in ENAM causes hypoplastic AI, mutations in proteases cause hypomaturational ARAI¹⁶.

Human X-linked AI is associated predominantly with mutations in the AMELX gene ARAI has been associated with mutations in the genes encoding KLK4 at 19q13.4, MMP20 at 11q22.3-q23 and ENAM at 4q21. KLK4 and MMP20 are enamel-specific proteases that have only recently been characterized. Both MMP20 and KLK4 have been found to degrade enamel matrix proteins early in the maturation stages^{14,17}.

Autosomal dominant AI (ADAI) has been associated with mutations in the ENAM gene and in the DLX3 gene at 17q21. The DLX family proteins that share similar DNA-binding sites and are thought to act as homeodomain transcription factors in a variety of developmental processes that include osteogenesis, is considered critical for craniofacial and tooth development¹⁴. Fifteen different mutations in the AMELX gene have

been identified and, depending on the mutation, the phenotype can vary from thin hypoplastic enamel to enamel that is normal in thickness but has a reduced mineral content and increased protein content¹⁷.

No cases of mutations in the Y-chromosome amelogenin gene have been identified¹⁸. ENAM defects usually show a dose effect: the enamel phenotype is typically much more severe when both ENAM alleles are defective. There are now 10 novel ENAM disease-associated mutations that have been characterized¹⁹.

GH deficiency could be seen in some AI patients of short stature. GH deficiency is the major prediction in hypoplastic AI and especially hypomaturation-hypoplastic with taurodontism AI cases. AI patients with GH deficiency exhibited a delayed dental age. Other findings have included colour changes in the hair and eyes, light hypersensitivity in the eyes, and deafness⁵. Comparison of the syndromic form of AI patients with non-syndromic form of AI patients, shows additional characteristic findings in craniofacial and other body regions. In the rest of the body that are derived from the mesoderm of the primitive streak, in the craniofacial complex the neural crest cells originating from the ectoderm give rise to the ectomesenchyme, from which much of the skull is formed⁹. The primary growth cartilages, the first skeletal components to appear in early embryonic life, control growth in the cranial base and the limbs. The timing is quite different in the craniofacial and limb areas, however. Growth of the cranial base parallels growth of the brain and is largely complete by age 6, while growth in the limbs proceeds much more slowly and peaks at adolescence.

Also in some studies AI and eye defects and/or skin defects have been seen together by the effect of discovery of some genes. The discovery of genes not only suggests the intriguing possibility of a direct link between tooth mineralization and retinal or skin function, but it may also give a novel insight into the role of metal transport in these processes^{20,21,22}.

Identification of WDR72 mutations as a cause of autosomal-recessive hypomaturation AI creates an opportunity for understanding amelogenesis and biomineralization¹³. Identification of CNNM4 suggested the direct link between biomineralization and retinal function^{20,22}.

Takamori et al. investigated the functional

significance of Fibroblast growth factor (FGFR1) signaling in regulating tooth development. In mice, ameloblasts differentiate normally at early stages, but the function of enamel-secreting ameloblasts is compromised at the newborn stage. They found that the enamel structure of all teeth was defective in adult mice, resulting in a phenotype similar to the human disorder, pitted hypoplastic AI²³.

Chan et al. proposed that all inherited enamel defects, including minor pitting and surface roughness, be included under the designation "amelogenesis imperfecta". That was appropriate because the threshold for including or not including a phenotype within the AI designation was arbitrary³¹. According to the Jaskoll et al. study, congenital cytomegalovirus (CMV) induces many highly significant stage dependent changes in the expression of genes essential for dentinogenesis and amelogenesis (amelogenin, enamelin and dentin sialophosphoprotein) as well as genes important for tooth development. Their results clearly demonstrated the time (stage and duration) dependency of (mouse) mCMV-induced tooth pathogenesis: the earlier the initial stage and the longer the duration of infection, the more severely abnormal the phenotype²⁴.

However, some human AI cases cannot be attributed to any of these gene mutations. Thus numerous efforts with the use of mouse models to investigate genes related to enamel formation have been carried out to identify additional candidate genes²³.

Diagnostic methods

Diagnosis is based on clinical examination and radiographic evaluation (panoramic and cephalometric radiographs). Both family and medical history are important components for diagnosis of AI. All patients should be evaluated for unusual extraoral findings, dental malocclusion, eruption pattern, skeletal age, dental age, and missing and malformed teeth. Patients should also be evaluated orthodontically by using casts.

Whenever the gene and mutation that cause AI in a given family are learned, careful description of the associated clinical phenotypes will allow genotype-phenotype correlations to be identified²⁵. Several investigators have suggested a classification system for AI, based on the phenotype and pedigree combined with scanning

electron microscopic examination, biochemical methods and molecular genetics²⁶.

Management including treatment

Excessive calculus formation occurrence in some AI types (most severe hypocalcified and hypomaturation) is the major problem. The factors contributing to the development of these calculus deposits can include a rough enamel surface prone to deposits, decreased oral hygiene abilities due to dental sensitivity, and altered oral microflora²⁷. Individuals with rapid calculus formation may require more frequent recall appointments and professional scaling to control these deposits and maintain gingival health. Prior to restorative treatment, optimal gingival health should be provided.

Treatment of different AI types depends on the specific AI type and the character of the affected enamel²⁸. 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 restorations²⁴.

In hypoplastic AI, therapy typically involves the use of bonding procedures to protect the malformed teeth from caries and improve esthetics. Hypoplastic teeth usually have reasonably well mineralized enamel, albeit thin or pitted, making them suitable for restorative therapies involving bonding to the enamel. In the anterior region, composite resin or porcelain veneers can be bonded to the teeth when incisor shape, size, and/or colour requires modification. Orthodontic therapy may be used to partially close the interdental spaces prior to restoration, or restorative therapy may be performed alone²⁸.

In hypomaturation and hypocalcified AI, enamel is severely hypomineralized and of insufficient strength to retain bonded or intracoronal restorations, full coverage restorations should be placed both in primary and permanent restorations.

Ultimately, porcelain fused to metal or other custom fabricated crowns can be placed on the dentition²⁸.

The reason skeletal open bite occurs with an increased frequency in people with AI compared with the general population remains unknown. Skeletal open bite can be present in 25-40 % of affected individuals. Treatment of malocclusions will typically involve orthodontic treatment, but in severe cases of skeletal open

bite, orthognatic surgery can be required to achieve a more optimal alignment of the jaws and teeth.

Treatment in syndromic forms of AI could be different, for example in growth hormone (GH) deficiency with AI patients, hormonal regulation is necessary in early childhood.

By studying the outcomes of different restoration procedures for each genotype/phenotype condition, practicing dentists will use gene-based diagnoses to choose among various treatment options, and thereby restore the dentition in a way that achieves the best results²⁵.

Unresolved questions

While it has long been recognized that there are multiple clinical forms of AI, it is only recently that the genetic bases of these heterogeneous conditions are being identified. As the underlying genetic etiologies for AI are elucidated, we have begun to establish genotype-phenotype correlations for these clinically and genetically diverse disorders. This carries significant implications for understanding the molecular mechanisms leading to the unique AI enamel phenotypes and ultimately for the diagnosis and treatment of these conditions. Phenotype differences that correlate with specific mutations are expected eventually to provide a better way to categorize AI, as well as providing fundamental information about the roles of this protein in tooth enamel development⁷. It is essential that a comprehensive and standardized nomenclature describing the genomic and protein alterations be adopted that will allow researchers and clinicians to communicate efficiently and effectively²⁹. A better understanding of the variations in the penetrance and expressivity of mutations in the genes implicated in the etiology of AI may lead to a broader definition of AI phenotypes (that would include enamel pitting, and other subtle phenotypes such as localized surface roughness or under-mineralization) and provide insights into how genetic variations relate to disparities in caries risk in the general population. Mutations in genes have now been demonstrated to result in AI. Continued mutational analysis of families with AI will allow a comprehensive standardised nomenclature system to be developed for this group of disorders that will include molecular delineation as well as mode of inheritance and phenotype³⁰.

AI was considered as a dental disease but in light of recent studies, it should be accepted as more than just an enamel disease. In some cases, AI may be suggested as signal of a systemic disease.

Declaration of Interest

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