A Global Compendium of Oral Health

A Global Compendium of Oral Health:

Tooth Eruption and Hard Dental Tissue Anomalies

Edited by

Morenike Oluwatoyin Folayan

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FOREWORD

Just as oral health lacks attention as a key aspect of child welfare around the globe, better recognition is also needed about the importance of dental pathobiology for our understanding of child oral health. This book brings together a global perspective on two pressing issues – anomalies of tooth development and tooth eruption – both uniquely and not a moment too soon. If children's oral health is to be improved worldwide as I'm sure we'd all like, international collaborative efforts exemplified by this book will be pivotal to gaining necessary understanding.

My viewpoint has been shaped over the past decade while establishing a global research and education network focussed on tooth development anomalies, which we refer to as "D3s" (being short for developmental dental defects, or DDDs). Through this network (*The D3 Group*), I've had the pleasure of meeting the editor and several other authors of this book. In all cases I encountered an immediate empathy regarding the "D3 problem" – by which I mean not only the clinical conditions themselves, but also the widespread ignorance about D3s across the healthcare sector and an allied lack of research-based understanding. My initial focus coming from a career in biomedical research was on D3 prevention – that is, What research needs to be done if we're to understand the causes and implement appropriate interventions? Recognizing a major gap in understanding, we embarked on a biochemical investigation of demarcated enamel opacities (being the commonest type of D3 and the defining pathology of Molar Hypomineralization). Our findings provided novel clues about pathogenesis and so opened up an exciting new avenue of etiological investigation. It soon transpired however that education and advocacy were even stronger priorities – for instance, Who would fund major research if the global need for it wasn't clear, and how could research outcomes be "translated" into public good given widespread deficits at healthcare policy and delivery levels? Consequently, *The D3 Group* was launched as a "cross-sector" initiative spanning key stakeholders from academia through healthcare providers to industry and public consumers. This bold mission brought many challenges, not least the need to communicate amongst disparate parties and to make a competitive case for research. We soon learned the importance of gathering opinions from far

and wide, and also from "small fry" as well as (supposedly expert) "big fish". Moreover, anecdote was switched from something I'd rejected in my career as a scientist to being a valuable library for conceptualization. Such holistic collaborations spurred the development of a translational terminology for D3s framed around the public-friendly concept of "chalky teeth". Likewise, we cultivated a socioeconomic argument for research leveraging the stunning but underrated connection between childhood tooth decay and Molar Hypomineralization ("chalky molars"). Having established a working formula across home ground (Australia and New Zealand), *The D3 Group* and its *Chalky Teeth Campaign* were recently opened to international membership and today our "D3 family" has members in 33 other countries. Which takes me back to this book that coincidentally has a similarly diverse international representation.

The compendium provides a comprehensive and well-structured tour of current thinking about tooth eruption and D3s – that is, an impressive 30 chapters dedicated to country-specific perspectives are sandwiched between 5 chapters of generalized introduction and future aspirations. Through this amalgamation, readers will see not just consensus commonalities but also the diversity of country-specific nuances, all of which provides inspiration for research hypotheses and new initiatives to improve healthcare. Importantly, voice is given to several lower-income countries that, despite having at least the same needs as others, are often at risk of being sidelined from research and product-development considerations. This information will be useful for a broad audience including dentistry, medicine, anthropology, evolutionary biology and forensic science. It will be no surprise that the authorship comprises an impressive multi-ethnic raft of academic clinicians and scientists from around the globe, aptly honoring the ubiquity of the problems under consideration. To have assembled such a collective is testament to the networking skills and academic prowess of the editor Morenike Folayan, whose vast publication record includes several impressive studies of Molar Hypomineralization in Nigeria. Being less familiar with the tooth-eruption side of things, a notable eye-opener for me was learning about the diversity of tooth-emergence patterns in different races, with African and Japanese teeth erupting particularly early and late, respectively. Such diversity has immediate practical impacts for age estimation (as routinely done in orthodontics and forensically) as discussed and, I venture, may also hold etiological ramifications for many D3s.

In conclusion, I admire this book both for its important topic and the internationalized collaborative approach taken to address it. The content comprises an unprecedented set of data and expert viewpoints, the latter clearly sharpened by cross-learning accrued during the networked writing process. So, although a cliché, I think this compendium is a great example of the whole being greater than the sum of its parts. If we (as researchers, healthcare providers and policy makers) aim high to improve child oral health substantially, and preferably through prevention, more of such international collaboration and think-tanking will be needed. Hopefully this book will inspire others to follow suit.

Mike Hubbard
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www.thed3group.org, www.chalkyteeth.org

INTRODUCTION TO TOOTH ERUPTION, TOOTH EMERGENCE AND DEVELOPMENTAL DENTAL HARD-TISSUE ANOMALIES

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Introduction

Tooth eruption is a complex and dynamic process that involves the timely action and interaction of cells – osteoclasts and osteoblasts – of the dental enamel organ, follicle, and alveolus (Suri et al., 2004). It is the axial movement of a tooth from its non-functional position in the bone to functional occlusion. Eruption movement occurs in a three-dimensional space, with varying speed, and emerges into a functional position defined by heritable patterns (Marks and Schroeder, 1996). Eruption movement leads to tooth emergence – the time of tooth penetration of the overlying gingiva and its appearance in the oral cavity.

Many animal studies have helped in understanding some of the complex and dynamic processes involved in tooth eruption and emergence. Tooth formation commences with the formation of the mandible and maxilla from the neural crest cells that migrate from various areas on the neural crest of the neural tube. The cells have different molecular origins and different innervations (Kjaer, 2012). Tooth formation then starts from an ectodermal epithelial bud surrounded by regionally specific

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ectomesenchyme in the jaw, referred to as the early tooth primordium (Kjaer, 1998). The odontogenic potential of the epithelium is transferred to the ectomesenchyme (Jussila and Thesleff, 2012) through interaction between the epithelium and the ectomesenchyme, leading to the formation of dental papillae in nonodontogenic, neural crest-derived mesenchymal cells (Mina and Kollar, 1987). The ectomesenchyme in the incisor region, however, differs from that of the molar region (Jussila and Thesleff, 2012), and Wise et al. (2001) cautioned against comparing the rat incisor with the human incisor. There is also a complex process of innervation of the early tooth primordium, which undergoes rapid development, starting from the apical part of the primordium (Kjaer and Nolting, 2008).

Bmp4, Fgf3 and Fgf4 are essential for tooth morphogenesis. The Fgfr2b-mediated epithelial-mesenchymal interaction coordinates tooth morphogenesis and the primordium innervation – dental trigeminal axon patterning with neuroendocrine cells found in the dental epithelium (Kettunen et al., 2007). When axon patterning is defective, there may be the histological absence of the mesenchymal dental follicle, absence of the Tgfβ1, which controls the adjacent Semaphorin 3A-free dental follicle target field, and down regulation of the Sema3A in the dental mesenchyme (Kettunen et al., 2007). Also, the epithelial primary enamel knot fails to express Bmp4, Fgf3 and Fgf4. The importance of tooth innervation in tooth eruption had been demonstrated; when the nerve connection to the teeth is interrupted, eruption stops (Fujiyama et al., 2004).

The critical role of the dental follicle in defining the eruption pathway by bone resorption and alveolar bone formation has been established through multiple animal studies (Marks and Cahill, 1987). Colony-stimulating factor-1, expressed in the dental follicle of erupting teeth, down regulates osteoprotegerin, which is needed for tooth eruption (Wise et al., 2005). Tooth eruption, therefore, depends largely on the signals generated by the dental follicle, which are often inherited patterns. When the epithelium of the crown follicle is inefficient and incapable of initiating resorption of the overlying hard tissue, tooth eruption is arrested (Kjaer, 2014). Tooth eruption is further modulated by the local conditions under which teeth are moved (Kjær, 2014). For example, the quality of the bone tissue surrounding the tooth and factors affecting growth will affect tooth eruption (Helfrich, 2005; Wise et al., 2011).

Factors that affect tooth eruption and emergence

Human studies on tooth eruption and the emergence pattern have been largely limited to clinical and radiographic studies. There is a strong correlation between eruption time and dental maturity: the teeth usually erupt when two-thirds of the tooth-length formation is completed (Haavikko, 1970). There are very few studies showing factors that affect tooth maturation. Yet, the correlation between chronological age and eruption time is weak indicating that the paths for tooth maturation and tooth eruption differ (Kjær, 2014).

The eruption of each of the primary and permanent teeth into the oral cavity occurs over a broad age range. Yet, within this emergence time, there is a significant concurrence on the emergence of individual teeth on either side of the jaw (Wedl et al., 2005) and concurrence on the time of emergence of groups of morphologically similar teeth. The correlation of the time of tooth emergence was reported as higher within tooth groups (incisors, canines and premolars, and molars) than between the groups (Kjær, 2014). While the first permanent molar erupts at about the same time as the central incisors, the eruptions of these two different groups of teeth are not interrelated (Parner et al., 2002).

Genetics, hormonal factors, gender, ethnicity, nutrition and growth parameters, craniofacial morphology, body height and weight are also determining factors for tooth movement from early root formation until teeth appear in the mouth (Kochhar and Richardson, 1998). Also, normal eruption is determined by racial, ethnic, sexual, and individual differences. Liu et al. (1999) reported that heritability is higher for tooth development than for tooth eruption.

Friedlaender and Bailt (1969) reported that Melanesians had an earlier emergence of permanent teeth than European and Asian populations and had a later emergence than African populations. Studies on African population groups have also shown that the teeth of African children emerge earlier than the teeth of Caucasians and Asians. Olze et al. (2007) compared the timing of emergence of a wisdom tooth among Germans, Japanese, and black South Africans and found that emergence was earliest for black South Africans and latest for Japanese. Even within the same population, there are differences: Warren et al. (2017) reported that American Indian children had earlier emergence times of primary teeth than black and white children.

A few studies have reported a relationship between the time of tooth emergence and the weight and height of children, although not all studies concurred. Children who are below average weight and height have later emergence times than those who are within the standard range (Billewicz, 1975). Khan et al. (2011) reported that tall children had delayed tooth emergence irrespective of their weight, while heavy and short children had early emergence. Kutesa et al. (2013), on the other hand, reported that the height of the child had no influence on tooth emergence times, while the influence of weight on tooth emergence times was non-conclusive.

Recent studies have found differences in relationships of height and tooth eruption with the pre-puberty, during puberty and post-puberty periods, as tooth eruption continues even after teeth have reached occlusion (Björk and Skieller, 1983). Tooth eruption and growth of the alveolar process are mutually correlated events (Björk, 1955; Björk, Jensen and Palling, 1956), and growth in height is strongly correlated with jaw growth (Björk and Skieller, 1983). Growth of the alveolar process and gains in height are both slow during the pre-pubertal period. The growth of the alveolar process, however, increases significantly during puberty, during which time tooth eruption is also accelerated. Tooth eruption decelerates during the post-pubertal period when growth in height and growth of the alveolar process end (Kjær, 2014).

Wedl et al. (2005) reported that the sequence of tooth emergence differs significantly in the lower and upper jaw. Tooth emergence in the lower and upper jaw of male and female probands is symmetrical. There is a tendency for earlier tooth emergence in the lower jaw of both sexes. However, the emergence sequence differs between the lower and upper jaws.

The nine-year cohort study by Poureslami et al. (2015) provided conclusive evidence of the link between the time of emergence of the first-appearing primary tooth and the first-appearing permanent tooth. Delay in the emergence of primary teeth resulted in a delay in the emergence of permanent teeth. Correlations have been demonstrated also between root formation and chronological age and between root formation and skeletal age. The correlation is, however, stronger for root formation and chronological age. Grøn (1962) suggested there was the impact of sexual maturation (pre-pubertal period, during puberty, and post-pubertal period) on the effect of height and weight on tooth movement, tooth formation and bone development.

Disturbances of tooth eruption

Delayed tooth eruption: The causes of delayed tooth eruption are not well known, although the most commonly seen disorder of tooth eruption is that caused by mechanical interference. Mechanical interference may result from the presence of supernumerary teeth, crowding, soft-tissue impaction, and, sometimes, odontogenic tumors and cysts. When there is a disturbance of the tooth eruption, the regular development of the craniofacial complex, which is mostly determined by the physiologic process of eruption, is also disturbed (Suri et al. 2004). Among people with supernumerary teeth, 28-60% usually have associated delay in tooth eruption. Failure of emergence of maxillary incisors is caused mostly by a supernumerary tooth (Patchett et al., 2001; Wise et al., 2002; Jung et al., 2017). Odontomas and other tumors in both the primary and permanent dentitions may lead to delayed tooth eruption. Also, tooth emergence might be obstructed by dense connective tissue or acellular collagen covering the tooth. Such a mucosal barrier could be caused by gingival hyperplasia, which might occur because of hormonal or hereditary causes, vitamin C deficiency, or drugs such as phenytoin (Suri et al., 2004).

Malformations, premature loss of primary teeth, traumatic injuries, malocclusions and some systemic diseases also may modify the rate of tooth eruption (Poreslami et al., 2015). When trauma or pathologies occur at the time when tooth formation is ongoing or when tooth emergence is incomplete, there may be cellular changes in the periodontal ligament. Ankylosis can then occur as fusion of cementum or dentine to the alveolar bone. Damages to the primary teeth can cause delay in the eruption of the permanent teeth. Also, crowding and impactions are believed to be the result of arch-length deficiency, which may be an etiologic factor for them (Suri et al., 2004).

Malnutrition is one of the systemic conditions that can lead to delayed tooth eruption. Agarwal et al. (2003) reported that chronic malnutrition extending beyond early childhood correlates with delayed teeth eruption, and most teeth had a one-to-four-month variation from the mean eruption time. The high metabolic demand of the growing tissues might be negatively influenced by malnutrition during the eruptive process (Almonaitiene et al., 2010). Other systemic disorders associated with delayed tooth eruption are craniofacial dysostosis, hypothyroidism, hypopituitarism, and renal symptoms (de la Tranchade, 2003; Martelli-Júnior, 2011). Ramos et al. (2006) reported that delayed eruption may be related to premature birth and not to a delay in dental development.

Many genetic disorders and syndromes are also associated with delayed tooth eruption. Hereditary gene disorders that affect the cells involved with dental tissue formation may result in disturbances of histogenesis, which may result from disorders of congenital metabolism, infections, nutritional deficiencies, and endocrinopathies (Wise et al., 2002). Genetics influence the timing of tooth emergence, with heritability accounting for as much as 96% of the variation (Wise et al., 2002). Responsible genetic mutations have been found for nearly half of the 25 known human syndromic conditions that play a role in tooth eruption disturbances (Sandgren, 1995). Gapo syndrome is associated with delayed tooth eruption (Sandgren, 1995), but the cause of delayed eruption in people with this syndrome is unknown.

Many other factors may cause delay in tooth eruption. These include inadequate expression of various cytokines (epidermal growth factor, transforming growth factor, interleukin-1, and colony stimulating factor-1), lack of an appropriate inflammatory response, and increased bone density that impedes resorption (Suri et al., 2004; Poureslami et al., 2015). Dental anomalies, such as amelogenesis imperfecta (Collins et al., 1999; Aren et al., 2003), dentinogenesis imperfecta, regional odontodysplasia, and dentine dysplasia may also be associated with delayed tooth eruption (Suri 2004).

Retention of the primary teeth: This often occurs as isolated findings in single teeth. The primary molars are most often affected. Retention may result from associated space problems or failure of the dental follicle to initiate resorption of the overlying bone (Beckto et al., 20002; Kjær, 2010). Secondary retention occurs after the molar has emerged. The cause is largely unknown although Raghoebar et al. (1989) identified interradicular ankylosis as a cause of 81% of the cases. This form of ankylosis can rarely be identified radiographically. Several genetic and medical syndromes such as hyper IgE syndrome, also cause ankyloses and retention of the primary canines and the primary molars (Esposito et al., 2012). Secondary ankylosis is of special importance as it may result in the difficulty of the periodontal membrane to adapt naturally during eruption, resulting in the arrest of eruption. İt also leads to retardation in the growth of the alveolar process compared with that of the neighboring teeth (Kjaer, 2014).

Ectopic tooth eruption: The causes of ectopic tooth eruption are multiple. They may be genetic predispositions (Marks and Schroeder, 1996) or may

result from space anomalies, which may be hereditary such as small jaws (Larsen et al., 2010), or acquired such as from early tooth extraction or retained primary teeth. Artmann et al. (2010) suggested there is a correlation between ectopia and morphological ectodermal deviations.

The most common tooth to erupt ectopically is the maxillary permanent canine. The palatal displacement of canines is genetically linked (Peck, Peck and Kaya, 1994) and largely found in dentitions that are late in developing (Becker and Chaushu, 2000). Palatally displaced canines are more prevalent in females (Sacerdoti and Baccetti, 2004) and are associated with malformed teeth (Becker and Chaushu, 2000; Chaushu, Sharabi and Becker, 2002), a reduced vertical relationship, and tooth agenesis (Sacerdoti and Baccetti, 2004). Also, most palatally erupting canines are associated with insufficient space in the dental arch (Jacoby, 1983; Artmann et al., 2010) and deviation of the cranio-skeleton (Caspersen, Christensen and Kjær, 2009; Larsen et al., 2010). The profile of a bucally erupted canine differs from that of a palatally erupted canine, suggesting a different pathway for both types of displacement (Kjaer, 2014).

The ectopic eruption of other teeth, such as the mandibular canine and third molars has also been reported. Transposition, a form of ectopic eruption, is rarely seen in primary dentition, although it is well reported in the permanent dentition (Kjaer, 2014). Transposition is associated with craniofacial alterations of the maxilla (Perk, Perk and Keya, 1994).

Natal and neonatal teeth: These are prematurely erupting teeth (Fauconnier and Gerardy, 1953) arising from a superficial positioning of the tooth germ (Boyd and Miles, 1951), although other etiological factors, such as infection, malnutrition, hypovitaminosis, febrile illnesses, hormonal stimulation and heredity, have been suggested (Cunha et al., 2001). Associated syndromes that have been implicated are Hallerman-Streiff, Ellis-Van Creveld, craniofacial dysostosis, multiple steacystoma, congenital pachyonychia, and Sotos Syndrome (Cunha et al., 2001). Cohen (1984) reported a prevalence of one in every 2000 births, with a predilection for females (Cunha et al., 2001).

Developmental Dental Hard-tissue Anomalies

Developmental defects of the enamel

The laying down of enamel is a gene-determinant activity that occurs in the presecretory, secretory and maturation stages. The presecretory stage is when ameloblasts acquire all the apparatus to enable them to secrete the enamel matrix; the secretory phase is when ameloblasts secrete the entire thickness of the enamel; and the maturation stage is when the ameloblasts allow inorganic ions to be secreted and exchanged for the water and organic contents, resulting in an increase in the inorganic content and the length and width of the enamel prisms.

Amelogenin (*AMEL*), enamelin (*ENAM*), ameloblastin (*AMBN*), enamelicin (*MMP20*), kallikrein (*KLK4*) and tuftelin (*TUFT1*) are the genes responsible for the synthesis of the enamel matrix proteins (Bartlett 2013). Mutations of those genes that play a role in laying down the enamel matrix result in enamel defects. Damage to secretory ameloblasts may also result in enamel defects. When damage occurs during the maturation stage, there is a failure of degradation of some amino acid fractions, leading to organic contaminants residing between the apatite crystals. This contamination can result in the retardation or arrest of further growth of the crystals, which present as bands or patches of chalky, opaque porous enamel (Wong, 2014). Salanitri and Seow (2013) reported that 10% to 49% of healthy children in advanced countries had defects of the emanel in primary dentition and 9% to 63% in permanent teeth.

Demarcated opacities: One form of developmental defect of enamel is that of demarcated enamel opacity. This defect results from trauma to the ameloblasts in either the early or late enamel maturation phase, or results from infection in the secretory or early maturation phases. Trauma can result from an intrusion or lateral luxation of the primary tooth impining on the succedenous tooth. Also, the product of a necrotic primary tooth pulp could be toxic to ameloblasts (Lo, Zheng and King, 2003). Trauma could result from surgery, such as extraction of the primary tooth (Williamson, 1966) or cleft palate repairs (Dixon, 1968).

Suckling, Nelson and Patel (1989) suggest that the cause of the opacity can be determined by the color. Yellow-demarcated opacities result from an insult causing the death of the ameloblasts early in their maturation stage, whereas white-demarcated opacities result from disturbances in secretion in the early and late maturation phases. The insult that causes the

demarcated opacity is also less severe but longer lasting than that responsible for causing hypoplasia. Jälevik and Norén (2000) were unable to substantiate this assertion and suggested that the lesion results from two or more interacting non-specific factors. Suga (1989) on the other hand, felt the defect resulted from disturbances in the degradation of the enamel matrix, which is required for enamel maturation.

Fluorosis: This is a diffuse opacity associated with alterations in the translucency of enamel. It results from a continuous low-grade insult due to the exposure of a daily low dose of fluoride over a period during the secretory phase of amelogenesis. There is also the arrest of enamel maturation characterized by a delayed breakdown of amelogenins, which may become entrapped in the defective enamel (Wong, 2014). The diffuse opacities are subsurface hypo-mineralized defects covered by a well-mineralized outer enamel surface. The lesion appears white. If the insult is confined to the secretory phase of amelogenesis, normal maturation occurs, resulting in translucent enamel even if the matrix is abnormal (Wong, 2014). The pathophysiology of fluorosis is unclear. Suggested mechanisms include the toxic effect of flouride on ameloblasts (Denbesten, Crenshaw and Wilson, 1985); the tight binding of proteins to fluorohydroxyapatite crystal, making proteinolysis difficult (Tanabe et al., 1988); and fluoride inhibition of enamel proteinases (DenBesten and Heffernan, 1989). Dental defects resulting from malnutrition diabetes insipidus and residence at high altitude may mimic fluorosis (Wong, 2014).

Enamel hypoplasia: This is a defect of enamel associated with a reduced thickness of enamel due to the reduced quantity of enamel matrix laid down. It is characterized by pitting of the enamel due to the cessation of ameloblastic activity. The duration of the disturbance is reflected in the width of the band of the defect (Wong, 2014). An insult of ameloblasts occurs during the secretory phase of amelogenesis. The severity of the insult determines the extent of the defect and the translucency of the partially formed enamel (Wong, 2014). High daily doses of fluoride may cause hypoplasia (Suckling and Purdell-Lewis, 1982; Suckling and Thurley, 1984). Other causes are irradiation of the head and neck (Pajari, Lanning and Larmas, 1988), poor respiratory response in the postnatal period (Via and Churchill, 1959), malnutrition, infectious diseases during early childhood, gastrointestinal disturbances, cyanotic congenital heart disease, neurological disorders, renal disorders (Wong, 2014), allergies, and lead poisoning (Hartsfield and Cameron, 2016). Suckling, Herbison

and Brown (1987) were only able to show a relationship between hypoplasia and chicken pox and could not implicate many of the conditions listed here as risk factors for enamel hypoplasia. Wilson and Cleaton-Jones (1978) also found no association between hypoplasia and exothermal fevers, whereas Jackson (1961) considered exanthematous fevers a cause of hypoplasia of the permanent first molars and a risk factor for hypoplasia of other teeth. Urinary tract infections, convulsions and pneumonia have also been associated with hypoplasia (Suckling and Pearce, 1984).

Amelogenesis imperfecta: This is a hereditary defect of enamel, with an estimated prevalence of 1:800 (Bäckman and Holmgren, 1988) to 1:14,000 (Witkop, 1957). The global prevalence is estimated at less than 0.5% (Gadhia et al., 2012). Amelogenesis imperfecta results from the mutation of five genes: *AMEL* (amelogenin), *ENAM* (enamelin), *MMP20* (matrix metalloproteinaise-20), *KLK4* (kallikrein-4) and *FAM83H* (Gadhia et al., 2012). It appears as varying degrees of hypoplasia, hypomineralization or a combination of the two (Winter and Brook, 1975), affecting both the primary and permament dentition. It results from a gene defect inherited as an X-linked, autosomal dominant or autosomal recessive trait (Wright et al., 2003; Kim et al., 2004). Amelogenesis imperfecta is part of a hereditarily determined syndrome complex that affects the structure and appearance of dental enamel in association with intra-oral and/or extra-oral pathologies, such as tooth sensitivity and fragility (Gadhia et al., 2012), and it is less common than acquired enamel defects (Wong, 2014). Associated features include delay in dental eruption, microdontia, deviant crown and morphology, root resorption, short roots, enlarged pulp chamber, pulp stones, dens in dente, tooth agenesis, crowding of teeth, gingival enlargement, gingivitis and periodontitis (Gadhia et al., 2012).

Molar incisor hypomineralization: This is a developmental defect of enamel, which may result from environmental insults such as dioxins and high concentrations of chemical compounds in the atmosphere. Other possible toxins include hypervitaminosis D, chronic lead poisoning, diphosphonate, and polychlorinated biphenyl poisoning (Wong, 2014). Children at increased risk for the lesion are those with low birth weight (Seow, 1996), frequent medical problems at the time of delivery, and respiratory diseases resulting in oxygen deprivation (van Amerongen and Kreulen, 1996). Beentjes, Weerheijm and Groen (2002) could not establish an association between molar incisor hypomineralization and pregnancy-

related and birth-related complications. There is also no clarity about whether it is caused by childhood diseases, therapeutics commonly used for the management of these diseases, or environmental toxins (Hubbard et al., 2017). The suggestion has been made, however, that there is a genetic predisposition to the lesion, with one or more systemic insults leading to its expression (Krishnan and Ramesh, 2018). The sporadic occurrence of distinctively well-delineated hypomineralized enamel lesions (termed "demarcated opacities") on one to all four permanent first molars precludes a simple causal association with systemic disturbances (Hubbard, 2018).

More recently, Mangum et al. (2010) found a correlation between molar incisor hypomineralization and albumin present in blood, tissue fluid, and saliva. It is speculated that albumin inhibits enamel mineralization. Although Farah et al. (2010) demonstrated albumin in both normal enamel and demarcated opacities, the albumin may also have resulted from post-eruptive contamination with blood or saliva (Hubbard et al., 2017). Also, there are suggestions that molar incisor hypomineralization is a phenotype of amelogenesis imperfecta because of the absence of amelogenin in the chalky opacities, thus making it look like a hypocalcification defect (Hubbard et al., 2017).

Molar incisor hypomineralization is a result of an insult to the ameloblasts during the maturation phase of enamel formation (Jasulaityte, Veerkamp and Weerheijm, 2007), causing changes in the organic and inorganic composition of the affected teeth (Alaluusua, 2010). The defect does not result in a reduction in the thickness of enamel but appears as a discoloration of the enamel (white, cream, yellow, or brown), sharply demarcated from normal enamel. However, the post-eruption disintegration of enamel is possible due to masticatory stress. The teeth affected are one or more permanent first molars with or without an effect on the incisors, although effects on the primary second molars have been reported (Elfrink et al., 2014; Temilola, Folayan and Oyedele, 2015). Hypomineralization usually affects the cusp tip and follows the incremental lines to the cemento-enamel junction (Farah et al., 2010).

A pooled global prevalence of 14.2% has been reported (Dave and Taylor, 2018), with prevalences ranging from 2.4% to 40.2% (Jälevik, 2010). The pooled prevalence is highest in South America (18%) and lowest in Africa (10.9%), with the prevalence in countries in Europe ranging from 3.6% to 25% (Weerheijm and Mejàre, 2003). There is no difference in the

prevalence between male and females, and the prevalence is higher amongst children aged ten years or younger than amongst older children (Dave and Taylor, 2018).

Developmental defects of dentine

Dentinogenesis imperfecta: It is the most common type of developmental defect of dentine (Seow, 2014). It is a hereditary disorder caused by various mutations in the dentine sialophosphoprotein gene (Koruyucu et al., 2018, Seymen et al., 2015; Yang et al., 2015), which is inherited in an autosomal dominant fashion, with an associated abnormal dentine structure affecting the primary and/or secondary dentitions (Barron et al., 2008). The loss of scalloping of the dentino-enamel junction allows for easy and early enamel loss and exposure and wear of the dentine. The tooth usually appears opalescent. Three types of anomalies are associated with dentinogenesis imperfecta.

The Shield Type I anomaly is an autosomal dominant lesion resulting from missense mutations of the genes *COL1A1* and *COL1A2* that encode type I collagen (Barron et al., 2008). The clinical features are varied and complex (Seow, 2014). Shield Type II and III anomalies do not have associated bone defects. Type II and III defects are associated with mutations of the dentine sialophosphoprotein gene. The absence of associated bone defects may be due to the low expression level of the gene in bone, molecular redundancy involving other extracellular matrix proteins found in bone, or altered proteolytic processing. It is also possible that associated bone defects go undetected because they are very mild in nature (Barron et al., 2008). Type II lesions are associated with teeth that have bulbous crowns, marked cervical constriction, short roots, or obliterated pulp chambers and root canals. Type III, known as the Brandywine type, is found in the triracial Brandywine population of Maryland (Shapir and Shapira, 2001); the teeth in the primary and permanent dentition have large pulp chambers (Shapir and Shapira, 2001).

Dentine dysplasia: This is a rare genetic disturbance of the radicular (type 1) or coronal (type II) dentine formation associated with the loss of organization of dentine during tooth formation (Kwon and Jiang, 2018). Type 1 is inherited in an autosomal-dominant fashion and affects both the primary and permanent dentitions. The mutation causing the defect is within the *DSPP* gene (Bloch-Zupan, Sedano and Sculy, 2012). The roots are short and may appear more pointed than normal. The pulp is often

completely obliterated in the primary dentition and reduced in space in the permanent dentition (Bloch-Zupan, Sedano and Sculy, 2012). In most cases, the morphology of the crown is normal, but there are few cases in which the crown is small with an aberrant shape. Lesions associated with aberrant crowns are present in those with a splice-site mutation in the *SMOC2* gene (Hartsfield and Cameron, 2016). Dentine dysplasia is associated with premature tooth exfoliation, root fracture (Kwon and Jiang, 2018) and delayed tooth eruption (Bloch-Zupan, Sedano and Sculy, 2012).

Type II dentine dysplasia is also inherited in an autosomal-dominant fashion, with features of the crowns of the primary teeth being like those of dentinogenesis imperfecta Shield Type II. The crown of the prinar tooth is bulbous with cervical constriction, thin roots, and early obliteration of the pulp (Kwon and Jiang, 2018). The permanent teeth appear normal, but the pulp configuration is like a thistle tube, with the pulp chamber enlarged with an apically extended pulp chamber (Kwon and Jiang, 2018) and pulp obliterated with pulp stones (Hartsfield and Cameron, 2016). Type II dentine dysplasia results from a dentine sialophosphoprotein gene missense mutation, which causes the disruption of signal-peptide processing and/or related biochemical events that interfere with dentine formation protein processing. This sequence is like that in dentinogenesis imperfecta Shield Type II, a similarity that suggests that dentine dysplasia type II is a milder form of dentinogenesis imperfecta Shield Type II (Hartsfield and Cameron, 2016).

Developmental defects of cementum

Hertwig's epithelial root sheath is derived from the cervical loop of the enamel organ. The sheath determines root number, shape, and length. Mesenchymal fibroblast growth factor 10 and epithelial growth factor receptors are associated with Hertwig's epithelial root sheath development. Hertwig's epithelial root sheath cells are active in cementogenesis (Luder 2015).

Hypophosphatasia: This is a systemic disorder associated with anomalies of root development (Reibel et al. 2009, Luder 2015). Anomalies associated with cemental formation defects may disrupt the dentition through premature loss of primary and permanent teeth. Hypophosphatasia is characterized by reduction of total serum alkaline phosphatatase activity, excretion of phosphoethanolamine, and defective bone and tooth

mineralization. There is aplasia and hypoplasia of the cementum and abnormal interglobular dentine in the predentine area (Reibel et al. 2009).

Regional odontodysplasia: This is a rare inherited disorder affecting enamel, dentine, root, pulp, and follicle of primary and permanent dentitions. Usually, the teeth on one quadrant of the dentition are affected. The prevalence is unknown. İt is assumed to result from local circulatory disorders, viral infections, teratogenic drugs, neural crest cell defects, vascular defects, irradiation, rhesus incompatibility, local trauma, local somatic mutation, hypophosphatasia, hypocalcemia, hyperpyrexia, nutritional deficiency, circulatory disorders, and idiopathic factors (Koruyucu et al. 2018).

Anomalies of tooth number, size, and shape

Usually, these anomalies are asymptomatic but of significance as they may lead to problems such as delayed eruption, poor esthetic occlusal interference, accidental cusp fracture, interference with the tongue space causing difficulty in speech and mastication, temporomandibular joint pain and dysfunction, malocclusion, periodontal problems, and increased susceptibility to caries (Shresth et al., 2015). Local and systemic disturbances, including genetic disorders associated with any of the over 300 genes responsible for odontogenesis (Thesleff, Keranen and Jernvall, 2001), occurring before or after birth, may be responsible for these anomalies. Recently, the role of heredity in the cause of these anomalies has been examined.

Supernumerary: This refers to an additional tooth that can be seen in either the primary or permanent dentition. The most widely accepted theory about its cause is the hyperactivity theory, which proposes that supernumeraries result from local, independent hyperactivity of the dental lamina. The prevalence of this developmental anomaly ranges from 0.1% to more than 3% (Aly Ahmen et al., 2018). Supernumerary teeth may be associated with tooth agenesis. Also, enamel defects, such as molar incisor hypomineralization tend to be associated with developmental dental hard-tissue anomalies, such as agenesis of second premolars or co-occurrence of tooth agenesis and supernumerary teeth (Koruyucu et al., 2018).

Hypodontia (tooth agenesis): This common dental anomaly is the congenital absence of at least one tooth. Its cause is thought to be multifactorial, with many genetic and environmental factors contributing

to its expression. It is also associated with many syndromes, cleft lip and palate, congenital deformities, and some systemic diseases. Mutations in *MSX1*, *PAX9*, *EDA1*, *WNT10A* and *EDARDD* genes are responsible for isolated hypodontia (Bilgin and Kaya, 2018). In addition to *MSX1* and *PAX9*, the genes *TGFA*, *IRF6*, *FGFR1*, *AXIN2*, *MMP1*, and *MMP20* have been associated with hypodontia, an association suggesting that the lesion fits a polygenic mode of inheritance rather than a single-gene disorder (Küchler et al., 2001; Vieira et al., 2004; 2007; 2008; Callahan et al., 2009). Hypodontia in the primary dentition is less common than in the permanent dentition, with a prevalence of 0.5% to 2.4%. In the permanent dentition, the prevalence ranges from 4% to 6% of the population (Larmour et al., 2005). It is frequently non-syndromic, but may be associated with a syndrome. Abnormalities commonly associated with hypodontia are ectodermal dysplasia, cleft lip and palate, Van der Woude Syndrome, Down syndrome, and others (Lamour et al., 2015).

Concrescence: Concrescence is a rare twinning dental anomaly of the union of juxtaposed teeth in the cementum only – not in the dentine (Gunduz et al., 2006; Mehdizadeh et al., 2016). It is most frequently present in the posterior maxilla, especially the third molar and supernumerary teeth. It is rarely present in the mandible (Foran et al., 2012). Concrescence may be present in either the primary or permanent teeth. Its reported incidence is 0.8% for permanent teeth and 0.2% to 3.7% for primary teeth (Syed et al., 2016). The cause of concrescence is not known, but implicated factors are space restriction during the development of dental follicles, local trauma, excessive occlusal force, or local infection after development (Mehdizadeh et al., 2016). Concrescence may cause complications during dental treatment, including periodontal destruction, alveolar bone fracture, tooth fracture, and sinus opening during extraction (Syed et al., 2016).

Fusion: Fusion (synodontia or false gemination) is defined as the union of two or more separate developing tooth germs at the dentinal level, yielding a single large tooth during odontogenesis when the crown is not yet mineralized. The possible causes of this tooth anomaly include trauma and environmental factors such as thalidomide embryopathy, fetal alcohol exposure, and hypervitaminosis. These anomalies are more common in the anterior region. Approximately 0.1% occur in permanent and 0.5% in primary dentition (Tuna et al., 2009).

Gemination: Geminated teeth (twinning) are similar to fused teeth. They have two crowns or one large partially separated crown with a shared single root and root canal. In geminated teeth, division is usually incomplete and results in a large tooth crown that has a single root and a single root canal. It is difficult to differentiate fusion and gemination, especially if the supernumerary tooth bud is fused with the adjacent one. Although the cause of these anomalies is unknown, it is believed that some physical force or pressure/trauma causes contact between developing teeth, thus producing necrosis of the epithelial tissue that separates them and leads to fusion or gemination (Tuna et al., 2009). Both types of tooth-shape anomalies may result in esthetic problems and, thus, may require endodontic, restorative, surgical, or orthodontic treatment. They can also cause psychological problems, especially in children.

Dens evaginatus: Dens evaginatus is a developmental deviation of a tooth that results in an accessory cusp formation described as an abnormal tubercle, elevation, swelling, extrusion or protrusion in various ways (Levitan and Himel 2006). The projection has enamel covering a dentinal core that contains pulp tissue, possibly a thin pulp horn that can extend various distances up to the length of the tubercle's dentin core (Neville et al., 2002). It most often arises from the occlusal surface of a posterior tooth and primarily from the lingual surface of the associated anterior teeth. Although dens evaginatus was first reported in 1892 and has been documented since 1925, its cause remains uncertain (Leigh, 1925; Kocsis et al., 2002). It is present predominantly in people of Asian descent (Chinese, Malay, Thai, Japanese, Filipino, and Indian populations), with a prevalence of 0.5% to 4.3% in the various populations (Kocsis et al., 2002; Levitan and Himel, 2006). A higher incidence (15%) has been reported in Alaskan Natives and North American Indians (Yip, 1974). These patterns suggest the lesion may be inherited. The association of dens evaginatus with other developmental anomalies, such as shovel-shaped incisors that also occur frequently in Asian populations makes the possibility of inheritance likely (Yip 1974; Levitan and Himel, 2006).

Dens invaginatus: Dens invaginatus is a rare malformation of the teeth, with a wide range of morphological variations. The affected teeth have an enamel and dentine swelling extending into the crown and/or root and sometimes even reaching the root apex, as can be seen radiographically. In addition, the dental crowns may vary in size and form. This anomaly was first described by Ploquet in 1794 in the teeth of a whale (Hülsmann, 1997; Mupparapu et al., 2004). The cause of dens invaginatus

malformation is controversial (Hülsmann, 1997). Rushton (1937) suggested that the cause is embryological, with stimulation of the cells of the enamel organ during development and subsequent proliferation and cell growth. Its reported prevalence in the permanent dentition is 0.3% to 10%, and it has been reported in 0.25% to 26.1% of individuals examined (Alani and Bishop, 2008).

Peg-shaped teeth: This is an undersized, tapered tooth that may be associated with other dental anomalies. The incisal mesiodistal width of the crown is less than the cervical width (Kim et al., 2017; Mittal and Mohandas, 2018). It is linked genetically with tooth agenesis (Izgi and Ayna, 2005; Karatas et al., 2014; Mittal and Mohandas, 2018). Its prevalence is 0.6% to 9.9% in various populations (Devasya and Sarpangal, 2016; Kim et al., 2017; Mittal and Mohandas, 2018).

Tuberculum paramolare: Tuberculum paramolare is defined as an additional tuberculum, localized on the mesio-vestibulo coronal surface of the molar teeth. It is present mostly in the upper second and third molars. Due to its growth potential, it might develop a specific root. The cause is unknown, although it is assumed to be genetic in origin (Kucukerler, 1978).

Taurodontism: Taurodontism is an anatomical developmental anomaly with vertically extended pulp chambers and apical displacement of the root furcation area (Ashwin and Arathi, 2006; Manjunatha and Kovvuru, 2010). Suggested causal factors are the failure of Hertwing's epithelial root sheath to complete root formation and interference in the epithelia-mesenchymatose induction, as well as genetic inheritance (Benazzi et al., 2015). Its overall prevalence has been reported by some (Luder, 2015; Aren et al., 2018) to be 0.25% to 11.3%, but Kırzıoğlu et al. (2018) reported a higher prevalence of 23.8%.

Dilaceration: This is an anomaly in which there is a sharp bend of either the crown or root axis (Andreasen, Sundström and Ravn, 1971). Its reported prevalence is 0.42% to 98%. This wide range of prevalence may be due to differences in its definition, including a mix-up with a smooth physiologic or abnormal curvature of the root (Luder, 2015). Posterior teeth are more frequently affected. Dilaceration of the anterior teeth is often associated with trauma to the primary predecessors at the age of 2-3 years when the crown of the developing permanent tooth lies lingual to the root of the primary predecessor. Its cause in the permanent teeth is not

clear. Intrusive trauma to the primary tooth may cause dislocation of the crown to the lingual side, leading to crown dilaceration. When intrusive trauma occurs at about the age of 4-5 years at a time when crown formation of the permanent successor is largely complete, root dilaceration occurs (Luder, 2015).

Enamel pearls: The enamel is normally limited to the anatomical crowns of the human permanent teeth. If the enamel is present ectopically on the root, especially in the furcation area and close to the semento-enamel junction, it is named enamel pearls or cervical enamel projections (Colak et al., 2014; Mariz et al., 2018). It can be classified into three groups based on its structure: simple, composite, and composite with a pulp chamber. A simple enamel pearl is composed of only enamel; a composite enamel pearl is composed of dentine and enamel; and a composite enamel pearl with a pulp chamber consists of enamel, dentine, and the pulp chamber. The pulp chamber can be an extension of the coronary or root pulp (Rocha et al., 2018). Its cause is unknown. The most plausible hypothesis is that it develops from residues that remain attached to the root surface during the localized formative activity of Hertwig's epithelial root sheath (Colak et al., 2014; Al-Zoubi et al., 2018). Its prevalence is 0.83% to 9.7%. Enamel pearls are rarely found on single-rooted teeth and are more common in molars, especially in second and third maxillary molars, where they are most commonly located in the bifurcation area between the distobuccal and palatal roots (Rocha et al., 2018).

Microdontia: Microdontia is a tooth smaller than the normal size for that tooth in a given population. Localized microdontia is the most common expression. Generalized microdontia is associated with congenital diseases such as hypopituitarism, ectodermal dysplasia or Down syndrome. Radiation therapy to the jaws during tooth development is also an ethiologic factor. The most frequently affected teeth are the maxillary lateral incisor and third molars (Rohilla, 2017).

Macrodontia: Macrodontia is defined as teeth that are larger than normal. It is detected more often in the primary teeth than in the permanent teeth and can be classified into general and local macrodontia. In general macrodontia all the teeth are larger than normal, and there are associated syndromes such as gigantism. Local macrodontia involves a single tooth, which is difficult to keep within the dentition. Double formations, such as fusion or gemination, are not macrodontia (Rohilla, 2017).

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