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Review Article

Dentinogenesis imperfecta: An update

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Abstract

The term *Dentinogenesis Imperfecta* refers to diseases that affect the dental tissue, consisting of enamel or dentin. The disease leads to insufficient quantitative or qualitative enamel and dentin tissue formation, leading to *Amelogenesis Imperfecta* or *Dentinogenesis Imperfecta*, respectively. These diseases have a similar clinical appearance and their differential diagnosis requires good knowledge of their characteristics. They are hereditary, have a great diversity in clinical, radiological and histological appearance and require a long-term and combined treatment plan. Finally, they are often found as part of syndromes and in-depth understanding of their characteristics can help in the early diagnosis of these congenital disorders. A very common metabolic disease, in which incomplete dentinogenesis is found as a subsequent finding in more than 50% of patients, is *Osteogenesis Imperfecta*. In the present work, we have attempted, to review the latest data on *Dentinogenesis Imperfecta*, thus enabling a specialist clinician to more easily diagnose and treat these patients.

Keywords: Amelogenesis, Dentin, Dentinogenesis, Metabolic disease, Osteogenesis

Introduction

The tooth enamel and dentin comprise the basic components of the outer hard structure of the tooth and surround its central part; the pulp. The pulp is the vital part of the tooth as it involves the nerves and blood vessels as well as the connective tissue. This soft tissue is necessary to be protected by the aforementioned hard tissues. Cementum also surrounds the dentin tissue of tooth root, but it is classified with the periodontal tissues.

Enamel is derived from the ectoderm and it is formed by specialized cells, the ameloblasts, during the tooth formation developmental stage. It is a very brittle tissue composed of mostly hydroxyapatite mineral (~96%), water (~3%), and trace organic matrix (~1%)[1,2]. In contrast, dentin, which is derived from the mesoderm is formed by odontoblasts, is a flexible, mineralized tissue composed of 70% (weight%) inorganic material, 20% organic material most of which is collagen type I and other proteins, and 10% fluid[1,2].

Dental disorders are classified according to the affected tissue (tooth enamel or dentin), their specialty (congenital or not), or the mode of hereditary transmission. They are also distinguished in shape and structure disorders such as *Amelogenesis Imperfecta* or *Enamel Hypoplasia*, *Dentinogenesis Imperfecta* I, II and III, type I and II *Dentin Dysplasia* and in a number of disorders such as oligodontia, hypodontia, anodontia, supernumeral teeth etc[1,2].

Amelogenesis Imperfecta

Amelogenesis Imperfecta (AI) is a heterogeneous group of inherited disorders where the production of a defective enamel matrix is observed, in the absence of proper structure

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and chemical composition. It follows many different inherited patterns such as autosomal dominant, autosomal recessive, sex-linked or sporadic. The prevalence of the disease is low and ranges between 1/700 and 1/14,000 depending on the population studied and has a significant effect on the health care system[3,4]. AI has great diversity in its clinical expression. Mutations have been observed in different genes. The main genes that have been associated so far with cases of non-syndromic AI are: a) genes encoding proteins involved in the production and maintenance of the enamel matrix, including amelogenin (*AMELX*), enamelin (*ENAM*), and ameloblastin (*AMBN*), b) genes encoding enamel matrix proteases such as *MMP20* and *KLK4*, c) genes encoding proteins responsible for intercellular or cellular adhesion, such as *ITGB6, LAMB3, LAMA3, COL17A1, AMTN* and *FAM83H*, d) genes encoding transporter proteins; *WDR72* and *SLC*, e) basic regulators of enamelogenesis; *FAM20A* and *DLX3*[3-6].

To date, no correlation between genotype and phenotype has been established. Tooth enamel can be modified in terms of its width, its microstructure or its degree of calcification. Thus, its clinical symptoms range from mild discoloration to complete collapse of the enamel of the tooth. According to the Wiktop categorization[6,7], there are three distinct phenotypes, which are described below.

The Hypoplastic AI type (type I)

In AI of hypoplastic type, a quantitative change of enamel is observed. All barrier is usually affected. The appearance of the teeth is completely typical. Due to the thin enamel shell, there are often no contact points, so large interdental spaces are observed. The color of the teeth initially appears pale yellow, because the dentin projects through the transparent enamel shell, which is soon discarded and followed by absorption of pigments, with a corresponding change in color to brown. There is no pain except for a slight sensitivity to heat. Radiographically, the tooth enamel, due to its thin layer which is up to 1/8 of normal, is usually not shown[6,7].

The Hypomature AI (type II)

The hypomature type results from disturbances in the architectural structure of the enamel prisms. The thickness of the enamel is normal and its surface has a chalk appearance with white, orange or brown color with or without pigments. Its strength is reduced and as it receives chewing forces, its surface collapses in small parts. Radiographically, the tooth enamel presents with approximately the same radiodensity as that is the dentin. This type of AI is its mildest form and is often undiagnosed. Deteriorated aesthetics is the main reason for seeking treatment, in this type[6,7].

Hypocalcified AI type (III)

Hypocalcified type is an inherited heterogeneous developmental disorder of the enamel and affects the entire barrier. It is the most serious form of AI. The clinical characteristics depend on the severity of the lesion. During eruption, the thickness of the enamel is normal. The hypo-calcified enamel, however, has a chalk texture, absorbs pigments, and is very easily discarded. Teeth are very sensitive to temperature, chewing or even brushing. If the condition is not treated in time, symptoms appear from the pulp and the periapical tissues. The teeth are usually yellow-brown. Radiographically, enamel, due to incomplete calcification, provides same or lower radiopacity than the dentin[6,7].

AI-Associated Deficiencies

Other dental abnormalities that may be associated with AI are taurodontism, pulp stones, delayed tooth eruption, anterior open bite or other craniofacial abnormalities[6,8,9]. Surprisingly, no increased rate of caries has been observed in these patients[6]. However, there is poor oral hygiene, increased plaque deposition and gingival hyperplasia. Patients are also characterized by poor aesthetics, intense hypersensitivity and reduction of the vertical dimension of the face, with severity that differs depending on the type[10]. Patients with AI need special dental management from different specialists, such as pediatric dentists, orthodontists, maxillofacial surgeons and prosthodontists and not necessarily in this order. Management is complicated and time consuming because it lasts from the period of the newborn to the restoration of permanent dentition. An important question is the effectiveness of bonding restorations to the defective enamel. From clinical experience so far, even a minimal layer of thin, prism-free enamel seems to be sufficient for satisfying adhesion.

In children and adolescents, direct resin restorations are recommended as they can be easily modified depending on the tooth development and are minimally invasive. Adults are offered indirect rehabilitation where a more comprehensive and invasive therapeutic approach is required[8]. More specifically, in the period of deciduous dentition, the goal of treatment is to ensure the ideal conditions for the smooth eruption of permanent teeth and the normal development of jaw bones. Stainless steel crowns are usually placed in the permanent molars to prevent abrasion of the defective enamel or the development of caries as well as to maintain the vertical dimension of the occlusion. In mixed dentition, the goal is to maintain the teeth, their vitality, the vertical dimension of the face, to reduce the hypersensitivity and to have satisfactory aesthetics. Direct or indirect resin restorations or poly-carboxylic crowns are used in some cases.

In permanent dentistry, the goal is to eliminate hypersensitivity and to restore the vertical dimension of occlusion, the oral function and the aesthetics. The final stage of treatment begins as soon as the clinical height of the crown is established, the periodontal tissues are stabilized and the pulp tissue has receded. The treatment at this stage is multidimensional and involves a multidisciplinary approach of many specialties, depending on the severity, as we mentioned before[8,10].

Dentinogenesis Imperfecta

Dentinogenesis Imperfecta (DI) shows an autosomal dominant pattern of transmission and has high penetrance and a low mutation rate. It affects both deciduous and permanent dentition, although deciduous teeth are usually more severely affected[11]. DI corresponds to a local form of mesodermal dysplasia observed at the stage of histo-differentiation[12,13]. In fact, it is one of the most common autosomal recessive disorders in humans[13-15]. The incidence of the disease is 1 in 8000 births in the United States of America[13]. According to Shields, there are 3 types of DI[12,13,16-18].

Dentinogenesis Imperfecta type I (DGI-I)

Dentinogenesis Imperfecta type I (opaque dentin) (DGI-I) is a rare inherited abnormality of the dentin, with a frequency of 1/6,000 to 1/8,000. It is caused by mutations in the procollagen type I *COL1A1* or *COL1A2* gene and affects both deciduous and permanent dentition[12,13,16,17]. It is associated with *Osteogenesis Imperfecta* (OI).

Dentinogenesis Imperfecta type II (DGI-II)

In Dentinogenesis Imperfecta type II (DGI-II) the characteristics are similar to those of DGI-I, but osteogenesis imperfecta is not a sign. Bulbous molars with marked cervical stenosis are a key feature of the syndrome. It is caused by a mutation in the DSPP gene[12,13,16-18].

Dentinogenesis Imperfecta type III (DGI-III)

Type III Dentinogenesis Imperfecta(DGI-III) is quite similar to the previous two. It is quite rare and has only been found in the Brandywine population in Maryland, USA. The clinical features are various and the new teeth show multiple pulp revelations. It is also caused due to the mutation in the *DSPP* gene as well as the DGI-II type[12,13,16-18]. The *DSPP* gene is located on chromosome 4q21 and encodes the major non-collagenous protein in the dentin matrix. DSPP is converted from proteases to three major proteins, dental sialoprotein, dental glycoprotein and dental phosphoprotein. Mutations in this gene lead to a decrease in DSPP protein and/or improper calcification leading to inadequate dentin mineralization, as well. Alternatively the mutated gene accumulates in the odontoblasts, leading to cell destruction and affecting the process of protein processing or their transport system during the rapid production of dentin matrix[13].

Clinically, the main manifestations of Dentinogenesis Imperfecta are the discoloration of the crown, where the color ranges from amber, yellow, brown, purple or even blue translucent and the intense dental abrasion. The enamel is usually detached leaving the dentin below unprotected, which in turn may become sclerotic with a vitreous appearance and that is the reason why many patients do not complain of hypersensitivity. In cases that are not treated in time, the entire dentition can be abraded up to the gingival contour as well as sometimes there is intense mobility and premature tooth loss[11-13,19].

Radiographically, the teeth are presented with bulbous molars due to the marked cervical stenosis that exists, conical roots with periapical constrictions or even the absence of the root is observed. The density and thickness of the enamel matrix seems normal. The pulp in the early stages of the disease looks abnormally wide but then it is gradually subject to progressive devastation. Pulp stones are also observed in many cases[11-13,19].

Histologically, in normal teeth the dentoenamel juction is scalloped and this special surface helps in the mechanical retention of the two tissues. In Dentinogenesis Imperfecta, this scalloping does not exist leading to a problematic connection of enamel and dentin. Thus, there is an early loss of enamel and exposure to dentin that is subject to severe and rapid abrasion. Mantle dentin may be normal but atubular dentin shows reduced calcification and reduced number of odontoblats. The dental tubules are coarse, sparse and irregular and their total number is less[11,13,15,19].

Conditions with similar clinical and radiographic findings included in the differential diagnosis of Dentinogenesis Imperfecta are[12,13,15]:

- Dentin Dysplasia.
- Amelogenesis Imperfecta- hypocalcified type III that leads to loss of enamel and exposure of dentin.
- Internal discolorations of the dental substance such as congenital erythropoietic porphyria, rhesus incompatibility, tetracycline staining etc.
- Conditions leading to premature tooth loss such as hypophosphatasia, vitamin D-dependent Rickets syndrome, vitamin D-resistant Rickets syndrome, immune deficiency syndromes, etc.

Treatment

The goal of treatment is to maintain the vitality, structure and size of the affected teeth and to achieve satisfactory aesthetics and function in patients, which will improve their eating habits and psychological state. It will also help to maintain the vertical dimension of the face and will allow the smooth development of the jaw bones and the temporomandibular joint[12,13,15,19].

The most important part of the treatment, which is beyond the control of the clinician, is the time that the patient will ask for treatment at the doctor's office. The chances of providing optimal treatment decrease as the patient ages, thus demonstrating the need for early diagnosis[12,13,15,19]. It is worth noting that patients with DI present in primary dentition, it is not necessary to show it in permanent dentition, while the opposite is not true[12]. General Instructions for treatment include the following[12,13,15,19]:

a. In order to prevent excessive loss of the dental structure, it is recommended to place stainless steel crowns on the new permanent posterior teeth, as soon as they erupt.
b. Pulpotomy, when needed.

c. In case of caries below the gingival contour, extraction of the tooth is recommended.
d. The space-maintenance devices are necessary, in case of early tooth loss, until the final treatment plan.
e. Polycarboxylic crowns are recommended as a temporary solution for permanent anterior teeth.
f. Although resin restorations are considered risky in these patients due to insufficient adhesion, it is proposed as a solution for the new anterior permanent teeth with AI.
g. In permanent dentition, the use of porcelain veneers or porcelain crowns, inlays, fixed or removable prosthetic restorations as well as implant restorations are recommended after, of course, the patients reach adulthood.

Frequent examinations are important for the outcome. The treatment plan is selected based on the patient's age, the severity of the problem and the main reason for the patient's visit to the doctor's office. The treatment of mixed and permanent dentition is often challenging and requires the cooperation of many specialties, such as pediatric dentist, orthodontist and prosthodontist[12,13,15,19].

Osteogenesis Imperfecta related with Dentinogenesis Imperfecta

Type I collagen and DSPP are the major organic components of dentin matrix and mutations in the genes encoding these proteins are the leading causes of inherited dentin disorders. DSPP is tooth specific and mutations in its gene lead to individual dental disorders. Type I collagen is an important component of many other tissues such as bone, skin and tendons. Thus mutations in the *COL1A1* and *COL1A2* genes cause syndromic dentin disorders, as occurs in Osteogenesis Imperfecta. Many genes contribute to the production of type I collagen but due to the predominant inheritance pattern more than 80% of the mutations that cause Osteogenesis Imperfecta are mutations in the *COL1A1* or *COL1A2* genes[20]. In inherited dentin disorders, primary dentition is often more severely affected than the permanent and the disorder is therefore obvious from the first years of life. These patients are usually diagnosed with Type II Dental Dysplasia, Type II or III Dentinogenesis Imperfecta, until an episode of bone fracture leads to the right diagnosis, this of Osteogenesis Imperfecta.

Osteogenesis Imperfecta is an autosomal dominant trait of connective tissue, commonly known as "Brittle Bone Disease". Genes that are commonly involved in the pathology of the disease are *COL1A1*, *COL1A2*, *CRTAP* and *LEPRE1*. Based on the most common classification, patients are classified into 4 types, type I which is a mild form of Osteogenesis Imperfecta, type II which is the lethal form, type III which causes progressive limb deformation of the patients and type IV which includes all patients with moderate or severe form of the disease who do not fall into any of the above categories[11,21]. Reduction of synthesis in type I collagen leads to Osteogenesis Imperfecta type I, while quantitative and qualitative changes in collagen type I lead to Osteogenesis Imperfecta type II, III and IV.

The incidence of the disease, according to the literature, varies between 1/20,000[22,23] to 6/10,000[11] newborns while the prevalence is around 4-10/100,000 newborns[11]. The most common clinical sign of the disease is reduced bone mass and frequent bone fractures. Hyperelastic joints, blue sclera, growth retardation and short stature, kyphoscoliosis, early hearing loss are often signs of the disease. Also craniofacial disorders such as macrocephaly, mid-face hypoplasia and subsequent skeletal class III malloclusion and unilateral or/and bilateral crossbite as well as Dentinogenesis Imperfecta are quite common[11,21-23]. More precisely, Dentinogenesis Imperfecta occurs in over 50% of patients with Osteogenesis Imperfecta[11].

Other genetic syndromes show manifestations in the oral cavity and specifically in enamel and dentin, giving the image of Dentinogenesis Imperfecta. Clinical Image of Amelogenesis Imperfecta is found tricho-dento-osseous syndrome, nephrascalosis/McGibbon Syndrome, Blister Epidermolysis Syndrome, Bartter Syndrome and others, the extensive report of which goes beyond the scope of this review[24-26].

Other genetic syndromes that ,except the systematic symptoms, show abnormalities in Dentin are Hypophosphatemic Rickets, Hypophosphatasia, Familial Tumoral Calcinosis/Hyperostosis-Hyperphosphatemia Syndrome, Goldblatt syndrome, Schimke's immunoosseous dysplasia, Ehler- Danlos syndrome[21,23,27-29].

When the clinician notices any of the symptoms of Dentinogenesis Imperfecta during the dental examination, he should be vigilant for the presence of any concomitant symptoms suggestive of enamel or dentin syndromic disorders because these patients require further evaluation and a different and multi-disciplinary treatment.

Conclusion

Dentinogenesis Imperfecta is a common disease, known for years that affects dental tissue, whether tooth enamel or dentin, and can be diagnosed as a primary disease or as part of a genetic or metabolic disease. For example, Dentonogenesis Imperfecta is a very common clinical finding in patients with Osteogenesis Imperfecta. It is a disease with great clinical diversity and deep knowledge in the subject leads to early diagnosis and correct assessment of some serious and rapidly evolving metabolic bone diseases. The latest progress in the field of biology and genetics made easier the early diagnosis of the disease, the identification of the responsible genes, which helps to identify its inheritance pattern and if it is part of other syndromes or not. Moreover, this new genetic insight can translate into improved patient care in the short term and will promote the development of new therapeutic strategies.

References

1. Nanci A. Ten Cate's oral histology-e-book: development, structure, and function: Elsevier Health Sciences; 2017.
2. Bath-Balogh M, Fehrenbach MJ. Illustrated Dental Embryology, Histology, and Anatomy-E-Book: Elsevier Health Sciences; 2014.
3. Smith CEL, Poulter JA, Antanaviciute A, Kirkham J, Brookes SJ, Inglehearn CF, et al. Amelogenesis Imperfecta; Genes, Proteins, and Pathways. Frontiers in physiology 2017;8:435.
4. Lu T, Li M, Xu X, Xiong J, Huang C, Zhang X, et al. Whole exome sequencing identifies an AMBN missense mutation causing severe autosomal-dominant amelogenesis imperfecta and dentin disorders. International journal of oral science 2018;10(3):26.
5. Smith CE, Murillo G, Brookes SJ, Poulter JA, Silva S, Kirkham J, et al. Deletion of amelotin exons 3-6 is associated with amelogenesis imperfecta. Human molecular genetics 2016;25(16):3578-87.
6. Toupenay S, Fournier BP, Maniere MC, Ifi-Naulin C, Berdal A, de La Dure-Molla M. Amelogenesis imperfecta: therapeutic strategy from primary to permanent dentition across case reports. BMC oral health 2018;18(1):108.
7. Adorno-Farias D, Ortega-Pinto A, Gajardo P, Salazar A, Morales-Bozo I, Werlinger F, et al. Diversity of clinical, radiographic and genealogical findings in 41 families with amelogenesis imperfecta. Journal of applied oral science: revista FOB 2019;27:e20180359.
8. Alachioti XS, Dimopoulou E, Vlasakidou A, Athanasiou AE. Amelogenesis imperfecta and anterior open bite: Etiological, classification, clinical and management interrelationships. Journal of orthodontic science 2014;3(1):1-6.
9. Arshad M, Shirani G, Mahgoli HA, Vaziri N. Rehabilitation of a patient with amelogenesis imperfecta and severe open bite: A multidisciplinary approach. Clinical case reports 2019;7(2):275-83.
10. Chen CF, Hu JC, Bresciani E, Peters MC, Estrella MR. Treatment considerations for patient with Amelogenesis Imperfecta: a review. Brazilian dental science 2013;16(4):7-18.
11. Biria M, Abbas FM, Mozaffar S, Ahmadi R. Dentinogenesis imperfecta associated with osteogenesis imperfecta. Dental research journal 2012;9(4):489-94.
12. Surendra P, Shah R, N MR, Reddy VV. Dentinogenesis Imperfecta : A Family which was Affected for Over Three Generations. Journal of clinical and diagnostic research: JCDR 2013;7(8):1808-11.
13. Syriac G, Joseph E, Rupesh S, Mathew J. Complete Overlay Denture for Pedodontic Patient with Severe Dentinogenesis Imperfecta. International journal of clinical pediatric dentistry 2017;10(4):394-8.
14. Bencharit S, Border MB, Mack CR, Byrd WC, Wright JT. Full-mouth rehabilitation for a patient with dentinogenesis imperfecta: a clinical report. The Journal of oral implantology 2014;40(5):593-600.
15. Goud A, Deshpande S. Prosthodontic rehabilitation of dentinogenesis imperfecta. Contemporary clinical dentistry 2011;2(2):138-41.
16. Wang SK, Chan HC, Rajderkar S, Milkovich RN, Uston KA, Kim JW, et al. Enamel malformations associated with a defined dentin sialophosphoprotein mutation in two families. European journal of oral sciences 2011;119 Suppl 1(Suppl 1):158-67.
17. Napierala D, Sun Y, Maciejewska I, Bertin TK, Dawson B, D'Souza R, et al. Transcriptional repression of the Dspp gene leads to dentinogenesis imperfecta phenotype in Col1a1-Trps1 transgenic mice. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 2012;27(8):1735-45.
18. Devaraju D, Devi BY, Vasudevan V, Manjunath V. Dentinogenesis imperfecta type I: A case report with literature review on nomenclature system. Journal of oral and maxillofacial pathology: JOMFP 2014;18(Suppl 1):S131-4.
19. Akhlaghi N, Eshghi AR, Mohamadpour M. Dental Management of a Child with Dentinogenesis Imperfecta: A Case Report. Journal of dentistry (Tehran, Iran) 2016;13(2):133-8.
20. Yang J, Kawasaki K, Lee M, Reid BM, Nunez SM, Choi M, et al. The dentin phosphoprotein repeat region and inherited defects of dentin. Molecular genetics & genomic medicine 2016;4(1):28-38.
21. Foster BL, Ramnitz MS, Gafni RI, Burke AB, Boyce AM, Lee JS, et al. Rare bone diseases and their dental, oral, and craniofacial manifestations. Journal of dental research 2014;93(7 Suppl):7S-19S.
22. Shetty SR, Dsouza D, Babu S, Balan P. Osteogenesis Imperfecta (Type IV) with Dental Findings in Siblings. Case reports in dentistry 2011;2011:970904.
23. Opsahl Vital S, Gaucher C, Bardet C, Rowe PS, George A, Linglart A, et al. Tooth dentin defects reflect genetic disorders affecting bone mineralization. Bone 2012;50(4):989-97.
24. Kumar ACV, Alekya V, Krishna M, Alekya K, Aruna M, Reddy MHK, et al. Association of Amelogenesis Imperfecta and Bartter's Syndrome. Indian journal of nephrology 2017;27(5):399-401.
25. Bhesania D, Arora A, Kapoor S. Enamel renal syndrome with associated amelogenesis imperfecta, nephrolithiasis, and hypocitraturia: A case report. Imaging science in dentistry 2015;45(3):181-5.
26. Al-Batayneh OB. Tricho-dento-osseous syndrome: diagnosis and dental management. International journal of dentistry 2012;2012:514692.
27. Hoddinott P, Craig LC, Britten J, McInnes RM. A serial qualitative interview study of infant feeding experiences: idealism meets realism. BMJ open 2012;2(2):e000504.
28. Wray J. Hoddinott P, Craig LCA, Britten J et al (2012). 'A serial qualitative interview study of infant feeding experiences: idealism meets realism'. BMJ open, 2: 000504. The practising midwife 2013;16(3):32-4.
29. Luo E, Liu H, Zhao Q, Shi B, Chen Q. Dental-craniofacial manifestation and treatment of rare diseases. International journal of oral science 2019;11(1):9.