

Heritable Dentin Defects: Nosology, Pathology, and Treatment

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Heritable dentin defects have been divided into 2 main categories: dentinogenesis imperfecta (DI) and dentin dysplasia (DD). Recent studies have shown that they share many features in common. Of the connective tissue diseases, only osteogenesis imperfecta (OI) has been linked to these disorders. So far, no definitive relation between the type of OI and the dental involvement can be established. Familial occurrence of DI with OI cannot be comprehensively explained by mutations in type I collagen genes. No information about the gene defects in DD is available. At the ultrastructural level, the organization of the normally cross-striated collagen fibers in the dentin matrix varies markedly in patients affected by DI. © 1993 Wiley-Liss, Inc.

KEY WORDS: dentinogenesis imperfecta, dentin dysplasia, type I collagen genes

INTRODUCTION

In the current classification of human heritable dentin defects 2 main groups are recognized: dentinogenesis imperfecta (DI) and dentin dysplasia (DD) [Shields et al., 1973]. DI is further divided into types I–III and DD into types I and II. Focal odontoblastic dysplasia, possibly representing type III DD [Eastman et al., 1977] and fibrous dysplasia of dentin [Bixler, 1976] have not been included in the classification.

With the exception of osteogenesis imperfecta (OI), no other generalized connective tissue disorders have been associated with these defects of dentin. Recently, a large family with isolated DI and possibly Ehlers-Danlos syndrome type II has been described [Komorowska et al., 1989]. The classification of heritable dentin defects is essentially based on clinical and morphological findings. It should also be emphasized that DD and DI share

many clinical, radiographic, and histopathological features in common. The classification proposed by Jorgenson [1989] includes both isolated dentin dysplasias (types II and III DI, types I and II DD in the Shields classification; fibrous dysplasia of dentin) and those associated with other defects. However, the need for revision of the classification of dental defects has been questioned [Witkop, 1989].

The mode of inheritance appears to be autosomal dominant in both DD and DI. Type II DI occurring as a single trait has been linked to the Gc locus on human chromosome 4 [Ball et al., 1982]. The information of known mutations in collagen genes and their phenotypic effects in OI is increasing, but so far, no definitive relation between the type of OI and the manifestations of the dental defects can be established.

DIFFERENTIATION OF ODONTOBLASTS

The organic matrix of dentin is produced by odontoblasts derived from the dental mesenchyme. Cell differentiation and morphogenesis of the developing tooth are dependent on sequential inductive tissue interactions [Kollar and Baird, 1970; Thesleff and Hurmerinta, 1981]. The role of type I collagen during organogenesis has been studied in the Mov13 mouse mutant [Kratochwil et al., 1986; Schwarz et al., 1990]. The $\alpha 1(I)$ collagen gene carrying a retroviral insert is transcriptionally silent in most tissues but this mutant gene is expressed in odontoblasts and possibly mandibular osteoblasts [Kratochwil et al., 1989] suggesting tissue-specific differences in the regulation of the $\alpha 1(I)$ collagen gene expression [Schwarz et al., 1990]. The findings on molecular changes in the dental mesenchyme [Thesleff et al., 1990] support the regulation of step-by-step activation of new cell type-specific genes (possibly only transiently expressed) by sequential epithelial-mesenchymal interactions.

DENTIN DYSPLASIA

Type I

The major radiographic findings in type I DD, also known as radicular type, include pulpal obliteration in primary dentition, crescent-shaped remnants of pulp chambers with denticles in permanent teeth, periapical radiolucencies of unknown etiology, and most characteristically, defective root development [Shields et al.,

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1973; Witkop, 1975; Steidler et al., 1984]. With the exception of mantle dentin (the initial dentin layer subjacent to the enamel of epithelial origin), the dentinal tubules run irregularly in both primary and permanent teeth. This condition is a consequence of the disintegration of Hertwig's epithelial root sheath and the subsequent migration of epithelial cells to the dental papilla and induction of synthesis of dentin matrix [Witkop, 1990].

Type II

In the primary dentition, type II DD (coronal dentin dysplasia) shares some common features with type I DD, but in the permanent dentition, thistle-tube-shaped pulp chambers with denticles are observed (Fig. 1) [Shields et al., 1973; Witkop, 1975; Steidler et al., 1984; Ranta et al., 1990]. Interestingly, similar dental findings have been described in association with OI [Lukinmaa et al., 1987; Levin et al., 1988]. Histologically, the pathway of the dentinal tubules in primary teeth is irregular. In the permanent teeth, the coronal dentin exhibits a regular tubular pattern, but at the level of enamel-cementum junction, there is an abrupt transition to irregular radicular dentin (Fig. 2a,b) [Steidler et al., 1984; Ranta et al., 1990].

The abnormal dentin matrix has been reported to stain positively for reticulin, suggesting the presence of type III collagen [Witkop, 1989]. Type III collagen is not a normal matrix component of mineralized dentin [Linde, 1989]. Whether type III (pro)collagen is present in normal predentin (nonmineralized dentin matrix next to pulp tissue) is somewhat controversial [Cournil et al., 1979; Thesleff et al., 1979; Wright and Leblond, 1980; Becker et al., 1986; Takita et al., 1987; Andujar et al., 1988]. In type II DD, type III collagen could not be demonstrated using specific antibodies to type III collagen and the N-terminal propeptide of type III procollagen [Ranta et al., 1990].

At present, no information about the gene defect(s) in dentin dysplasias is available.

DENTINOGENESIS IMPERFECTA

Types I and II

Type I DI has been defined to the dental defect(s) associated with selected types of OI [Shields et al., 1973; Sillence, 1988]. Segregation of type II DI, or hereditary opalescent dentin, as an isolated trait has been substantiated by extensive studies [Bixler et al., 1969; Miller et al., 1973; Vikkula et al., 1992].

Clinical and radiographic findings in both types are similar, but the manifestations of type I appear to be more varied [Shields et al., 1973; Levin, 1981]. Both dentitions are affected and the color of the teeth varies from brown to blue. Unaffected enamel tends to crack off and consequently, the exposed defective dentin will wear very rapidly. The crowns are bulbous and cervical constrictions at the cemento-enamel junction are pronounced. Initially, pulp chambers may be abnormally wide ("shell-teeth"), but they will progressively obliterate (Fig. 3a-c).

Histologically, in most cases the structure of the mantle dentin is normal, whereas in the circumpulpal dentin, the dentinal tubules are coarse and branched. They run irregularly and the total number of tubules is reduced. Pronounced lamination, cellular inclusions and wide structures resembling canals, and even capillary loops can be found (Fig. 2c,d). Some of these features have been suggested to be unique to type I DI [Witkop and Rao, 1971].

It has become evident from transmission electron microscopic studies that in different patients with OI associated with DI, and even in different areas of a given tooth, the organization of the fibers forming the collagenous dentin matrix is characteristically varied (Fig. 4a-d). The presence of atubular areas in dentin is, however, a consistent finding.

There are a number of observations indicating that in different OI syndromes both collagenous and noncollagenous constituents of the dentin matrix may be abnormal. The presence of type III collagen in affected

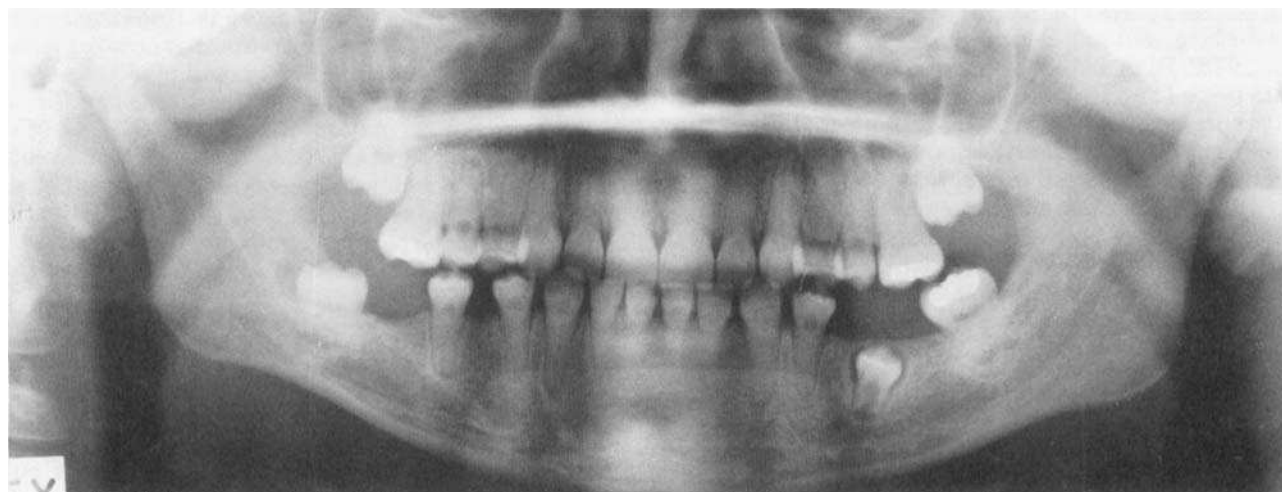


Fig. 1. Panoramic tomogram of a 12-year-old boy affected by type II dentin dysplasia and coincidental hypodontia. In the thistle-tube shaped pulp chambers denticles can be observed.

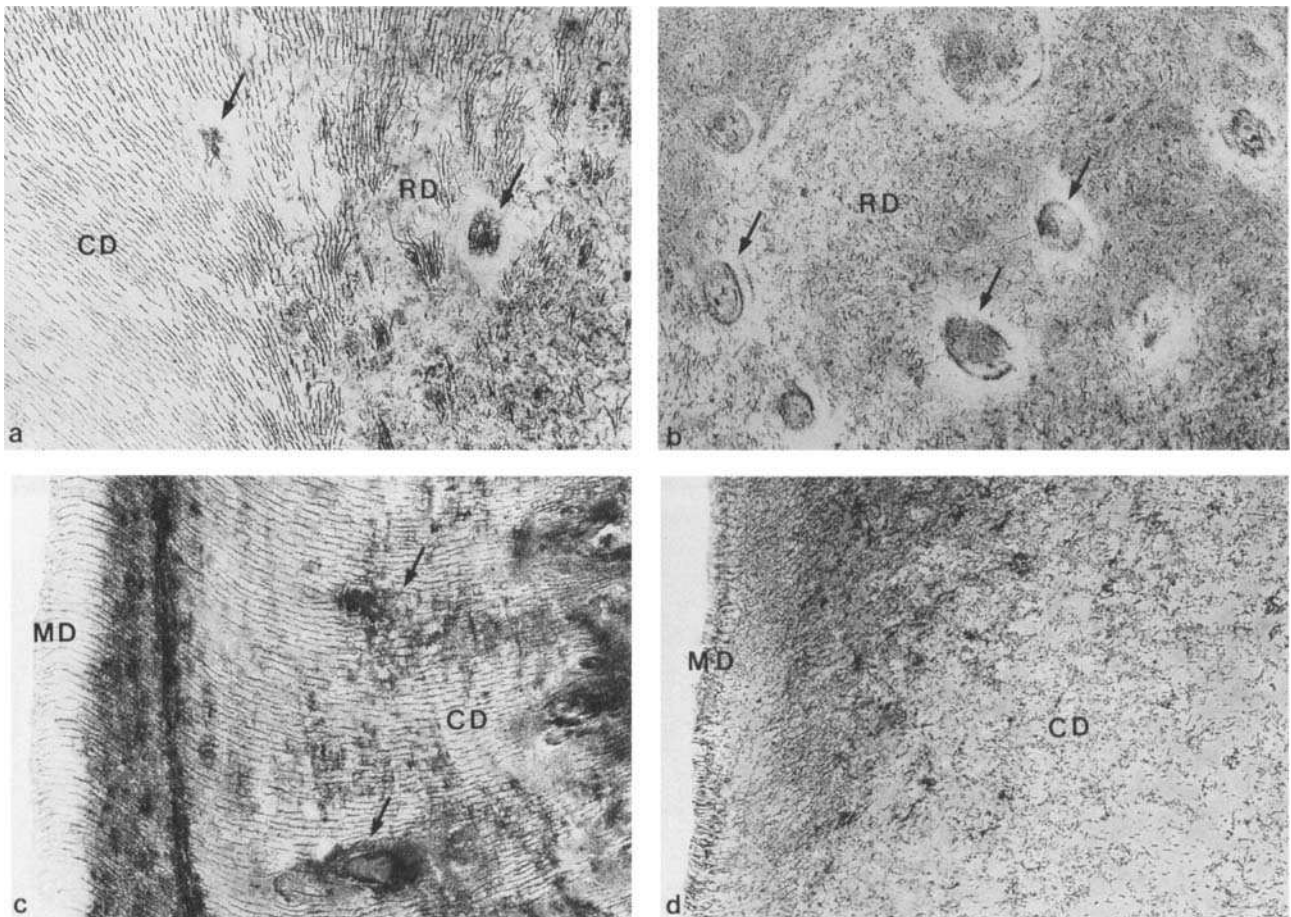


Fig. 2. Photomicrographs of demineralized longitudinal sections of human permanent teeth affected by heritable dentin defects. Abbreviations: dentin dysplasia, DD; dentinogenesis imperfecta, DI; osteogenesis imperfecta, OI. **a:** In type II DD, the coronal dentin (CD) is normal, whereas the radicular dentin (RD) displays an irregular tubular pattern and wide, pathological canal-like structures (arrows), which are also seen in **b**. **c:** In type I DI (type IVB OI), the coronal mantle dentin (MD) is normal; in the circumpulpal dentin (CD), the course of the tubules is slightly aberrant, and canal-like structures (arrows) are also seen. Note the lamellar structure of dentin. **d:** In type II DI (single trait), the tubular pattern in the coronal mantle dentin (MD) is regular; in the circumpulpal dentin (CD), only occasional tubules are seen. Schmorl's picrothionin stain; original magnification, $\times 116$.

dentin in type I DI has been demonstrated both immunohistochemically [Sauk et al., 1980; Lukinmaa, 1988] and biochemically [Gage et al., 1986]. Abnormalities of noncollagenous dentin constituents include changes in the amount of different glycosaminoglycans [Brown et al., 1975], presence of fibronectin [Lukinmaa et al., 1988] and depletion of dentin phosphoprotein content in human [Takagi and Sasaki, 1986] as well as in bovine teeth [Termine et al., 1984]. Furthermore, reduced amounts of lysine and increased ratio of hydroxylysine to lysine have been observed even in clinically normal teeth [Gage et al., 1986]. Whether these changes are secondary to the primary defect of type I collagen remains to be clarified.

While an association between dentin phosphoprotein gene locus and types II and III DI has been excluded [MacDougall et al., 1992], studies suggest that dentin in type II DI is deficient in phosphophoryn [Takagi et al., 1983; Veis, 1985; Takagi and Sasaki, 1986], the major

dentin phosphoprotein contributing to the mineralization [Weinstock and Leblond, 1973; DiMuzio and Veis, 1978a,b; Sauk, 1990]. Thus, types I and II DI have been suggested to share a common disturbance in the differentiation of odontoblasts [Takagi and Sasaki, 1988; Sauk, 1990].

Type III

Separate type III DI was first described in a triracial isolate in Brandywine, Maryland [Hursey et al., 1956; Witkop et al., 1966]. The clinical features closely resemble those of type II DI. The major radiographic finding is the diminished width of mineralized dentin giving the teeth of selected patients a shell-like appearance. Eventually, the pulp chambers will become obliterated with age, as also observed in types I and II DI. These findings are suggestive of a profound disturbance in the regulation of dentin matrix formation and deposition in all 3 types of DI.

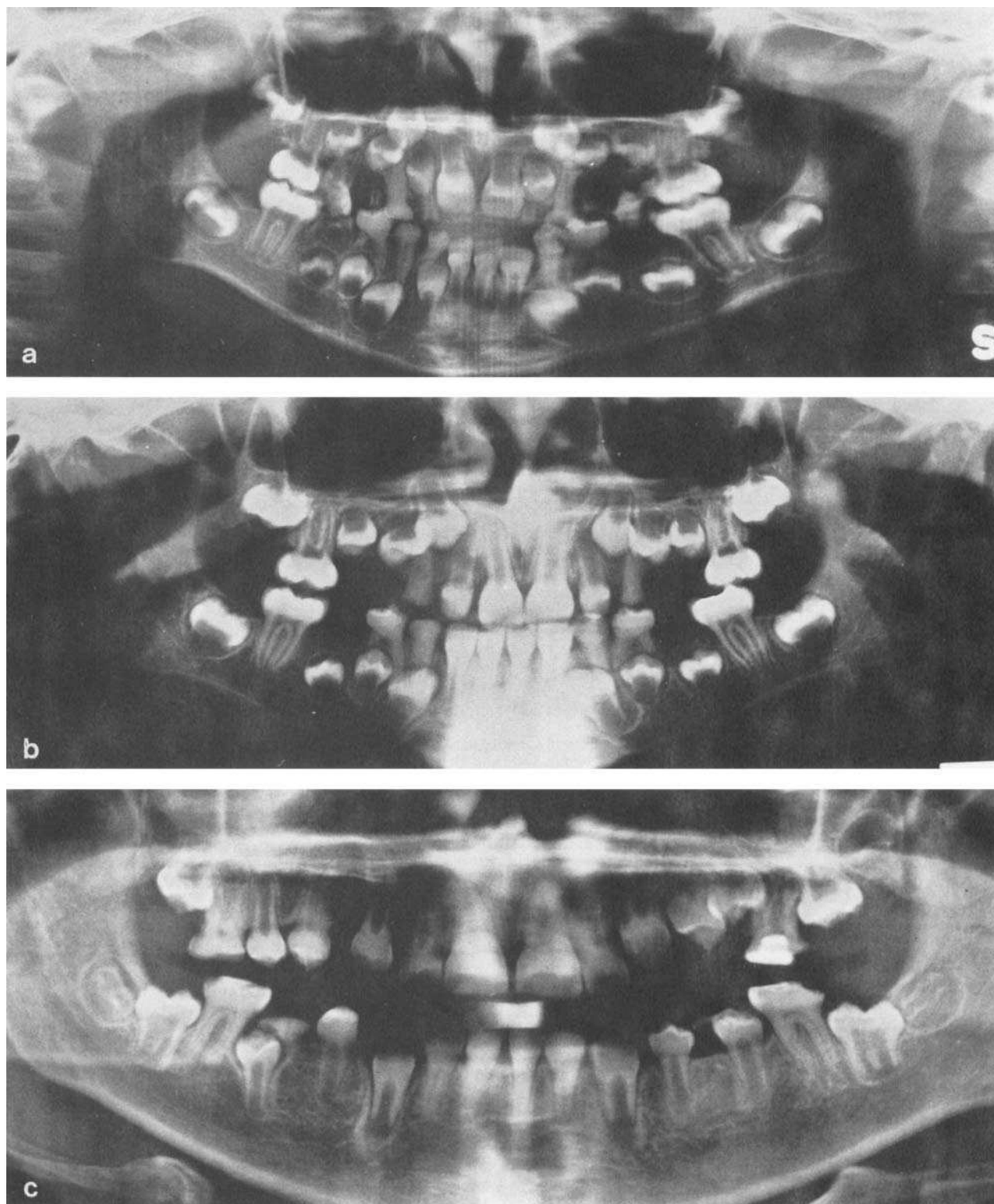


Fig. 3. Sequential panoramic tomograms of a boy affected by type IVB osteogenesis imperfecta and type I dentinogenesis imperfecta at the ages of 6 (a), 8 (b), and 12 years (c). Gradual obliteration of pulp chambers is clearly seen in the permanent dentition.

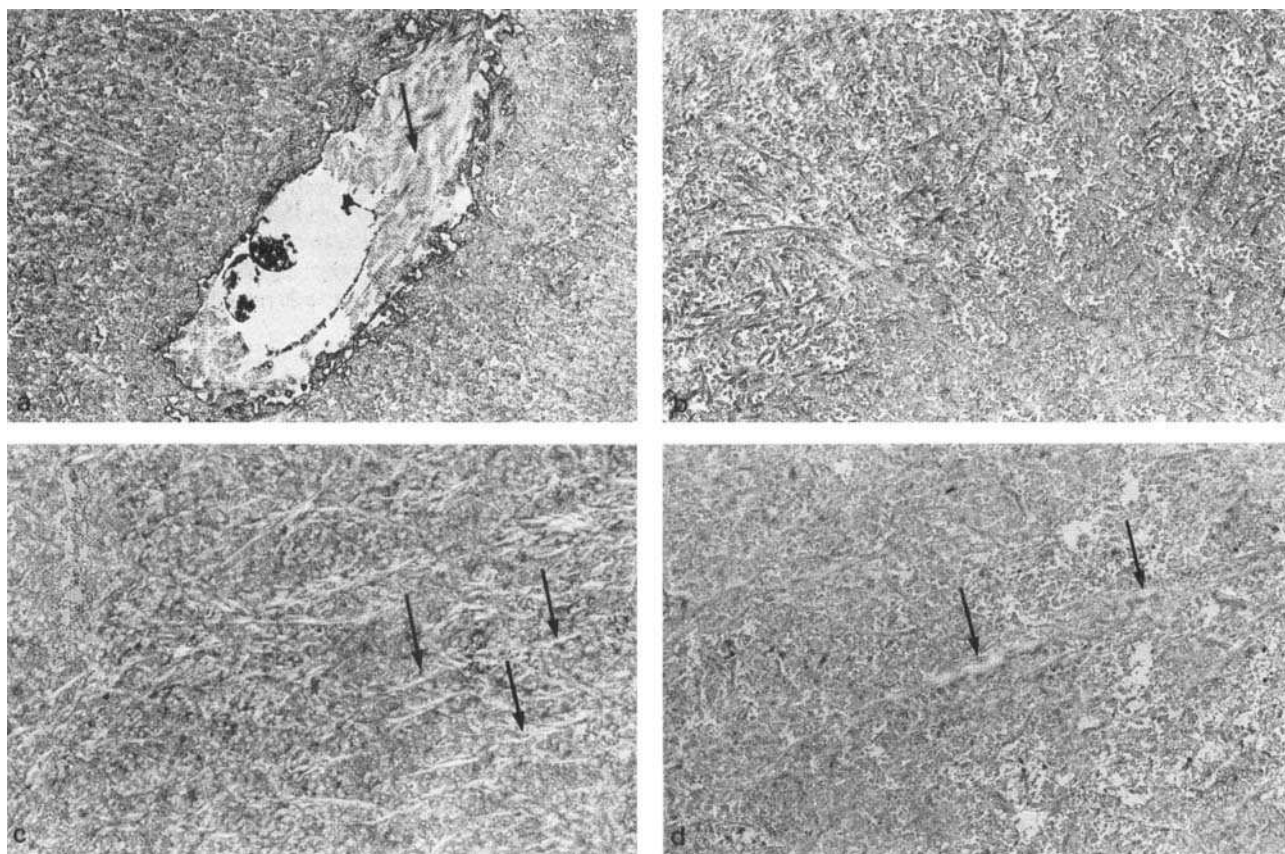


Fig. 4. Transmission electron microscopic appearance of demineralized dentin of deciduous teeth from patients with type I dentinogenesis imperfecta associated with different types of osteogenesis imperfecta (OI). **a, b:** Type IB OI. **a:** A coronal dentin tubule with peritubular cross-striated collagen fibers (arrow) and electron dense remnants of the intratubular contents are seen. Panel **b** illustrates an atubular area of root dentin of the tooth seen in **a**. **c:** Type III OI; in the atubular dentin occasional parallel collagen fibers (arrows) are present. **d:** Unclassifiable OI; atubular dentin also contains collagen fibers of increased thickness (arrows). Original magnification, $\times 7,800$.

DENTAL INVOLVEMENT IN OSTEOGENESIS IMPERFECTA

The clinical manifestations of OI include a wide variety of extraskeletal abnormalities involving tissues rich in type I collagen. To date, several aberrations of type I collagen at the structural and the genomic levels have been specified in patients and families with different types of OI and the molecular basis of clinical heterogeneity relating mutation to phenotype has been intensely studied [Byers et al., 1988; Byers, 1989]. However, the current classification into 4 main types and several subtypes is based on clinical and radiographic findings [Sillence, 1988].

It is well established that the dental defect associated with OI, designated as type I DI in the Shields classification, segregates in some families with OI only. Types I and IV OI, both inherited as autosomal dominant traits, can be subdivided into type A without DI and type B with DI [Levin et al., 1978, 1980; Sillence, 1982]. Based on unusual dental findings resembling those of type II DD in a large family with type I OI, further heterogeneity has been suggested [Levin et al., 1988]. In addition,

the presence or absence of type I DI may imply heterogeneity in a perinatally lethal form of OI [Levin et al., 1982]. Within type I OI, a minority of patients have DI and they have been reported to be more severely affected than those without any dental defect [Paterson et al., 1983].

GENE ANALYSES

By means of restriction fragment length polymorphism analyses and linkage studies, the gene defect in type II DI occurring as a single trait has been assigned to the Gc locus of the long arm of human chromosome 4 [Ball et al., 1982]. This linkage has been confirmed by further studies [Conneally et al., 1984; Corney et al., 1984]. An autosomal dominant form of juvenile periodontitis in association with type III DI (Brandywine isolate) has been assigned to the same locus [Boughman et al., 1986] implying that type III is a variant of type II DI as suggested by Heimler et al. [1985].

Linkage studies have been performed in a large Finnish family with type II DI. In pairwise linkage analysis both COL1A1 and COL1A2 genes were excluded as the

site of mutation [Vikkula et al., 1992]. Further analyses to several polymorphic markers in the vicinity of the Gc locus revealed no evidence for linkage. On the other hand, gene analyses excluding the localization of the gene coding for dentin phosphoprotein to human chromosome 4 suggest that the gene is not directly associated with types II or III DI [MacDougall et al., 1992].

TREATMENT

The degree of tooth involvement is a major factor to be considered in the dental treatment of patients with OI and DI. Primary dentition appears to be more severely affected resulting in an eventual decrease of occlusal height. The dental treatment of affected children aims to ensure favorable conditions for the eruption of the permanent teeth as well as for the normal growth of the facial bones and the temporomandibular joints. In case of severe general bone involvement, orthodontic and surgical procedures can be complicated. As soon as possible after eruption, the primary molars are protected with stainless steel crowns. In the restorative treatment of pediatric patients, glass ionomers as fluoride releasing and chemically attaching materials are recommended in occlusally non-stressed areas, whereas the new composites, combined with a dentin bonding agent, provide acceptable resistance to occlusal wear. Fortunately, dental caries does not appear to be a major clinical problem in patients with OI and DI. Hypodontia is not an uncommon finding in OI (even without DI), and an early diagnosis of missing teeth is important.

After the eruption of the permanent first molars, temporary stainless steel crowns will be cemented to prevent occlusal wear. In young patients, the other permanent teeth when functionally and/or esthetically compromised, may be restored with composite veneers, prepared and finished on models and then bonded [Mackie and Blinkhorn, 1991]. The final prosthetic treatment in early adulthood aims to restore vertical dimension and functional capacity of occlusion. Extracted or congenitally missing teeth can be replaced by either resin-bonded or conventional bridges. Prosthetic crowns on short-rooted teeth may be coupled to improve resistance to occlusal stress. In elderly patients with extensive wear of dentin, overdentures without preceding extractions may be needed. The remaining roots should be covered with fluoride-releasing glass ionomer fillings. In the planning of prosthetic treatment, the patient's capability to maintain adequate oral hygiene should be considered.

In type II DI and type I DD, selected principles of the dental treatment described above are applicable as well. Additional problems may arise because of the tendency of teeth affected by type I DD to exfoliate. No special clinical problems should appear in type II DD.

DISCUSSION

It has become evident that classified heritable dentin defects share strikingly many features in common. This is clearly indicated by the fact that although types I and II DI may be genetically distinct entities, they are definitely distinguishable only by the association of type I DI with OI. However, DI is not a consistent finding in

any particular type of OI, and on the other hand, the dentition can be affected in conjunction with any type of OI, irrespective of the severity of bone involvement. The familial occurrence of DI in association with OI and the finding that interfamilial variability is greater than intrafamilial are consistent with the concept of different mutation(s) in different families.

Until more information on the ultrastructure and biochemical defects of dentin is available, the Shields classification, though not comprehensive, can be used. In addition, studies at the gene level will help in the revision of the classification.

Inasmuch as type I collagen is the main constituent of the organic matrices of both bone and dentin, familial occurrence of DI in association with OI cannot be comprehensively explained by mutation(s) in genes encoding type I collagen chains. It has been reported that homozygous mouse mutants (Mov13) carrying a retroviral insert in the first intron of the collagen $\alpha 1(I)$ gene [Schniecke et al., 1983; Harbers et al., 1984] fail to synthesize type I collagen due to a transcriptional block [Hartung et al., 1986]. As a consequence, the mutants die during early embryonic life because of rupturing of blood vessels [Jaenisch et al., 1983]. Yet in heterozygotes, odontoblasts and possibly mandibular osteoblasts contrary to other mesodermal cells transcribe this mutant allele [Schwarz et al., 1990] and it has been suggested recently that the regulation of the expression of $\alpha 1(I)$ collagen gene may differ even in odontoblasts and osteoblasts [Andujar et al., 1990]. The "illogical" mode of association of DI with OI in different families and the variety of dental defects found in the affected patients could, at least partly, be explained by the existence of an independent expression of collagen genes under developmental tissue-specific control.

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