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Developmental defects of enamel and dentine: challenges for basic science research and clinical management

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ABSTRACT

Abnormalities of enamel and dentine are caused by a variety of interacting factors ranging from genetic defects to environmental insults. The genetic changes associated with some types of enamel and dentine defects have been mapped, and many environmental influences, including medical illnesses that can damage enamel and dentine have been identified. Developmental enamel defects may present as enamel hypoplasia or hypomineralization while dentine defects frequently demonstrate aberrant calcifications and abnormalities of the dentine-pulp complex. Clinically, developmental enamel defects often present with problems of discolouration and aesthetics, tooth sensitivity, and susceptibility to caries, wear and erosion. In contrast, dentine defects are a risk for endodontic complications resulting from dentine hypomineralization and pulpal abnormalities. The main goals of managing developmental abnormalities of enamel and dentine are early diagnosis and improvement of appearance and function by preserving the dentition and preventing complications. However, despite major advances in scientific knowledge regarding the causes of enamel and dentine defects, further research is required in order to translate the knowledge gained in the basic sciences research to accurate clinical diagnosis and successful treatment of the defects.

Keywords: Enamel, dentine, hypoplasia, hypomineralization.

Abbreviations and acronyms: AI = amelogenesis imperfecta; BSP = bone sialoprotein; CPP-ACP = calcium phosphopeptide-amorphous calcium phosphate; DMP1 = dentine matrix protein 1; DSPP = dentine sialophosphoprotein; EB = epidermolysis bullosa; EDI = Enamel Defects Index; FGF = fibroblast growth factor; MEPE = matrix extracellular phosphorylated glycoprotein; MIH = molar-incisor hypomineralization; OPN = osteopontin; TDO = tricho-dento-osseous.

INTRODUCTION

The three types of dental hard tissues, enamel, dentine and cementum, are formed through specialized cellular and biochemical pathways. These highly complex mechanisms are controlled by genes and influenced by epigenetic and environmental factors.[1] Abnormalities of the developmental pathways may result in reduced quantity of tissue produced and/or poor quality of mineralization.[2,3] If the affected genes are expressed predominantly in dental tissues, such as the amelogenin gene, *AMELX* on enamel, the teeth are the main structures affected.[4] On the other hand, if the genes are also involved in the formation of other tissues, such as genes encoding for laminin-332 and type XVII collagen, generalized effects involving other organs are found in addition to the dental malformations.[3,5]

The genetic control of enamel and dentine formation can be influenced by environmental changes such as systemic medical illnesses, chemical poisons, radiation and trauma, as well as epigenetic effects, e.g. DNA methylation.[6,7] Recent advances in clinical and basic science research have improved clinical diagnosis and treatment of developmental dental disorders. Importantly, identification of specific genetic aberrations for individual conditions has enhanced the possibilities for specialized treatments that can be targeted to correct specific defects.

The aims of this paper are to review current understanding of genetic and environmental influences on the development of enamel and dentine, and to discuss how knowledge gained from basic science research can be translated to the clinic to improve clinical diagnosis and treatment of developmental defects of enamel and dentine.

DEVELOPMENTAL DEFECTS OF ENAMEL

Dental enamel, the hardest tissue in the body, consisting of over 98% mineral and less than 2% organic matrix and water, is produced by specialized,

end-differentiated cells known as ameloblasts.[8] The formation of enamel can be separated into initial stages which involve secretion of matrix proteins such as amelogenin, ameloblastin and enamelin, and later stages of mineralization and maturation, although these processes may be present simultaneously in any developing tooth.[8] Developmental defects of the enamel may be inherited as mutations in the genes that code for enamel proteins, or as a feature of generalized familial conditions. These systemic conditions often involve tissues, such as skin, that share common embryologic origins of neuroectodermal mesenchyme with teeth.[9] In addition, congenital abnormalities involving the mineralization pathways, such as parathyroid gland disorders also commonly show enamel abnormalities.[10] Furthermore, enamel defects can also be caused by many acquired environmental and systemic perturbations such as metabolic conditions, infections, drugs and chemicals, as well as radiation and trauma.[6]

Although damage to the ameloblasts can result from a variety of agents, the abnormality in enamel is usually expressed in only a few ways: hypoplasia, which is a reduction in quantity, presenting as pits, grooves, thin or missing enamel, or hypomineralization, which is reduced mineralization presenting as soft enamel, or hypomaturation where there is altered translucency affecting the entire tooth, or in a localized area known as an opacity.[11] Hypoplastic enamel defects are thought to result from changes occurring during the stage of matrix formation whereas hypomineralization defects result from changes that affect the major part of the calcification process, and hypomaturation refers to the changes that occur at the last stages of mineral accumulation.[12] The terms commonly applied to describe the alterations in enamel development are defined in Table 1.

Inherited conditions involving enamel formation

Inherited conditions which show enamel defects may be generally grouped into conditions known as amelogenesis imperfecta where the developmental defects are limited to the teeth, and hereditary systemic conditions that are associated with defects in epithelial tissues or mineralization pathways.

Amelogenesis imperfecta

Amelogenesis imperfecta (AI) is a group of inherited disorders of enamel that have been reported to occur at prevalence rates of approximately 1.4:1000 to 1:16 000 depending on the population studied[13–15] (Table 2). AI can be clinically classified into hypoplastic, hypocalcified (hypomineralized) or hypomature types depending on the stage of enamel formation that is affected by the genetic defect. As the hypoplastic types are caused by reduction in the amount of matrix protein secreted, the clinical presentation is usually thin enamel, surface pitting or vertical grooving.[14,16] In contrast, the hypomineralized and hypomaturation types are characterized by the presence of normal amounts of enamel matrix that is deficiently mineralized. Hypomineralized AI shows soft enamel, while hypomaturation AI usually presents as opaque and discoloured enamel that fractures easily.[17] The majority of children with AI have problems with dental aesthetics, tooth sensitivity and increased caries risk. In addition, anterior open bite and an increased calculus formation are commonly encountered.[17] Figures 1a–c show the dentition of a child with the hypoplastic type of AI, and presenting with typical features of thin/absent enamel, poor oral hygiene and anterior open bite.

Gene-mapping helps to elucidate the roles of numerous genes that are involved in enamel formation, and studies correlating genotypes with phenotypes of AI provide valuable information regarding the genetic mutations that are found in the various phenotypes. There is recent evidence that approximately only half of all AI phenotypes are caused by mutations in one of the genes, *AMEL*, *ENAM*, *FAM83H*, *WDR72*, *KLK4* and *MMP20* that are

Table 1. Terms and definitions relevant to developmental enamel defects

Term	Definition
Opacity	Altered translucency
Diffuse opacity	An opacity that is distributed over a relatively large area
Demarcated opacity	An opacity that is confined to a relatively small area
Hypoplasia	Reduction in quantity of tissue formed
Hypomineralization/ Hypocalcification	Reduction in deposition of mineral
Hypomaturation	Reduction in the deposition of mineral at the maturation (end) stage of mineralization

Table 2. Prevalence of amelogenesis imperfecta and dentinogenesis imperfecta

	Country	Prevalence	Author, Year
Amelogenesis imperfecta	USA	1:14 000–1:16 000	Witkop, 1957[98]
	Israel	1:8000	Chosack *et al.*, 1979[15]
	Sweden	1.4:1000	Bäckman and Holm, 1986[13]
Dentinogenesis imperfecta	USA	1:6000–1:8000	Witkop, 1957[98]
			Kim and Simmer, 2007[3]
Dentine dysplasia	USA	1:100 000	Witkop, 1957[98]
			Kim and Simmer, 2007[3]

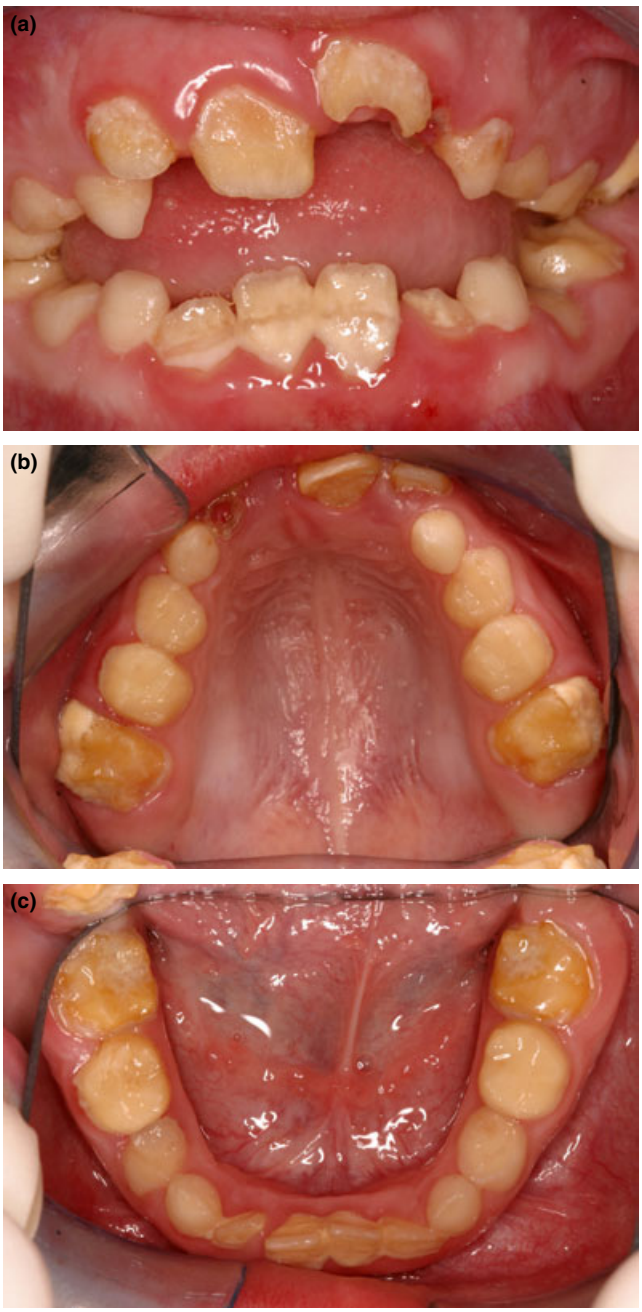

Fig. 1 (a) Photograph of the anterior teeth of an 8-year-old child with the hypoplastic type of amelogenesis imperfecta. Note the thin enamel which has fractured from the maxillary left permanent central incisor and poor oral hygiene that was associated with severe tooth sensitivity. A severe anterior open bite was present. (b) Photograph of the maxillary teeth of the child in Fig. 1(a) showing thin enamel of the primary teeth and missing enamel on the permanent first molars. (c) Photograph of the mandibular teeth of the child in Fig. 1(a) showing thin enamel of the primary teeth, missing enamel on the permanent first molars and calculus on the mandibular incisor teeth.

known to affect only enamel formation while the genes involved in the other half of AI phenotypes are currently unknown.[18,19] Human mutations for genes coding enamel proteins *AMEL* and *ENAM* generally cause enamel defects such as surface pits and thin enamel.[4] The *AMELX* gene encodes for the enamel protein amelogenin, and mutations in this gene are associated with X-linked forms of AI.[4] Human mutations in genes coding for kallikrein 4, *KLK4* and metalloproteinase 20, *MMP20* as well as *WDR72,* an intracellular protein with unknown function, result in hypomineralization or hypomaturation defects with varying degrees of hypoplasia, and are associated with autosomal recessive types of AI.[16,20] On the other hand, mutations in the *FAM83H* gene are associated with an autosomal dominant hypomineralization AI, the most common form of AI in North America.[21]

Phenotypic variation among individuals within a family having the same mutation is well known in AI, and may result from differences in expression of the gene, variation in response of the developing enamel at different locations on the tooth, as well as from post-eruptive breakdown.[1,22,23] Furthermore, in X-linked AI, affected females may show vertical grooving of the tooth surface, with bands of normal enamel alternating with areas of missing enamel while affected males in the same family show complete absence of enamel.[17]

Mouse models for the candidate genes of AI such as *AMEL, ENAM, MMP20* and *KLK4* provide opportunities for investigating the relationship between phenotypes and genotypes.[2,4] However, while animal models are useful to study the effects of knock-out genes, they do not fully imitate the human forms of AI where the genes involved may be partially expressed.[1] Mouse enamel also differs from human enamel in that the growth in the incisors is continuous, and not likely to be subjected to the wide range of genetic influences found in humans.

Enamel defects in hereditary conditions associated with defects of epithelial tissues

Many inherited syndromes, particularly those that involve skin, hair and nail show generalized enamel defects. The involvement of enamel in these syndromes is likely to be due to the common embryologic neural origin of the ectoderm shared by skin, hair and nails so that mutations in common genes result in abnormalities seen in all tissues. Dermatological conditions in which enamel defects have been reported include congenital erythropoietic porphyria, ectodermal dysplasia, epidermolysis bullosa and tuberous sclerosis.[9] In congenital erythropoietic porphyria, there is haemolytic anaemia, photosensitivity, skin fragility, hypertrichosis and red-brown porphyrin pigmentation of bones and discoloured and hypoplastic teeth.[24] Furthermore, in many types of ectodermal dysplasias, enamel defects ranging from mild to severe have been described.[25,26] Similarly, in epidermolysis bullosa (EB), a group of major bullous conditions generally classified as intraepidermal EB (simplex),

junctional EB, dermolytic EB (dystrophic), and mixed EB (Kindler syndrome),[27] varying degrees of enamel defects may be found depending on whether the altered protein is also involved in enamel formation.

In the tricho-dento-osseous (TDO) syndrome, an autosomal dominant condition caused by mutations in the *DLX3* homeobox gene, the enamel defects are usually striking.[28] The genetic mutations lead to abnormalities in protein degradation and impairment of expression of cell cycle regulatory proteins and skin differentiation markers.[28–31] TDO is characterized by severe hypomineralization of the enamel, taurodontism, and abnormalities in hair (curly or kinky hair or a change from straight to curly hair or vice-versa), nails (dysplastic), and bones (thickening of the skull base).[28,31]

Enamel defects in hereditary conditions associated with defects in mineralization pathways

Many inherited conditions associated with defects of the mineralization pathways involving the parathyroid glands and vitamin D metabolism also show abnormalities of enamel development. Hereditary syndromes which feature hypoparathyroidism such as the velocardiofacial syndrome or DiGeorge syndrome or 22q11.2 deletion syndrome have been reported to show enamel hypomineralization and hypoplasia.[32] The association of hypoparathyroidism with enamel defects are also seen in rare congenital conditions such as the Kenny-Caffrey syndrome (growth retardation with short stature, cortical thickening and medullary stenosis of the tubular bones, congenital hypoparathyroidism, hyperopia, microphthalmia, micrognathia and enamel and dentine abnormalities)[33] and the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome (hypoparathyroidism, chronic mucocutaneous candidiasis and adrenocortical failure).[34] However, while hypocalcaemia is a common feature of these congenital parathyroid conditions, its role in the pathogenetic pathways that cause enamel defects is unknown.[34]

Vitamin D deficiency due to malnutrition or genetic metabolic conditions often results in rickets (failure of bone matrix to mineralize), and is commonly associated with severe enamel defects. Nutritional rickets is encountered in children who do not consume sufficient Vitamin D or do not receive sufficient sunlight to activate provitamin D.[35] Although nutritional rickets is now thought to be rare in developed countries, the prevalence may be increasing in poor communities which do not have milk fortified with Vitamin D, and have little sunlight exposure.[36,37]

By contrast, the inherited types of rickets which are dependent on Vitamin D are rare. Two genetic variants of Vitamin D dependent rickets are known, and both types show hypocalcaemia and severe enamel hypoplasia.[38] Type 1 or pseudovitamin D deficiency rickets is caused by deficiency of the enzyme 25-hydroxyvitamin D-1a-hydroxylase which leads to absence of synthesis of calcitriol, the active form of Vitamin D. In contrast, Type 2 Vitamin D dependent rickets is associated with non-responsiveness of the Vitamin D receptor.[38] Familial Vitamin D resistant rickets is associated with low serum phosphate (hypophosphataemia)[39] and severe dentine defects with minimal involvement of the enamel.[40] These defects are discussed in the section on dentine defects.

Acquired conditions affecting enamel development

In addition to genetic conditions, many environmental and acquired systemic changes can also disturb the formation of enamel. If an insult occurs during enamel matrix secretion, hypoplastic defects are likely to result, in contrast to an insult occurring during the mineralization stages which usually produces hypomineralization defects. However, as several teeth in a child's mouth may be undergoing different stages of enamel formation at the time of an insult, it is possible that a spectrum of effects ranging from mild opacities to severe enamel hypoplasia may be evident on different teeth, and even on a single tooth.[12]

Systemic conditions

Acquired systemic factors that are likely to affect enamel development may be conveniently considered as pre-, peri- and postnatal conditions in relation to the timing of the event. These causes of enamel defects may be classified into metabolic disturbances, infections and chemicals and drugs. Local factors can be grouped as local infections, trauma and radiation. As enamel does not remodel, the location of the defect on the tooth surface can indicate the approximate timing of the event in relation to the chronology of tooth development. Although animal experiments have provided proof of the damaging effects of some of these factors to developing enamel, most of the evidence has been derived from clinical cases and epidemiological studies.[41–45] In some reports, there is evidence of damage from the same factors to major organs which are developing at the same time. An example is the enamel hypoplasia commonly seen in children with cerebral palsy where systemic disturbances such as infections, foetal anoxia and hyperbilirubinaemia have damaged both the developing brain cells and the enamel.[46,47]

Prenatal factors which may contribute enamel hypoplasia include maternal smoking and vitamin D deficiency during pregnancy and neonatal tetany, while postnatal factors include nutritional

deficiencies. Preterm children and those with low birth weight have a higher prevalence of enamel hypoplasia compared to children born full term with normal birth weights.[45–48] The defects found in preterm children usually stem from adverse systemic conditions associated with premature birth, such as respiratory immaturity, cardiovascular, gastrointestinal and renal abnormalities, intracranial haemorrhage and anaemia.[48] Furthermore, hypocalcaemia, osteopaenia and hyperbilirubinaemia can increase the risk for enamel defects in preterm children.[49–51] Inadequate supply of calcium and phosphorus mineral and inability of the gastrointestinal tract to absorb minerals are also important contributors to enamel hypoplasia in preterm children.[48,51] Local trauma from laryngoscopy and endotracheal intubation which are often required in preterm children to manage respiratory distress further increase the risks of damage to the developing enamel in primary maxillary incisor teeth.[52]

Children with coeliac disease are also at risk to enamel hypomineralization due to malabsorption and mineral deficiencies associated with gut enteropathy from gluten intolerance.[53,54] Disruption of mineralization pathways as a result of chronic renal and liver disease also places affected children at risk for enamel defects.[55–57] In many infections, the causative microorganisms may infect the ameloblasts directly, or alter cellular function indirectly through their metabolic products or high fevers induced in the patient. Clinical reports have suggested that infections of the urinary tract, otitis and upper respiratory disease are associated with enamel defects.[44] Congenital syphilis acquired from maternal *Treponema pallidum* infections was a well-known cause of enamel hypoplasia in children in past decades.[58] Also, viral infections such as chicken pox, rubella, measles, mumps, influenza and cytomegalovirus have been associated with enamel defects in both the primary and permanent dentitions.[6] An example of an enamel defect caused by an acquired infection is shown in the child in Fig. 2 where meningococcal infection at 16 months of age has led to hypomineralization of the maxillary primary molars.

Chemicals and drugs which can damage ameloblasts include fluoride, tetracyclines and cytotoxic drugs. Enamel hypomineralization resulting from ingesting high levels of fluoride are thought to result from the direct effects of fluoride on the ameloblasts.[59] Environmental exposure to lead paint, or accidental or pica ingestion have also been reported to cause enamel hypoplasia.[6] In addition, intake of tetracyclines during the periods of tooth formation is well known to cause dental discolourations and enamel defects.[60] Although there is some evidence that amoxycillins can cause enamel defects, it is difficult to isolate the effects of the fevers and infections which had necessitated the use of these antibiotics.[61]

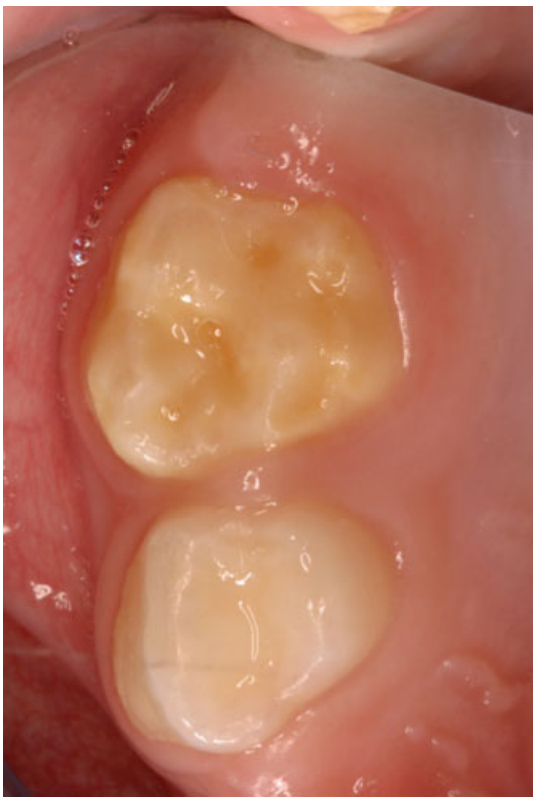

Fig. 2 Photograph of the hypomineralized maxillary primary molar of a child who had a meningococcal infection at 16 months of age.

Local insults to developing teeth

In contrast to systemic factors which usually affect all developing teeth, local factors such as trauma involve only the teeth in the immediate area of damage. For example, trauma exerted on a neonate's maxillary alveolus from laryngoscopy can cause localized defects in the maxillary incisors, ranging from mild enamel opacities to severe enamel hypoplasia to crown dilacerations.[48,62] Similarly, local trauma exerted through the thin buccal cortical bone is thought to be the cause of demarcated opacities commonly observed on the labial surfaces of primary canines.[63]

Molar-incisor hypomineralization

Classification of a type of chronological enamel hypoplasia known as molar-incisor hypomineralization (MIH) was first proposed by Weerjheim and coworkers in 2001 to describe a condition where the permanent molars and incisors show demarcated areas of hypomineralisation or opacities which may be coloured yellow or brownish.[64] In addition, the molar teeth often have posteruptive loss of the weak tooth structure and show high susceptibility to caries. There

is tooth sensitivity and difficulty in achieving adequate anaesthesia for dental treatment.[65,66] Figures 3a–c depict such a case of chronological enamel hypoplasia seen in the affected incisor and molar teeth of a child who had chicken pox at approximately 2 years of age.

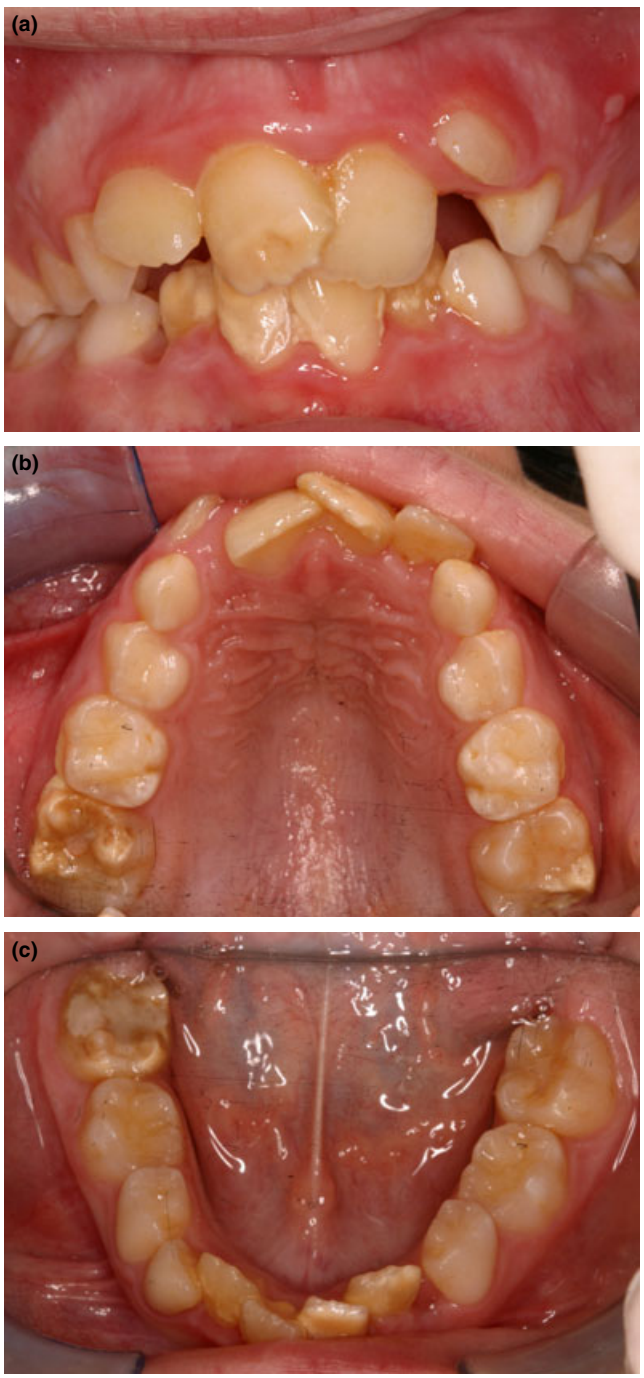

Fig. 3 (a) Photograph of the maxillary right central permanent incisor and all the mandibular incisors of an 8-year-old child showing hypomineralization of the enamel, probably resulting from a chicken pox infection at 3 years of age. (b) Photograph of the maxillary teeth of the child in Fig. 3a showing enamel opacities on the maxillary first permanent molars. The second primary molars also showed very mild opacities. (c) Photograph of the mandibular teeth of the child in Fig. 3a showing a severely broken down hypomineralized right permanent molar. Although the tooth was temporarily restored with glass ionomer cement, an interim restoration with stainless steel crown was inserted at a later date.

Reports of MIH have been mostly from Europe with reported prevalence rates ranging from 3.6% to 37.5%.[64,67] In Australia, 37–47% of first permanent molars were reported to show developmental enamel defects.[68] In other parts of the world, prevalence rates of approximately 40%, 22% and 3% were reported in Brazil, Iraq and Hong Kong respectively.[66,69,70]

Aetiological factors for MIH are thought to be essentially the same as those already known to cause enamel hypoplasia in the permanent dentition such as malnutrition, common childhood illnesses, including chicken pox, otitis media, respiratory and urinary tract infections and use of amoxycillin.[44,67,70] Although environmental toxins such as dioxins have been implicated in the aetiology of MIH, this hypothesis has been questioned in a controlled study.[71] For permanent incisors and first molars to be affected, the timing of occurrence of the insults is likely to be between the period of birth to approximately 3 years of age.[72]

Dental management of children with enamel defects

The need for treatment of enamel defects within the population is considerable.[73] As Table 3 shows, in a series of comparable populations studied using a standardized methodology,[76] some two-thirds of children have an enamel defect, while about 10% have 10 or more defects.[73] Early diagnosis and preventive care are essential for the successful management of developmental enamel defects. Children who have a family history of amelogenesis imperfecta, or medical syndromes that are commonly associated with enamel defects such as epidermiolysis bullosa or cerebral palsy or prematurity of birth should be assessed for enamel defects as soon as the teeth erupt. Also, as enamel formation of the permanent molars and incisors occurs at the same time as the primary molars, the presence of enamel defects in the primary molars indicates a risk for the defects occurring in the permanent dentition.[45] Thus, children with enamel defects in primary molars should have the permanent teeth

Table 3. Prevalence of enamel defects in the permanent dentition of white Caucasian children aged 12–15 years (each study used comparable criteria)

Country	Percent of individuals affected
New Zealand	63%
New Zealand	65%
Ireland	63%
England	68%

Data from Brook and Smith.[73]

monitored for the presence of similar defects. If both dentitions are affected, the possibility of a genetic cause should be considered, and the children referred to paediatric dentists and medical specialists for diagnosis, genetic testing and counselling.

Accurate recording of enamel defects is essential for diagnosis, treatment planning and follow-up. While the majority of previous indices for recording of developmental defects of enamel were employed for epidemiological purposes,[74–76] the Enamel Defects Index (EDI) proposed by Brook *et al.*,[77] was developed mainly for clinical use. The EDI contains a simple backbone and digital scoring which is particularly suited for clinical application and has a high degree of reproducibility.[22,23] Detailed scoring of subtypes of enamel defects is also possible in the extended form of the EDI.[22]

The major clinical problems encountered in children with enamel hypoplasia are compromised aesthetics, tooth sensitivity and increased risk for caries and tooth wear. For children with developmental defects of enamel, a preventive programme should be instituted immediately after diagnosis in order to manage these problems. Children with extensive enamel defects such AI usually require an interdisciplinary management team which includes general practitioners, specialist paediatric dentists and orthodontists. The treatment planning is likely to involve complex restorations, orthodontics, exodontia and prosthodontics.[78–80]

To reduce caries risk in teeth with enamel hypoplasia, neutral sodium fluoride gels or varnishes applied professionally 3 or 6 monthly may be recommended.[81] In addition, calcium and phosphate rich agents such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) can facilitate the remineralization of hypomineralized areas and early carious lesions on the tooth surface of teeth with enamel defects.[82–84] An additional benefit of CPP-ACP is that developmental opacities that compromise aesthetics may appear less noticeable after topical application of CPP-ACP.[85]

As the defective enamel is structurally weak, it readily deteriorates under masticatory stresses and this can result in marginal leakage around restorations, recurrent caries and pulp involvement.[86–88] Materials that can bond to both dentine and enamel such as resin modified glass-ionomer cements and polyacid modified composite resins are likely to be successful for restoration of teeth with enamel defects.[89–91] Although composite resins have good aesthetics, direct adhesion of the composite resins to teeth with minimal or poorly mineralized enamel is usually difficult to achieve.

In contrast to plastic restorations, stainless steel crowns are highly durable for restoring and protecting both primary and permanent molars affected by enamel hypoplasia.[92] Complete coverage of the teeth with stainless steel crowns reduces tooth sensitivity, prevents cusp fractures and helps maintain space and crown height. The crowns are best inserted using a conservative technique with minimal removal of tooth structure.[40,93,94] This method which involves interproximal separation and minimal occlusal surface reduction was proposed by Seow for placement of crowns to protect teeth with large pulps and dentine defects to prevent pulp exposures.[40]

DEVELOPMENTAL DEFECTS OF DENTINE

Dentine is composed of an organic matrix comprising approximately 70% mineral, 20% organic matrix and 10% water.[95] It is produced by the odontoblasts which are specialized, end-differentiated cells which, unlike the ameloblasts, continue to function throughout the life of the tooth. The odontoblasts secrete the dentinal matrix and their processes which are retained in the matrix, communicate with pulpal nerves and serve as a protective defence system.[8]

Dentine is similar to bone except that it does not remodel and does not regulate calcium and phosphate metabolism.[95] The extra-cellular matrix of dentine shares similar proteins with bone.[96] It is rich in Type I collagen, which is assembled as fibrils to form a structural framework for mineralization. Many of the non-collagenous proteins are involved in the initiation and control of the mineralization processes. They are associated with specific sites on collagen molecules, and aid in the nucleation and growth of the hydroxyapatite crystals.[3] Proteins with key roles in the mineralization processes of dentine and bone include members of the phosphoprotein family such as dentine sialophosphoprotein (DSPP), dentine matrix protein 1 (DMP1), bone sialoprotein (BSP), matrix extracellular phosphorylated glycoprotein (MEPE) and osteopontin (OPN).[96] Mutations in the genes coding for the proteins involved in type 1 collagen or in the extracellular matrix as well as in the mineralization processes are thus likely to present as dentine abnormalities. If the proteins involved are common to both dentine and bone such as type 1 collagen, both skeletal and dentine defects will be observed in the phenotype. However, if the proteins are specific to dentine, such as the dentine sialoproteins, the defects will be limited to dentine only.

Inherited conditions showing developmental defects of dentine

Inherited defects of dentine may be grouped into those that affect dentine tissues only and those that show bone involvement together with the dentine defect.

Shield's classification of inherited dentine defects,[97] which is based on clinical phenotypes, has been extensively applied for several decades, although this system is becoming outdated as molecular work provides more accurate linking of genotypes with phenotypes. As shown in Table 2, based on a couple of early studies, the prevalence of developmental defects of dentine range from approximately 1:6000 to 1:8000 for dentinogenesis imperfecta to 1:100 000 for dentine dysplasia[3,14,98] (Table 2).

Dentinogenesis imperfecta

Dentinogenesis imperfecta is the most common type of developmental disorder of dentine.

In Shield's classification, there are three types of dentinogenesis imperfecta (I-III) and two of dentine dysplasia (I and II).[3] Dentinogenesis imperfecta type I is the phenotype seen with a genetic fragile bone condition, osteogenesis imperfecta. Osteogenesis imperfecta is usually caused by defects in the two genes encoding type I collagen. The dentine defects associated with osteogenesis imperfecta often show complex and variable clinical expression. Both dentitions are affected with an opalescent brown discolouration, and due to reduced support of the dentine, the overlying enamel fractures readily. There is rapid wear and attrition of the teeth. There are also variable degrees of progressive pulp obliteration which usually begins soon after eruption of the teeth. Besides osteogenesis imperfecta, dentinogenesis imperfecta type I can also be seen in other conditions such as Ehlers-Danlos and Goldblatt syndromes.[65,99] Figures 4a–c show the typical opalescent appearance of the teeth in dentinogenesis imperfecta, together with severe wear of the teeth to the gingival level.

The second type of dentinogenesis imperfecta (type II) is an autosomal dominant condition with a prevalence rate of approximately 1:8000.[14] It is caused by a mutation in the DSPP gene.[3] The clinical and radiographic features are similar to dentinogenesis imperfecta type I, but are expressed more consistently.[100] Dentinogenesis imperfecta type III is also caused by the same DSPP mutation as type II, but shows variable discolouration and morphology of the teeth, ranging from normal appearing teeth to shell teeth with reduced dentine formation.[3,101] Figures 2a–c show the typical dental opalescence, discolouration and extreme wear observed in a child with dentinogenesis imperfecta type II.

Dentine dysplasia

Dentine dysplasia type I is a rare condition that shows normal appearing crowns and short roots in both primary and permanent dentitions. The pulps are reduced in size, and may have crescent shapes that run parallel to the cemento-enamel junction, and associated with periapical radiolucencies.[3,102] Although the genetic changes are unknown, dentine dysplasia type I is likely to be an allelic disorder of the DSPP gene.[3]

In contrast, in dentine dysplasia type II, while the primary teeth have similar features to dentine dysplasia type I, the permanent teeth appear clinically normal although they often show thistle shaped pulps

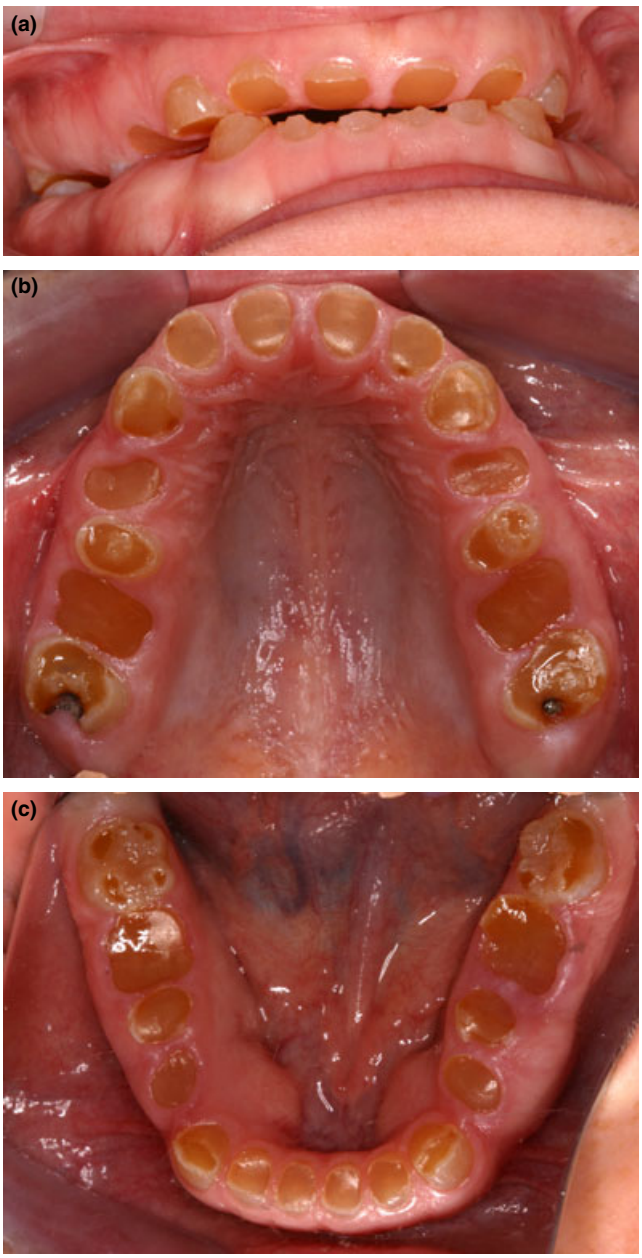

Fig. 4 (a) Photograph of the anterior teeth of a 15-year-old with dentinogenesis imperfecta type II showing typical brown opalescent appearance of the teeth and severe wear. (b) Photograph of the maxillary teeth of the child in Fig. 4a showing extreme wear of the teeth to the level of the gingiva. (c) Photograph of the mandibular teeth of the child in Fig. 4a showing loss of enamel and extreme tooth wear.

with pulp stones.[103] The root lengths are normal and there are usually no periapical radiolucencies. Occasionally, other abnormalities such as dental discolourations, bulbous crowns and pulp obliterations may be encountered. Dentine dysplasia type II is also caused by a mutation in the DSPP gene, and most clinical evidence suggests that it is a mild phenotype of dentinogenesis imperfecta type II.[3]

It is now well accepted that there is usually overlap of clinical features in Shields's classification of dentine defects. In many families showing dentine dysplasia, it is often difficult to place any one in a particular type of classification due to the presence of phenotypic variation among the affected family members. Furthermore, it is possible that dentine dysplasia type II, and dentinogenesis imperfecta types II and III may be varying phenotypic expressions of the same genetic defect.

Rickets

The most well-known condition that shows developmental dentine defects is familial hypophosphataemia, also known as 'vitamin D-resistant rickets' which displays cardinal features of X-linked dominant inheritance and renal phosphate wasting.[40] The condition is associated with reduced reabsorption of phosphate in the renal tubules and characteristic rachitic bone deformities. Other modes of inheritance including autosomal dominant and autosomal recessive modes of inheritance have also been described for familial hypophosphataemia.[104] Although the primary defect of familial hypophosphataemia is found in the PHEX gene which is expressed in osteocytes, the role of this genetic change in phosphate wasting is unclear.[104] A fibroblast growth factor (FGF) with endocrine properties, FGF23, that appears to mediate many of the hypophophataemic conditions has been found to have a major role in this disorder.[105,106] FGF23 is thought to facilitate phosphate supply by aiding the communication between the kidney and the skeletal stores.[104]

In familial hypophosphataemia, the occurrence of 'spontaneous' dental abscesses has led to the initial diagnosis of the condition in a few cases being made by the dentists as the general signs and symptoms of rickets usually are not obvious until the patients are more than 18 months of age.[103] These abscesses often appear initially in toddler children who do not have any history of caries or trauma. Histological examination of the teeth involved in familial hypophosphataemia often reveals poorly mineralized globular dentine, and tubular defects extending close to the dentino-enamel junction.[40,102,107] These defects predispose the pulp to exposures and infection as soon as the enamel is removed, either from minimal caries or attrition (Fig. 5). Enamel hypoplasia of the permanent teeth has been occasionally reported in children with familial hypophosphataemia, although it is unclear whether the enamel defects result primarily from the disease or are secondary to abscesses of the primary teeth.[40] As expected of an X-linked condition, a spectrum of manifestations ranging from minimal to severe has been described, with boys characteristically showing the most severe dental involvement and girls the least.

Management of children with developmental defects of dentine

As with enamel defects, early diagnosis and preventive care are essential for successful management of dentine defects.[108] Children who have a family history of dentine defects such as dentinogenesis imperfecta or those with medical conditions known to be associated with dentine defects such as hypophosphataemia and osteogenesis imperfecta should be screened early for dental problems.

As dentinogenesis imperfecta is associated with rapid toothwear and crown fractures, protection from toothwear is recommended soon after eruption.[108] Also, as some types of dentine defects, e.g. hypophoshataemia, show a high risk for pulpal exposures and infection due to the presence of large pulps, prophylactic coverage of the teeth is necessary to protect the pulp soon after eruption.[40] Covering the teeth with stainless steel crowns soon after eruption has been shown to reduce the risk of pulp exposure in teeth with dentine defects. As for enamel defects, the stainless steel crowns are best inserted using a conservative technique that was developed specially to protect teeth with large pulps.[40,93,94] When the children reach adulthood, the stainless steel crowns may be replaced with gold or porcelain crowns to provide long term protection of the teeth.

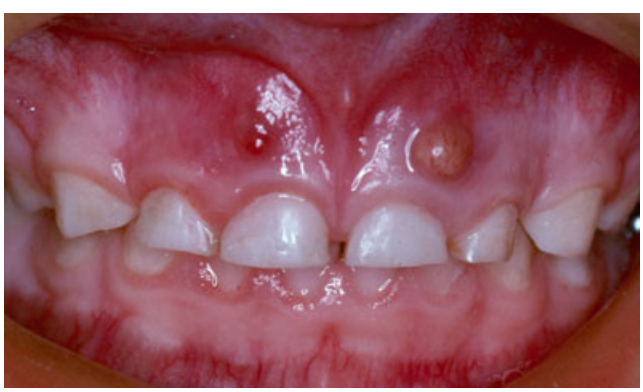

Fig. 5 Photograph of the anterior teeth of a child with X-linked hypophosphataemic rickets depicting abscesses associated with dentine defects and large pulps in the maxillary central incisors.

CONCLUSIONS AND FUTURE DIRECTIONS

Although the clinical significance of enamel and dentine defects is well known, the pathogenesis of the defects is still being studied. While the range of environmental insults that can damage the enamel organ have been identified, the threshold for damage, and the relative susceptibility of the enamel organ at the various stages of development have not been well researched. Furthermore, there is little information on how environmental pertubations interact with the genes that control enamel formation. Therefore, despite major advancement in knowledge regarding the nature of the defects and the genes involved in enamel and dentine defects, further research is required to fill these gaps in knowledge. Additionally, as enamel and dentine defects are currently managed by treating the symptoms, future research should also focus on development of suitable techniques and aesthetic restorative materials that can bond effectively to defects enamel and dentine.

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DISCLOSURE

The author has no conflicts of interest to declare.

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