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Severely hypoplastic amelogenesis imperfecta with taurodontism

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Background. The prominent dental feature of a boy was severely hypoplastic enamel in both primary and permanent teeth.

Case Report. Many permanent teeth were already infected while emerging in the oral cavity. Panoramic radiograph showed enlarged and elongated pulp chambers (taurodontism) in the permanent first molars. The clinical and radiological diagnosis was either hypomaturation-hypoplastic amelogenesis imperfecta with taurodontism (AIHHT) or tricho-dento-osseous syndrome (TDO). Histological examination of the upper right permanent first molar revealed thin lamellar or somewhat thicker amorphous enamel on approximal surface only with no rods or incremental lines visible. Histologically, the Witkop type AIG designated 'enamel agenesis' cannot be excluded. The medical and dental history of the family members, as well as the boy's medical examination, was noncontributing. He had thick, blond, curly hair. The bone structure of the jaws and skull was normal. For genetic analysis, *DLX3* gene was sequenced but no mutation was found.

Conclusions. Since the gene defect of TDO has been localized only in the *DLX3* gene, the more probable diagnosis was AI.

Introduction

Amelogenesis imperfecta (AI) is an inherited disorder that causes alteration in the quality and/or quantity of the dental enamel. In all types of AI the enamel is the only tissue affected. The amelogenesis imperfecta, hypomaturation-hypoplastic type, with taurodontism (AIHHT) is one of the types of AI[1]. In the tricho-dento-osseous syndrome (TDO), which is also characterized by enamel hypoplasia and hypomineralization with taurodontism, hair and bone abnormalities are present as well[2]. Although enamel defects and taurodontism are present in all TDO cases, nondental features like kinky or curly hair, thickened cortical bone, and dysplastic nails may not always be evident[3–6]. Additionally, in approximately half of TDO cases, the kinky/curly hair phenotype, which is seen in infancy, is lost by adolescence[5–7], whereas bone changes, which are also highly varied, appear to progress with age[7].

Dental findings in AIHHT appear to be very similar with those of TDO[6,8]. As there is a great variability in the expression of defects in both conditions, a diagnostic dilemma often exists as to whether a patient has AIHHT or TDO[9]. On the basis of clinical examination alone, it is not always possible to distinguish between TDO and AIHHT.

The characteristic light and scanning electron microscopic appearances of the enamel in AIHHT and TDO are identical[8]. Again, enamel hypoplasia and hypomineralization in AIHHT as well as in TDO are present to a varied degree[10]. Although TDO and AI essentially affects the enamel, abnormalities of the dentin can be observed in some TDO patients as well as in AIHHT[10].

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Although some authors suggest that TDO and AIHHT are separate conditions and should not be confused[5,9], others propose that TDO and AIHHT represent a spectrum of the same disease of mutations in a common gene[10]. In connection with TDO as well as in AIHHT, mutations in *DLX3* gene have been reported. In TDO families a four-base deletion in exon 3 of the *DLX3* gene has been identified[7]. In AIHHT a two-base deletion on *DLX3* gene has been confirmed[11]. In other AIHHT patients, no mutation of *DLX3* gene was found[6].

In addition to AIHHT and TDO, enamel formation is severely disturbed in another very rare type of AI, termed Witkop type AIG, or 'enamel agenesis'[1].

In this report, we describe an unusual phenotype of a boy resembling that of TDO, the histological structure of his teeth, and the results of sequence analysis of the *DLX3* gene.

Clinical and radiological description

A 7.5-year-old boy with severely defective enamel was seen for a fistula in the apical region of the lower right permanent central incisor in the Unit of Paediatric and Preventive Dentistry, University Medical Centre Ljubljana, Slovenia. In addition to this, he often had severe pain of dental origin. He could barely eat or drink. The boy was very frightened and uncooperative.

There was nothing remarkable in the medical or dental histories of his family. He had one healthy older brother who has brown hair. His paternal grandmother had type II diabetes mellitus; the rest of the family members were reported to be healthy. During the gestation period, his mother felt sick but otherwise the pregnancy was normal and full-time. At birth, the boy's weight was 3000 g and his height was 51 cm. He was born with long darker hair, which was replaced in a few months with blond curly hair. His brother, unlike the boy, was born with very fine blond short hair. Since birth, no history of any specific disease, allergy, trauma, or medication was reported for the boy. He underwent hernia operation at the age of 3. His nutritional status was good. The boy had frequent toothaches and dental abscesses. He had visited a dentist only when pain, often associated with elevated body temperature, had become extremely severe and intolerable. Occasionally he suffered from aphtous ulcers of the oral mucosa and herpes labialis. Because of his dental problems, he frequently underwent antibiotic therapy.

The boy was of short stature for his age. At the age of 7.5 years his height was 118 cm and his weight was 20 kg (both values are in 10. percentiles). Otherwise his body, head, and extremities were proportionate and well developed. No enlargement of neck lymphatic glands was present. His hair was thick, blond, and curly, and his skin was somewhat dry. The boy's nails were well developed. He was prone to breathing through his mouth. Apart from slower somatic development, no other deviation from normal was found. Results of his blood examinations were normal (white blood cell: $6.14 \times 10^3/\mu L$; red blood cell: $4.4 \times 10^6/\mu L$; haemoglobin 129 g/L). He never had frequent purulent infections other than those of dental origin. A possibility of immunodeficiency diagnosis was rejected. To exclude coeliac disease, antigliadine antibodies were determined. There was a moderate increase of immunoglobulin G (IgG) antigliadine antibodies values, but the values of IgA antigliadine antibodies were normal. Increase of IgG antigliadine antibodies was estimated as nonspecific. Serum alkaline phosphatase (ALP) was measured when the boy was 7.5, 8.5, and 11 years of age and the values ranged from 3.1 μkat/L to 5.2 μkat/L. These values were within normal limits in a growing child. In addition, levels of serum phosphates (P), measured at the same time as ALP, with the values ranging from 1.1 mmol/L to 1.3 mmol/L, were found to be normal.

The intraoral examination of oral soft tissues revealed a dental abscess in the region of the lower right permanent central incisor. Inevitable root canal treatment of this tooth with incompletely developed root was performed; apexification of the tooth with Ca $(OH)_2$ medicament later on did not proceed as desired, and despite antibiotic treatment inflammation in this region persisted, so the tooth had to be extracted due to abscess. Chronic gingivitis was also observed. He had mixed dentition; all eight permanent incisors and four permanent first molars had

already erupted. The enamel of all teeth looked hypoplastic and hypomaturated or the enamel even seemed to be absent. The teeth were thin and yellowish with rough surface (Fig. 1A,B). There were no contact points between the teeth. The molars were in angle class III occlusion and both central incisors and the left lateral incisor were in crossbite.

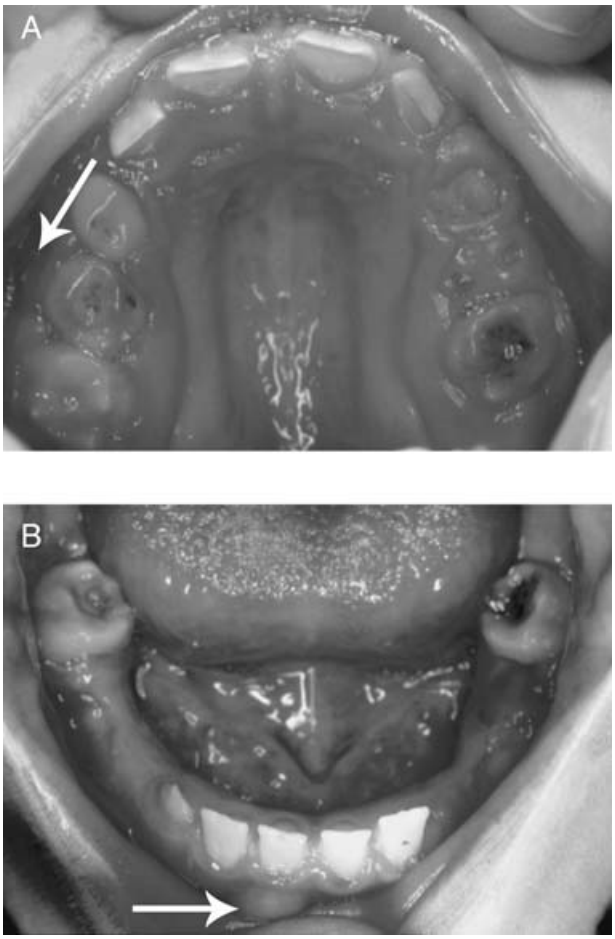

Fig. 1. Intraoral photograph of the boy with severely hypoplastic yellowish teeth. The photograph is taken at the age of 8 years. Enamel covering the entire dentition is extremely thin or absent. The teeth surfaces are rough. Gingivitis is observed. (A) Upper permanent incisors are sharp and thin. Above upper right deciduous second molar a fistula is present (arrow). (B) Lower incisors have also sharp edges. There are no contact points between the teeth. Premolars have not yet erupted. In apical region of lower right permanent first incisors abscess is evident (arrow). Inevitable root canal treatment of this tooth with incompletely developed root was performed after the photograph was taken; apexification of the tooth with $Ca(OH)_2$ medicament did not proceed as desired and the tooth had to be extracted.

Dental panoramic tomogram revealed that all permanent teeth including germs of all four third molars were present. Tooth development corresponded to his age. In translucency, there was no difference between dental enamel and dentin (Fig. 2). In fact, the question whether there was any enamel present on those teeth was raised again. The permanent first molars were taurodontic with large pulp horns. In the upper first molars taurodontic pulp chambers extended into palatal root. According to Seow's classification (1993)[9], both lower permanent first molars were hypotaurodontic. Crown-body/root ratios were 1.20 and 1.24 for the lower left permanent first molars (tooth 36) and for the lower right permanent first molars (tooth 46), respectively. The bone structure of the jaws was normal. Cephalometric radiograph also revealed that the bone structure of the skull was normal.

Informed consent was obtained from the boy's parents. The study was approved by the Slovenian Committee for Medical Ethics (no. 26p/10/06).

Histological examination of the tooth

Preparation of the specimen for histological examination

When the boy was 9 years old, the upper right permanent first molar was extracted because of infection, and was submitted for histological examination. It was fixed in 10% neutral buffered formalin, rinsed, and bisected axially in mesio-distal direction. The palatal half of the tooth was dehydrated and embedded in polymerizing methylmetachrylate monomer. After complete polymerization of the monomer, facilitated by benzoyl peroxide (2 g/100 mL), the tooth specimen was serially cut with a Leitz saw microtome at 100–150 μm and the unstained sections were mounted with DePex (Gurr, BDH, Poole, England). The buccal half of the tooth containing the mesio-buccal and disto-buccal roots was demineralized with ethylenediaminetetraacetic acid (0.33 mol/L) for about 16 weeks and embedded in paraffin in the usual way. A representative series of sections was cut and stained with haematoxylin and eosin and by Schmorl's picric acid and thionin method.

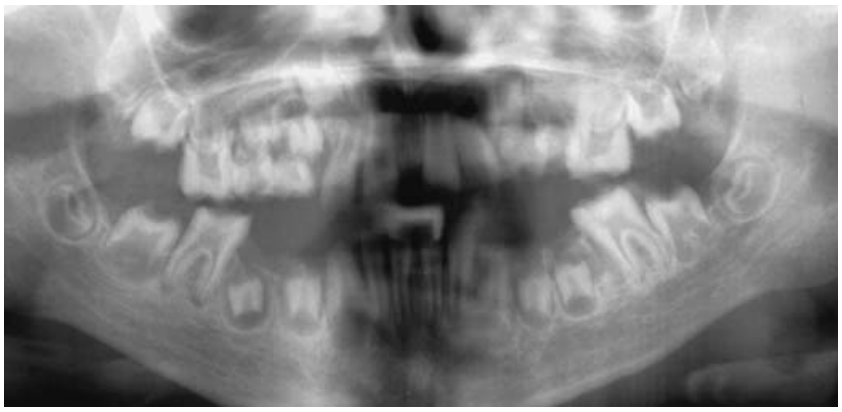

Fig. 2. No enamel is visible in the dental panoramic tomogram of the boy's dentition at the age of 8 years. All four permanent first molars have taurodontic pulp chambers. All permanent teeth are present, either already erupted or present as tooth buds of permanent teeth. Upper right permanent canine is impacted due to lack of space.

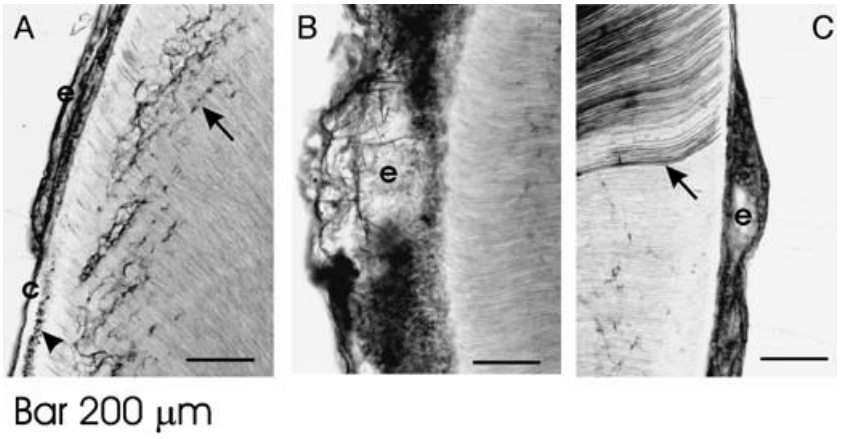

Fig. 3. Histological appearance of the upper right permanent first molar as seen in undemineralized, unstained ground sections. (A) A thin layer of lamellar enamel (e) with a smooth surface is visible cervically on the approximal surface. Interglobular dentin (arrows) is abundant in the crown and root where it is distinct from the granular layer of Tomes (arrowhead) in the vicinity of cementum (c). The enamel fails to increase in thickness in the coronal direction. (B) An area of amorphous enamel (e) with a rough, globular surface is present more coronally. No rods or incremental lines are visible. Tubular pattern in the dentin is regular. (C) Thin or absent enamel (e) appears to have facilitated invasion of bacteria in dentin tubules (arrows). Bar, 200 μm.

Histological findings

Macroscopically, the removed tooth seemed to be devoid of enamel. Examination of metachrylate-embedded ground sections of the palatal tooth half showed a thin smooth layer of lamellar enamel on the cervical part of the approximal surfaces (Fig. 3A). More coronally, areas of thicker, amorphous enamel with a globular surface were present. No rods or incremental lines were visible (Fig. 3B). Sharp margins of the enamel could have resulted from cracking. The occlusal surface virtually lacked enamel. Where enamel was thin or absent, bacteria had readily invaded dentin tubules (Fig. 3C). Defectively mineralized interglobular dentin was abundant in the crown and root, especially superficially. Paraffin sections of the buccal half of the tooth showed stellate mineralization defects traversed by dentin tubules. These were most abundant on the pulpal side of root dentin and superficially yet distinct from the granular layer of Tomes (Fig. 4). Bacterial plaque on the coronal tooth surface, which have possibly survived demineralization, could not be distinguished with certainty from sparse enamel matrix. Bacteria were seen in dentin tubules. Pulp tissue was necrotic and no odontoblasts were visible. With the exception of the innermost dentin, apparently formed in response to pulpal infection, the tubular pattern was regular. The loose-textured connective tissue present in the trifurcation was heavily infiltrated by chronic, mononuclear inflammatory cells. As seen in ground and paraffin sections,

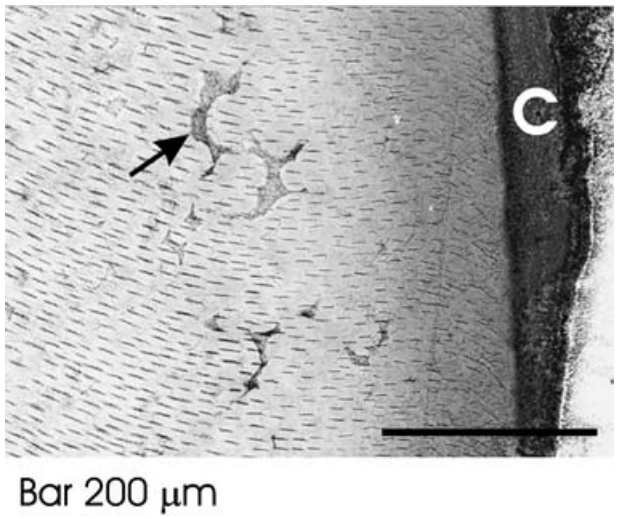

Fig. 4. Histological appearance of the upper right permanent first molar as seen in a paraffin section. Large, angular mineralization defects (arrow) showing a continuous tubular pattern are present in superficial root dentin (c, acellular cementum). Schmorl's picric acid and thionin stain. Bar, 200 µm.

the external contour of the crown dentin was normal. The trifurcation was shifted apically and the pulp cavity in the area of the root trunk was elongated and enlarged. The pulp chamber was contiguous with the enlarged palatal root canal. The structure and distribution pattern of acellular and cellular cementum were normal (Fig. 4).

DLX3 mutation analysis

Genomic DNA was isolated from the buccal swabs using the QiaAmp DNA Mini Kit (Qiagen, Valencia, CA, USA). The coding region and flanking intronic sequences of *DLX3* were amplified with three primer pairs (Table 1) with Dynazyme Ext DNA polymerase (Finnzymes, Espoo, Finland). The amplification consisted of 32 cycles with an annealing temperature of 57 °C. Polymerase chain reaction (PCR) products were purified with ExoSAP-IT (USB, Cleveland, OH, USA), sequenced with ABI BigDye v3.1 (Applied Biosystems, Foster City, CA, USA) reagent and subjected to capillary electrophoresis in an ABI 3730 Automatic DNA sequencer (Applied Biosystems) in the Molecular Medicine Sequencing Laboratory, Biomedicum Helsinki. Sequencing results were compared with the wild-type reference sequence (human chromosome 17 genomic contig NT_010783.14) with bl2seq.exe software (National Center for Biotechnology Information, Bethesda, MD, USA).

Sequencing of the coding regions and the flanking intronic sequence did not reveal any changes from the wild-type sequence. The results do not exclude mutations in the regulatory elements that are located either upstream of the gene or in the introns.

Table 1. Primers used for PCR amplification of all three exons of *DLX3* gene.

exon 1/F	CCTCGGCGACTCCACTATT
exon 1/R	CTTCCAGTCCATGCCTTTTC
exon 2/F	CTGGAGGGTCGCAGGAGT
exon 2/R	GAACCTTCCCACCGAAGTTG
exon 3/F	ATTGGGTTCTGGCCTTTCTT
exon 3/R	CCTCGATGATTCCTGAGTGG

Discussion

On the basis of clinical and genetic analysis, we suggest that the diagnosis for the boy was AI. In agreement with the diagnostic criteria proposed for TDO, which describe this condition as hypoplasia of enamel of all teeth and taurodontic posterior teeth and the patient having tightly curly hair, while nail or bone defect(s) is (are) not always present[12], the boy's diagnosis could also have been TDO. Exclusion of a mutated *DLX3* gene in genetic analysis, however, most likely excludes TDO.

The boy had curly blond hair at the age of 7.5 years, which has straightened over the 5 years during which he underwent dental treatment in the Unit of Paediatric and Preventive Dentistry. This is in agreement with reports about hair with TDO, which is often curly but can become straight. Unique kinky/curly hair at birth, reported in 85% of affected individuals, remains in 46% after infancy[5] and, according to another study, in half of the cases hair straightens over time[7].

In the literature it is stated that there is increased radiodensity of bones without any tendency to bony fractures present in TDO, which affects both endochondral and intramembranous bone formation[13], particularly the vault and base of the skull and the mastoid processes[10]. In more than 80% of cases of TDO, osseous changes are evident[6] and in 97% of affected

persons cranial bones are thick, there is lack of visible pneumatization of the mastoid process, and/or calvarial diploe is obliterated[5]. In the case of the boy described in this article, no bone changes in thickness or in density were observed.

It has been proposed that taurodontism can be used to differentiate clearly between TDO and AI[9]. True taurodontism as indicated by a change in the lower permanent first molars occurs consistently and in a severe form only in the TDO syndrome[9]. Taurodontism of the primary and permanent dentition is a fully penetrant feature observed in all affected TDO individuals[7]. Other authors state that taurodontism in the first molars in TDO are variable and therefore are not an inherently good delineator between AIHHT and TDO[5]. Taurodontism and attrition appear to be more severe in the deciduous than in permanent dentition in both conditions[10]. In this case, we have not had the opportunity to observe the boy's deciduous teeth with fully developed roots and to evaluate eventual enlargements of pulp chambers in deciduous molars. Evaluation of taurodontism of both lower permanent first molars in this boy revealed hypotaurodontism when criteria proposed by Seow were used[9]. According to these criteria, crown-body/root ratio of < 1.10 is considered normal (cynodont), between 1.10 and 1.29 is hypotaurodontic, between 1.30 and 2.00 is mesotaurodontic, and with ratio of > 2 is hypertaurodontic. During the follow-up, it became clear that the permanent second molars also had taurodontism.

At the dental examination, it seemed that there was no enamel covering the soft and yellowish teeth. Abrasion of the teeth was rapid. Clinical management in such conditions is centred on improving appearance with aesthetic restorations and preventing dental abscesses with stainless steel crowns. We failed in our treatment since during the follow-up of 5 years, 11 permanent teeth became infected. We assume that because of the severely altered enamel structure none of adhesive bonding technique restorations placed on these teeth remained in place. Because the pulp was infected already before the tooth was fully erupted, no stainless steel crown could have been placed.

Dental abscesses are a frequent finding in TDO[10] and are observed in 80% of affected individuals[7]. Because of the high frequency of abscesses, subjects usually become edentulous by early adult life[10] and 40% of affected TDO adults are edentulous[7]. In the present case, dental abscesses and fistulas most commonly appeared soon after a tooth erupted into the oral cavity but also at any time later. Severely defective enamel might be the reason for the very early onset of fistulas. As seen in histological examination, thin or absent enamel appeared to have facilitated invasion of bacteria into dentin tubules (Fig. 3C). Immense retention of plaque on rough tooth surface also predisposed to gingivitis which may have started as eruption gingivitis.

Histological dental findings in this case resemble those reported in literature for AIHHT, TDO, and Witkop type AIG designated 'enamel agenesis'. Microscopically, the AIHHT enamel is uniformly hypoplastic and hypomineralized[10]. In TDO enamel, hypoplasia, and hypomineralization is present to a varying degree[10]. The affected enamel is thin, only 10% of the thickness of normal enamel, with pitted surface and no prism formation in the bulk of enamel[4]. In another study, enamel thickness of TDO teeth is decreased, ranging from no enamel to about 60% of the thickness of normal teeth[14]. Enamel in those teeth is either prismless or has occasional areas of prismatic enamel[14]. The light and scanning electron microscopic appearances of the enamel in AIHHT are identical to those of TDO[8]. While the structure of dentin in some TDO patients appears essentially normal[4,10], in AIHHT patients as well as in some TDO patients dentinal abnormalities can be observed[10]. In our case, only traces of enamel were present resembling the Witkop type AIG designated 'enamel agenesis', and interglobular dentin was abundant but the tubular pattern was regular.

Identification of the gene connected with TDO and/or AIHHT has important implications distinguishing these conditions. In utilizing a genome-wide search strategy of TDO affected patients, the TDO syndrome locus was shown to be linked to markers on chromosome 17q21[15]. Two genes, members of the distal-less homeobox gene family (*DLX3* and *DLX7*), both involved in tooth development, map to the same region as TDO[7].

Genomic cloning and sequencing of human *DLX3* and *DLX7* genes in six TDO families identified a 571–574delGGGG mutation on the *DLX3* gene[7]. Later studies have also shown similar 4-bp deletion on *DLX3* gene in other TDO families[6,16]. It cannot be excluded, however, that TDO is a genetically heterogenous disorder with mutations in genes which act upstream or downstream of *DLX3*[16]. Mutational analysis and sequencing of the *DLX3* and *DLX7* genes in three AIHHT individuals revealed no mutations or polymorphisms in any of the exons[6]. Six years later, a 560–561delCT mutation in the *DLX3* gene was identified in 11 affected members of another AIHHT family[11].

It appears that AIHHT is a group of two or more genetically distinct conditions while all cases of TDO appear to be due to mutated *DLX3*. This is in agreement with conclusions that AIHHT is an entity distinct from TDO[6] and that TDO and some forms of AIHHT are allelic[11]. Clinical heterogeneity and overlapping phenotypes can result from, for example (i) variable expression of a single mutation in the *DLX3* gene; (ii) different modification on a single mutation in *DLX3* by another gene; (iii) allelic mutations of the *DLX3* gene; (iv) a mutation in a regulatory gene; or (v) a mutation in the promoter or intron region of the *DLX3* gene or mutation(s) affecting another gene or genes. The latter four cases therefore represent distinct genetic entities[6,17,18].

Variations of phenotypes, however, are expressed also within affected family members in AIHHT[8] and in TDO[16,18]. In the TDO affected, with the same 571–574delGGGG mutation found on the *DLX3* gene, variable bone phenotypes are described, including alteration in intramembranous bone formation in the skull, endochondral bone phenotypes and variability at central and peripheral locations of the skeleton[19]. The variable clinical phenotype observed in those families that share a common mutation shows that clinical variability is not the result of genetic heterogeneity at a major locus, but may reflect genetic heterogeneity at other epigenetic loci or contributing environmental factors or both[7].

Mode of inheritance in both mutations identified on the *DLX3* gene, the 571–574delGGGG mutation which is the only known mutation in TDO[7] and the 560–561delCT mutation which is connected to AIHHT[11], is autosomal dominant. In connection with AI, the autosomal recessive (AR) mode of inheritance for enamelin (*ENAM*) gene g.13185–13186insAG mutation is described[20]. Homozygous probands for g.13185–13186insAG *ENAM* mutation have severe generalized hypoplastic amelogenesis imperfecta (AR AI) and a class II open bites malocclusion, whereas heterozygous carriers of the same mutation have only localized hypoplastic enamel pitting defects and none have open bite[20].

Similarly, it would be possible that the boy described here would have been homozygous for the defined mutation on the *DLX3* gene with a severe dental phenotype expressed, while his parents phenotype as heterozygous carriers of the same mutation would be clinically unnoticeable. The sequencing of all three exons of the *DLX3* gene in the boy, however, revealed no mutation. We speculate that there must have been a mutation in some other gene than *DLX3*. It is also possible that the mutation is in regulatory elements that are located either upstream of the *DLX3* gene or in its introns.

While the present case could represent a new dominant mutation, an alternative explanation is that it results from autosomal recessive inheritance. This mode of inheritance and phenotype would be consistent with the Witkop type AIG termed 'enamel agenesis'[1]. Rapid rate of abscess formation is consistent with this diagnosis. If this is the diagnosis of the present case, 'enamel agenesis' would actually be a misnomer, since there was a very thin disorganized enamel layer visible only histologically.

What this case report adds

- AIHHT, the Witkop type AIG, and TDO are rare hereditary conditions that have common dental features. Gene mutation in *DLX3* gene can verify the diagnosis in some but not all cases.
- Further studies are needed to clarify the genetic background of these conditions.

Why this paper is important for paediatric dentists

- Paediatric dentist can be the key persons in diagnosing AIHHT, the Witkop type AIG, and TDO. In cases where bone, hair, and nail changes often seen in TDO are not obvious, genetic analysis may help in distinguishing between AI and TDO.

Conclusion

This paper highlights the structure of the tooth as well as differential diagnostic problems in a case with severely defective enamel with taurodontism. To decide upon the diagnosis, sequencing of the *DLX3* gene was done. As all known patients affected by TDO have mutated *DLX3* gene and no mutation in the *DLX3* gene was found in this case, the most probable diagnosis was AI. Hypotaurodontism supported this diagnosis. Presenting such a case is of importance to share knowledge of possible diversity of conditions and treatment in dentition with severely hypoplastic enamel with taurodontism.

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