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CASE REPORT

Dentinogenesis imperfecta associated with short stature, hearing loss and mental retardation: a new syndrome with autosomal recessive inheritance?

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The follow-up history and oral findings in two brothers from consanguineous parents suggest that the association of dentinogenesis imperfecta (DI), delayed tooth eruption, mild mental retardation, proportionate short stature, sensorineural hearing loss and dysmorphic facies may represent a new syndrome with autosomal recessive inheritance. Histological examination of the dentin matrix of a permanent molar from one of the siblings reveals morphological similarities with defective dentinogenesis as presenting in patients affected with Osteogenesis Imperfecta (OI), a condition caused by deficiency of type I collagen. A number of radiographic and histological characteristics, however, are inconsistent with classical features of DI. These findings suggest that DI may imply greater genetical heterogeneity than currently assumed.
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Cases

Two brothers with a similar association of congenital anomalies were referred for oral examination to the Centre for Special Care, Ghent University Hospital, at the ages of 3 and 7 years. Their parents were of Turkish origin and were consanguineous (first cousins). The older sister as well as both parents were phenotypically normal. Both boys presented at birth with a low weight and showed delayed psychomotor development on follow-up. They currently have a mild mental retardation with normal karyotype and normal brain MRI. In addition they suffer from sensorineural hearing loss. Physical examination revealed proportionate short stature with small hands and prominent knees. Their facial features include a prominent nose with high nasal bridge and short philtrum. Radiographic evaluation of the skeleton revealed osteoporosis, mild platyspondyly and cone-shaped epiphyses in the hands. Oral examination revealed in both boys an opalescent tooth discoloration with severe attrition, affecting both the primary and permanent dentition (Fig. 1). Eruption of the permanent dentition was delayed in both probands. Radiographic examination showed bulbous crowns, long and tapered roots, and progressive pulp obliteration of the permanent dentition in both siblings (Fig. 2). In the oldest proband, aggressive periodontitis was present in a localized fashion (i.e. affecting the supporting tissues of the crown-covered first molars), probably resulting from interaction between genetic and epigenetic/systemic factors (i.e. juvenile onset diabetes) (Fig. 2c). Histological examination of demineralized dentin sections of a first permanent molar from one of the brothers showed the alternating presence of normal and pathological areas, the latter presenting with sparse and unevenly distributed tubuli with varying diameter. In pathological areas, the course of dentinal tubules was indiscriminate and highly irregular, and clustered canal-like structures with inclusion of endothelial remnants were seen (Fig. 3). Abnormal areas, which were strongly resembling those presenting in teeth from patients affected with Osteogenesis Imperfecta (OI), were found in sections of both the coronal and radicular dentin. The pulp chamber of the permanent molar was completely obliterated with amorphous and atubular masses that were poorly demarcated from the secondary dentin. The clinical, radiographic and histological findings sustained a diagnosis of Dentinogenesis Imperfecta (DI) in both sibs. Staining for reticulin, however, was indicative of the absence of type III collagen in dentin matrix, which was in contrast to previous findings in DI. Because of the radiographic finding of an osteoporotic skeleton, mutation analysis of the Type I collagen genes was performed but no mutations were identified.

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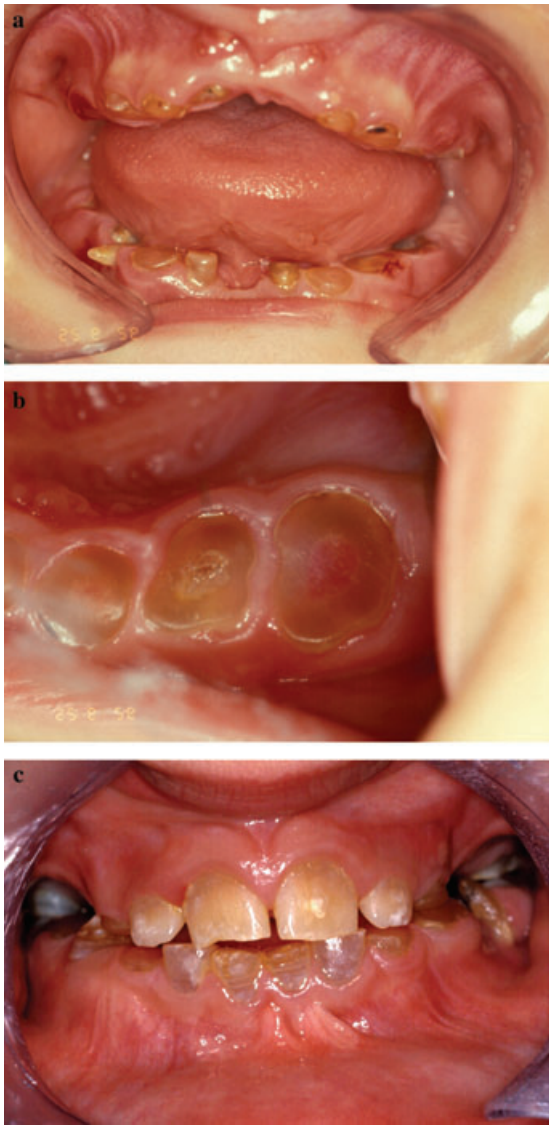

Figure 1 Clinical manifestations of Dentinogenesis Imperfecta (DI) in the deciduous (a, b) and the mixed dentition (c): generalized opalescent tooth discoloration, wear of the enamel, and atypical absence of pulp obliteration in deciduous molars.

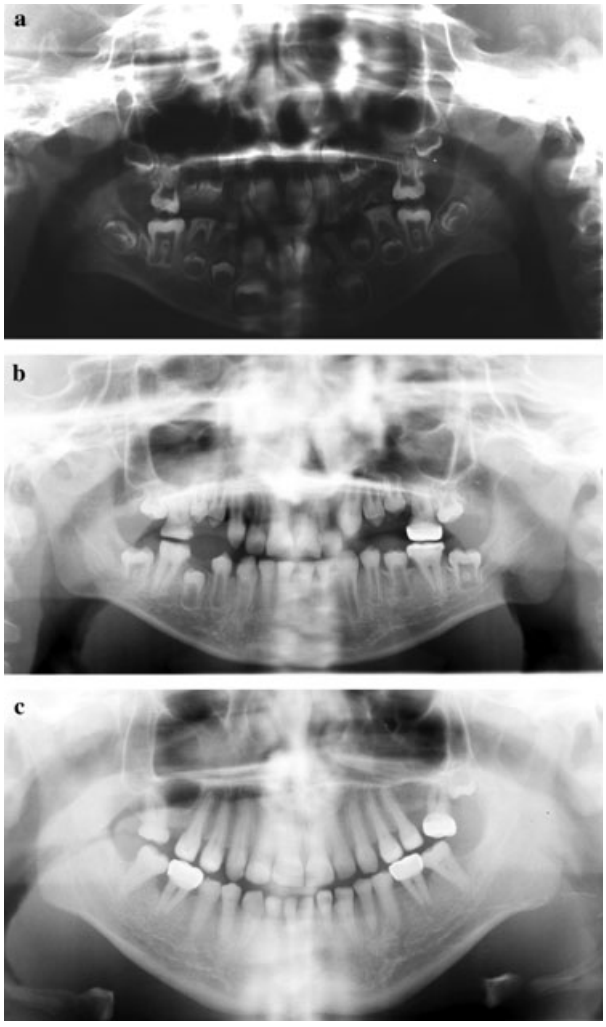

Figure 2 Sequence of panoramic radiographs over an 8-year period of the oldest proband, displaying progressive wear of the deciduous teeth, the formation of bulbous crowns, long and tapered roots, progressive pulp obliteration of the permanent dentition and aggressive periodontitis, affecting the supporting tissue of the crown-covered first molars.

Comments

Parental consanguinity increases the risk for autosomal recessive disorders in the offspring (1). First-cousin and uncle-cousin mating are not uncommonly observed in certain populations. In Turkey still 20–25% of the matings are inbred unions (2), while in some regions of Asia and Africa rates of 20–50% have been reported. First-cousin mating prevails in up to 70% in central Middle East; in Northern America and Western Europe the incidence is estimated at 0.5%. Short stature, growth retardation, mental retardation, skeletal malformations, cleft palate, micrognathia (3) and structural disorders of dental hard tissues, such as Amelogenesis Imperfecta and DI (4) have been reported as a consequence of inbreeding. The association of mental retardation, sensorineural hearing loss, proportionate short stature with osteoporosis and cone-shaped epiphyses, and DI, however, has to our knowledge not been reported before.

DI is the most common disorder affecting the structure of dentin, which is estimated to prevail in about 1:8000. It is a genetic condition of mesodermal derivatives presenting with similar clinical and radiographic features in both the deciduous and the permanent dentition. Type I DI has been defined as the dental defects associated with some forms of OI (OMIM Entry 166220), i.e. a heterogeneous group of disorders caused by a mutation in *COL1A1* or *COL1A2*. As type I collagen is an important structural protein in several connective tissues, deficiency of this protein results in altered structural and/or mechanical properties of a number of soft (skin, joint ligaments) and mineralized (bone, dentin) tissues. Type II DI (OMIM Entry 125490) occurs as an isolated trait, which has been substantiated by numerous studies. In both type II DI

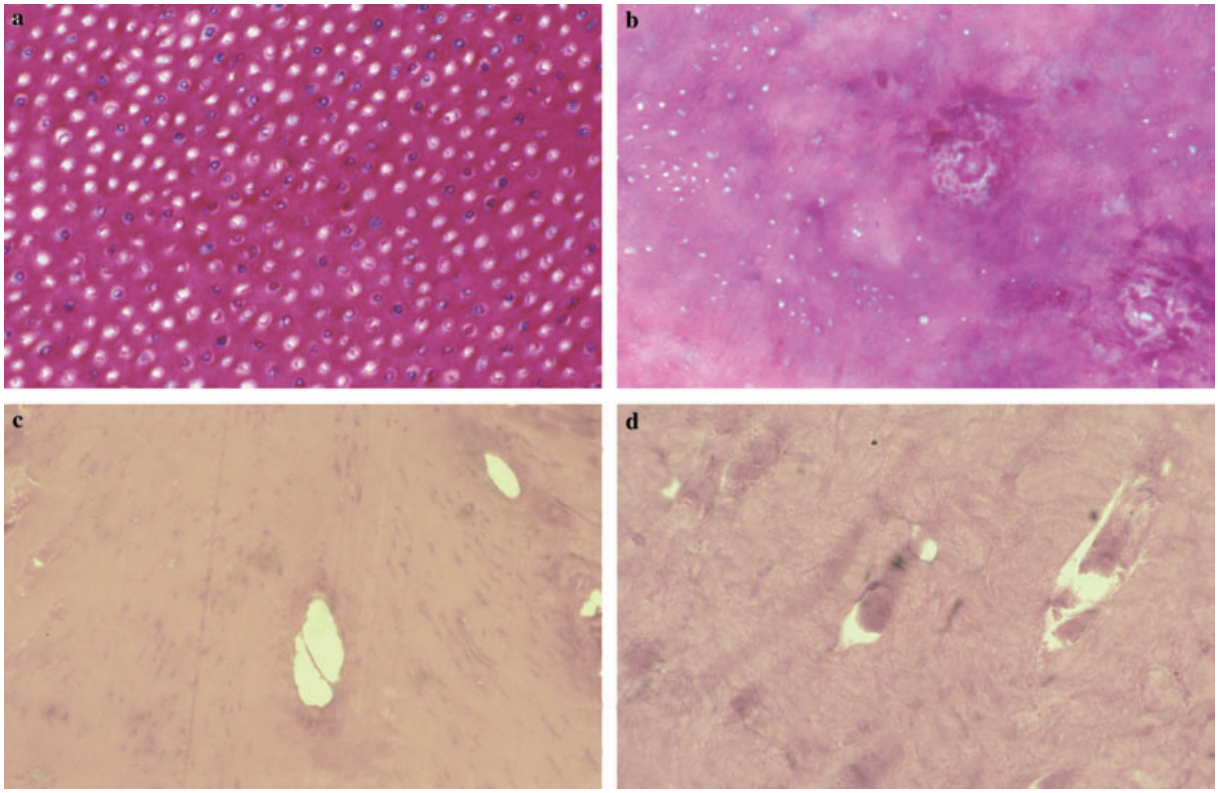

Figure 3 Histological appearances of dentin matrix of a permanent molar from one of the sibs, compared to an unaffected control tooth (a). Pathological dentin is characterized by the alternating presence of clustered canal-like structures among sparse dentinal tubules of varying diameter, and atubular areas (b, c). Some of the abnormally enlarged tubules are obliterated with amorphous material (d). Haematoxylin and eosin stain on paraffin sections; (a, b) ×100; (c) ×400; (d) ×1000.

and coronal dentin dysplasia (OMIM Entry 125420) mutations in the DSPP gene at 4q21.3 have been identified, suggesting that both disorders are allelic conditions. Mutation in DSPP may also be causal to an association of DI and sensorineural hearing loss (OMIM Entry 605594). The present cases suggest that DI may occur in association with additional symptoms other than hearing loss and moreover may be of autosomal recessive inheritance. Association of DI-like findings with several syndromes has been reported by various authors (5). There are also a number of observations indicating that both collagenous (i.e. type I and III collagens) and non-collagenous constituents (e.g. glycosaminoglycans, fibronectin, dentin phosphoprotein) of the dentin matrix may be abnormal in DI. In both sibs, pulp obliteration was absent in the deciduous dentition, pulp chambers of the permanent teeth appeared abnormally enlarged prior to obliteration, and in the permanent dentition roots were rather long and spindly tapered than short and dysplastic (Fig. 2), as featuring in 'classical' DI (6). Furthermore, staining for reticulin (consistent with immunostaining for collagen III) was absent in dentin samples from one of the boys, which is inconsistent with reports of abnormal presence of collagen III in DI. These findings suggest that DI may imply greater genetical heterogeneity than currently assumed. The association of DI, delayed eruption, mild mental retardation, proportionate short stature, sensorineural hearing loss and dysmorphic facies may therefore represent a new syndrome with autosomal recessive inheritance.

References

1. Stoltenberg C, Magnus P, Skrondal A, Terje Lie R. Consanguinity and recurrence risk of birth defects: a population-based study. *Am J Med Genet* 1999; **82**: 423–8.
2. Tuncbilek E. Clinical outcomes of consanguineous marriages in Turkey. *Turk J Pediatr* 2001; **43**: 277–9.
3. Stoll C, Alembik Y, Roth MP, Dott B. Parental consanguinity as a cause for increased incidence of births defects in a study of 238,942 consecutive births. *Ann Genet* 1999; **42**: 133–9.
4. Maatouk F, Laamiri D, Argoubi K, Ghedira H. Dental manifestations of inbreeding. *J Clin Pediatr Dent* 1995; **19**: 305–6.
5. Kantaputra PN. Dentinogenesis imperfecta-associated syndromes. *Am J Med Genet* 2001; **104**: 75–8.
6. Ranta H, Lukinmaa P-L, Waltimo J. Heritable dentin defects: nosology, pathology and treatment. *Am J Med Genet* 1993; **45**: 193–200.

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