Dental aberrations in children and adolescents with osteogenesis imperfecta

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The aim of this investigation was to study dental aberrations in a large sample of unrelated patients with different types and forms of osteogenesis imperfecta (OI). Sixty-eight non-related index patients aged 0.3 to 20 years (mean, 10 years) were examined clinically. Panoramic radiographs from 49 patients were analyzed. Dentinogenesis imperfecta (DI) type I was found in 27 of 65 patients and was significantly more common in OI type III than in types I and IV and in patients with a severe form of the disease. The presence or absence of DI showed almost complete accordance between affected parents and children and between affected siblings. Moreover, agenesis was found in 11 of 49 patients, apically extended pulp chambers in 20 of 48 patients, and impaction of second permanent molars in 7 of 19 patients older than 15 years. The percentage of patients with no apparent dental aberrations was approximately the same in patients with OI type I and type III and in patients with mild and severe form of the disease. The high prevalence of dental aberrations in OI stresses the importance of clinical and radiographic odontologic examination as part of the clinical investigation. In patients with mild forms of the disease, in whom the medical diagnosis is uncertain, demonstration of disturbances in dental development can be crucial for establishing the OI diagnosis. □ *Agenesis; dentinogenesis imperfecta; impaction*

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Osteogenesis imperfecta (OI) is an inherited disorder of the connective tissue caused by mutations in either the collagen 1α1 gene or the collagen 1α2 gene on chromosome 17 and 7, respectively (1, 2). The reported incidence ranges between 6 and 20 in 100,000 newborns (3, 4), and the prevalence between 4 and 10 in 100,000 individuals (4, 5). The disease is usually inherited in an autosomal dominant manner, although de novo mutations are common.

Patients with OI may show a plethora of signs related to the defective collagen: bone fragility, growth deficiency, blue sclera, hearing loss, joint laxity, and dentinogenesis imperfecta type I (DI-I) and also other dental abnormalities such as agenesis (6), apically extended pulp chambers (6), impaction (7, 8), invagination (6), and denticles (6, 9, 10). On the basis of clinical and radiographic findings and mode of inheritance, OI is classified into four types (Table 1) (1, 11, 12). The reported prevalence of DI in patients with OI type I varies from 8% to 40% (8, 9, 13), in type III from 43% to 82% (7, 8), and in type IV from 37% to 100% (8, 9). However, the number of patients and the distribution among the types of OI varied significantly in previous studies (Table 2) (7–9, 13).

Interestingly, DI also occurs as a single trait (DI–II)—that is, in the absence of OI. This form is also inherited in an autosomal dominant manner with almost complete penetrance and a very low frequency of de novo mutations (14, 15). The gene involved is distinct from the collagen type-1 genes, and genetic linkage was shown to chromosome 4q by Ball et al. (16). Recently, disease-specific mutations have been identified in the dentin-specific sialophosphoprotein (DSPP) gene (17, 18).

The clinical, radiographic, and histologic manifestations of DI-I and DI-II are similar, although the clinical picture is more varied in DI-I (14, 19). The primary dentition is more severely affected than the permanent. The teeth show a grayish-blue to brown hue varying among individuals and within the same individual over time. The enamel, which shows normal structure and normal or infrequently decreased mineral content (20), is often dislodged, exposing the soft dysplastic dentin. This may lead to a rapid and extensive attrition (7, 14, 15). The teeth may have short roots, bulbous crowns constricting at the cervix, pulpal obliteration, and periapical radiolucencies. On histologic examination the dentin is characterized by a dysplastic appearance with amorphous areas, irregular dentinal tubules, embedded cells, and occasionally interglobular dentin (6, 21).

Mild forms of OI can sometimes be difficult to diagnose, and the investigation of dental aberrations can then be of vital diagnostic importance. The aim of the present study was to delineate the dental findings in a large sample of unrelated patients with the disease, to establish an inventory of dental aberrations in patients with OI.

Materials and methods

Patient selection and diagnostic criteria

Eighty-one patients, 34 female and 47 male, referred

Table 1. Classification of osteogenesis imperfecta (OI)

OI type	DI	Clinical features	Inheritance*
IA	−	Normal or mild short stature Little or no deformity Blue sclerae Hearing loss common	AD
IB	+		
II	?	Extremely severe osseous fragility, stillbirth or death in the newborn period and beaded ribs	AD (de novo mutations) AR (rare)
III	+/−	Very short stature Progressively deforming bones, usually with moderate deformity at birth Scleral hue varies, often lightening with age Hearing loss less common than in type I	AD AR (uncommon)
IVA	−	Variable short stature Mild to moderate bone deformity Normal sclerae Hearing loss less common than in type I	AD
IVB	+		

Modified from Refs. 1, 11, and 12.
* AD = autosomal dominant; AR = autosomal recessive.

Table 2. Reported prevalence of dentinogenesis imperfecta (DI) in patients with osteogenesis imperfecta (OI)

	Type I		Type III		Type IV		Total	
	OI, *n*	DI, *n*	OI, *n*	DI, *n*	OI, *n*	DI, *n*	OI, *n*	DI, %
Schwartz & Tsipouras (8)	20	8 (40%)	7	3 (43%)	1	1 (100%)	28	43
Lukinmaa (13)*	45	4 (9%)	2	1 (50%)	16	13 (81%)	68	32
Lund et al. (9)	50	4 (8%)	16	13 (81%)	22	8 (37%)	88	28
O'Connell & Marini (7)	–		22	18 (82%)	18	11 (61%)	40	73
Malmgren & Norgren, present investigation	36	10 (28%)	15	10 (67%)	14	7 (50%)	65	42

* This study included also five patients with OI of undefined type. Four of these patients had DI.

consecutively to the national OI team at the Astrid Lindgren Children's Hospital in Stockholm between 1992 and 1999, were investigated. The study protocol was approved by the local Ethics Committee, and informed consent was obtained from the participants or guardians. In five patients OI was excluded. Two patients died before the age of 2 months. One of these died of complications due to severe prematurity, and one of sudden infant death syndrome (SIDS). Two patients were more than 20 years of age and were excluded from further analysis. The remaining patients included four sib pairs. To avoid skewing of the data by including multiple members of the same family, younger siblings were excluded from further analysis. The age at dental investigation and type of OI of the remaining 68 index patients are given in Table 3. OI was classified both in accordance with type and form (severity) (9, 11). It is noteworthy that all patients with OI type III had the severe form of the disease. There were no patients with OI type II. Forty of the 68 index patients were followed up for a period, varying from 1 to 14 years (median, 2 years). In 28 of these 40 patients both the primary and permanent teeth were examined. Only the primary teeth were examined in 20 patients, and only permanent teeth in 20 patients.

Twenty-eight of the 68 patients had 1 parent with OI, whereas 40 patients lacked a family history of OI. Twenty-four parents had OI type I: 16 mothers and 8 fathers. Four parents had OI type IV: three mothers and one father. Consanguinity was reported in the family history of five patients, all of Middle Eastern ancestry. Two of these patients had OI type I, one with a moderate and one with a severe form; one patient had a severe form of OI type III; and two patients had a moderate form of OI type IV. DI was diagnosed on the basis of a combination of clinical

Table 3. Age distribution and type of osteogenesis imperfecta (OI) at time of evaluation of the index patients (from each family)*

		Age in years			
	n	< 5	5 – 9	10 – 14	15 – 19
OI type I	37	11	7	10	9
OI type III	16	2	2	4	8
OI type IV	15	4	5	4	2
Total	68	17	14	18	19

* Five patients not having OI, 2 deceased newborn children, the youngest sibling in the 4 pairs of siblings, and the 2 patients older than 20 years of age were excluded from the original 81 referred patients.

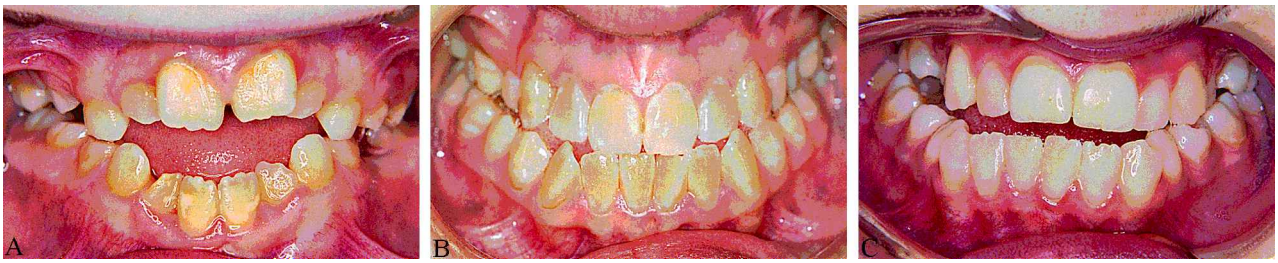

Fig. 1. Various appearances of dentinogenesis imperfecta (DI) in patients with different forms of osteogenesis imperfecta type I. In Patient A with a mild form and in Patient B with a moderate form clinical signs of DI are clearly visible. In Patient C with a severe form DI is visible only on radiographs. Note various types of malocclusions.

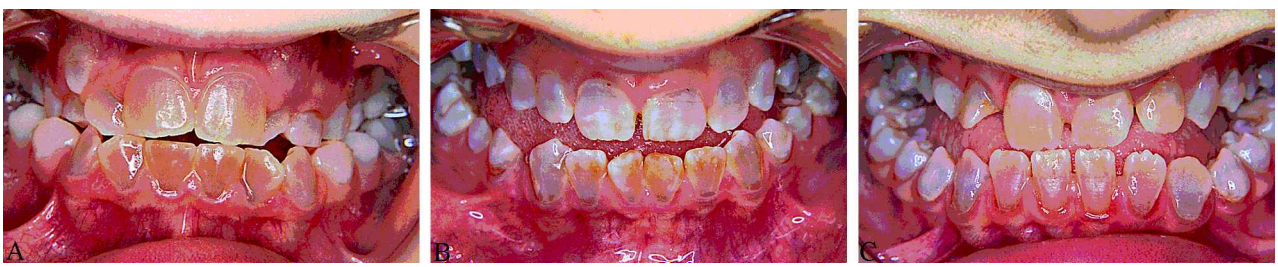

Fig. 2. Patients with dentinogenesis imperfecta and a severe form of osteogenesis imperfecta type III. The discoloration in the permanent dentition varies from a brown opalescent hue in Patient A to a grayish-blue in Patients B and C. Note various types of malocclusions.

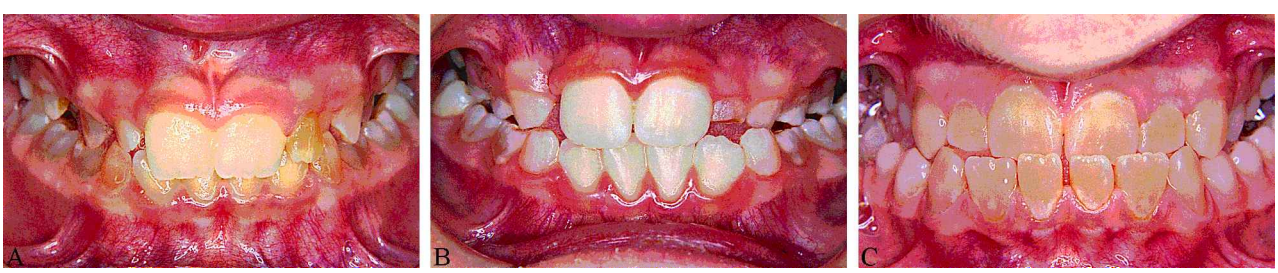

Fig. 3. Various appearances of dentinogenesis imperfecta (DI) in patients with different forms of osteogenesis imperfecta (OI) type IV. Difference in discoloration between primary and permanent dentitions is seen in Patient A with a moderate form of OI. In Patient B, with a severe form of OI, no clinical signs of DI in the permanent dentition are seen, whereas in Patient C, also with a severe form of OI, typical clinical signs of DI are visible. Note various types of malocclusions in Patients B and C.

and radiographic findings and by information provided by family members and their dentists.

Clinical examination

The dental examination was performed at the Department of Pediatric Dentistry, Eastman Dental Institute, in Stockholm and included registration of DI, discoloration, attrition, caries, traumatic injuries to the teeth and jaws, disturbances in eruption, and occlusion. The timing of tooth eruption was classified as early or late (22, 23). The dental status was documented photographically.

Radiographic examination

Due to shortness of the neck and largeness of the chest, low age, or lack of co-operation, it was not possible to obtain radiographs from 17 patients. Panoramic radiographs and lateral cephalograms were obtained from 47 patients. In addition, only panoramic radiographs were obtained from two patients and only lateral cephalograms from two patients. The dentition was evaluated with regard to abnormalities in crown shape, cervical constrictions, and abnormally large or obliterated pulp chambers. Agenesis, apically extended pulp chambers, impactions excluding third molars, invaginations, and denticles were noted. A radiologist, an orthodontist, and a pedodontist performed independent evaluation of apically extended pulp chambers and agenesis. Panoramic radiographs from healthy controls matching the stage of tooth development were used for comparison.

The extent of dental aberrations including discolora-

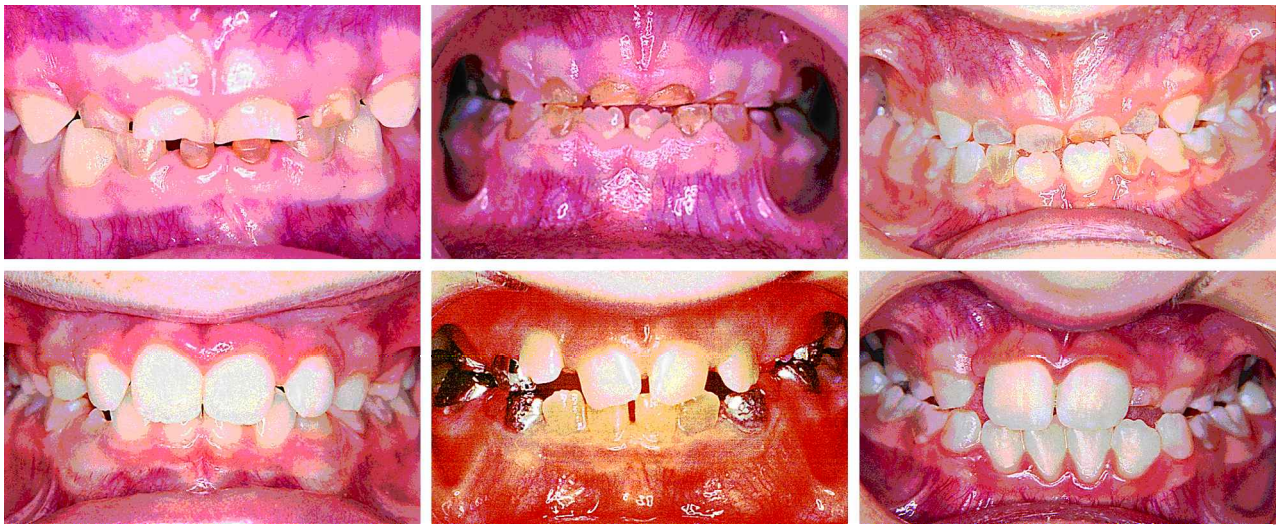

Fig. 4. Differences in clinical appearance of dentinogenesis imperfecta (DI) in primary and permanent dentitions in patients with osteogenesis imperfecta (OI) types I and IV. Primary dentitions are shown in the upper row and permanent dentitions in the lower. *Left:* Mild form of OI type I, showing discoloration and slight attrition in the primary dentition but no visible signs of DI in the permanent dentition. *Middle:* Moderate form of OI type IV, showing discoloration in both primary and permanent dentitions. *Right:* Severe form of OI type IV, showing slight discoloration in the primary dentition and no discoloration in the permanent dentition.

tion, agenesis, apically extended pulp chambers, ectopic eruption, and impaction was registered in accordance with an index system. The following clinical signs were registered and classified into four groups on the basis of severity of the disturbances:

Group 0 represented no disturbances.

Group 1 (mild disturbances) had no discoloration but DI visible radiographically, and/or one to two missing teeth, and/or apically extended pulp chambers, and/or ectopic eruption, and/or impaction of canines.

Group 2 (moderate disturbances) showed mild discoloration, and/or three to five missing teeth.

Group 3 (severe disturbances) had severe discoloration, and/or six or more missing teeth, and/or impaction of permanent molars.

Statistical analysis

The chi-square test was used to analyze the variation in frequency of patients with DI and dental disturbances among those with various types and forms of OI. $P < 0.05$ was taken to indicate significant deviation from the null hypothesis.

Results

Clinical findings

Three of the 68 patients had only a few erupted teeth, and presence of DI could not be confirmed or excluded. One of these patients showed a mild form of OI, another had a severe form, and the form of OI of the third patient was uncertain. DI was found in 27 of 65 (42%) index patients. The prevalence of DI was significantly higher in OI type III (10 of 15 patients) than in type I (10 of 36 patients) and type

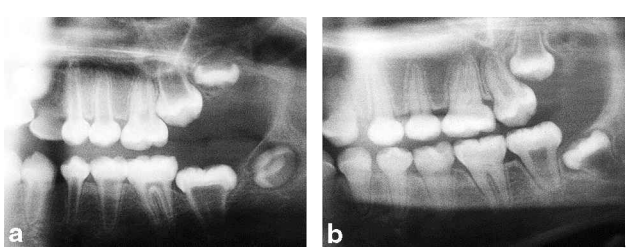

Fig. 5. Radiographs of a patient with a severe form of osteogenesis imperfecta type III and dentinogenesis imperfecta. At the age of 9 years (A) wide pulp chambers are seen. At the age of 14 years obliterations are visible (B). Note bulbous crowns with constriction at cervix.

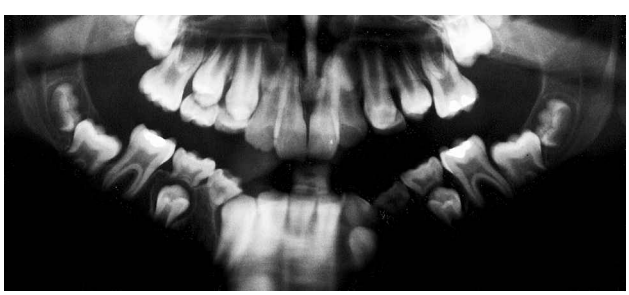

Fig. 6. Panoramic radiograph of a 10-year-old patient with a moderate form of osteogenesis imperfecta type IV. Four premolars are missing. Apically extended pulp chamber can be noted on the first left permanent molar in the upper jaw and ectopic eruption of the left lower canine.

Table 4. The distribution of agenesis in different types of osteogenesis imperfecta (OI) ($n = 49$)

Type of OI	*n*	No. of teeth missing					
		0	1	2	3	4	6
I	28	20	2	1	1	3	1
III	11	9	1	1			
IV	10	9				1	
Total	49	38	3	2	1	4	1

Radiographs were not available or not possible to evaluate in 19 patients.

IV (7 of 14 patients) ($P = 0.03$). The prevalence was also higher in patients with a severe form of the disease (16 of 23 patients) than in patients with a mild form (7 of 31) or a moderate form of the disease (4 of 11) ($P = 0.002$). As illustrated in Figs. 1–3, the degree of discoloration or attrition could not be related to the different types or forms of OI. In the mixed dentition the permanent teeth were less affected than the primary in terms of both discoloration and attrition (Fig. 4). Five of nine patients with OI type I or type IV had no clinical signs of DI in the permanent dentition, whereas four patients had discoloration, although all of them showed typical discoloration in the primary dentition. No correlation was found between discoloration in the primary dentition and the permanent dentition in patients with OI type I or IV. In patients with OI type III and DI, discoloration was always found in the permanent dentition. Severe attrition and fractures were observed in the primary dentition in 6 of 16 patients with DI. No excessive attrition or enamel fractures were found in the permanent dentition, except for a slight attrition of the incisors and first molars. Skeletal facial deviations were found clinically in all types of OI and will be addressed in a future investigation.

The presence or absence of DI showed almost complete accordance between affected parents and children and between affected siblings. The only exception to this was a mosaic patient, an individual who has genetically different cell lines derived from a single zygote, with OI type III (24) and severe DI. Her father had OI type I or IV and moderate DI. Of the 28 affected parents, 9 had DI, as did all of their OI-affected children. Conversely, in the remaining 19 families neither parents nor children had DI. It is interesting that several parents without clinical signs of DI showed crown fractures, particularly fracture of the lingual wall in the molars. None of the patients with consanguineous parents had clinical or radiographic signs of DI.

Forty of 60 patients were caries-free, and 5 patients showed 5 or more decayed surfaces, matching national epidemiological data (25). Eight of 60 interviewed patients (13%) had sustained traumatic injuries to the primary teeth, and 1 of 36 (3%) patients to the permanent dentition. All but one of these nine patients had OI type I. Tooth eruption was age-appropriate in all but 1 of the 68 index patients. In this patient only the lower medial incisors had erupted at 19 months of age, and at 30 months of age only eight teeth had erupted, although all expected teeth could be found on the radiographs.

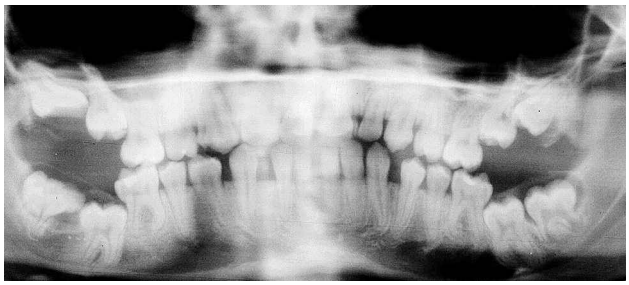

Fig. 7. Panoramic radiograph of a patient without dentinogenesis imperfecta and with a severe form of osteogenesis imperfecta type III at the age of 19 years. Impaction of all second molars can be seen.

All patients with OI type III showed malocclusion and 61% and 67% in patients with OI types I and IV, respectively. This was true even in patients with a mild form of OI type I with a normal thorax configuration.

Radiographic findings

In patients with DI, progression of the pulpal obliteration varied individually. Abnormally wide pulps, occasionally obliterated, were found in 55% of the patients (Fig. 5). Agenesis was found in 11 of 49 patients (22%) (Fig. 6, Table 4). Two of these patients had DI. Apically extended pulp chambers resembling taurodontism were found in 20 of 48 patients (42%). No patient with OI type III had apically extended pulp chambers. Impaction of second permanent molars, predominantly in the upper jaw, was found in 7 of the 19 patients in the oldest group. Three of these patients did not have DI (Fig. 7). No invaginations were found, whereas ectopic eruption, transposition, impaction of

Table 5. Distribution of patients ($n = 59$) with different types and forms of osteogenesis imperfecta (OI) classified into groups on the basis of severity of dental disturbances*

	Group*				Total
	0, *n*	1, *n*	2, *n*	3, *n*	
Type of OI					
I	8	9	5	11	33
III	4	0	0	10	14
IV	1	4	0	7	12
Total	13	13	5	28	59†
Form of OI					
Mild	7	10	2	9	28
Moderate	1	2	1	5	9
Severe	5	1	2	14	22
Total	13	13	5	28	59†

* Groups: 0 = no disturbances; 1 = dentinogenesis imperfecta only visible radiographically (obliteration, bulbous crowns, or abnormal pulp chambers), and/or one to two missing teeth, and/or apically extended pulp chambers, and/or ectopic eruption, and/or impaction of canines; 2 = mild discoloration and/or three to five missing teeth; 3 = severe discoloration, and/or six or more teeth missing, and/or impaction of permanent molars.

† Radiographs were not available or few teeth erupted in nine patients.

permanent canines, and denticles were each found in 2 of 48 patients. Approximately the same proportions of type I and type III patients had no signs of dental aberration, as was the case in patients with mild or severe forms of the disease. The extent of dental aberrations in accordance with the index is given in Table 5.

Discussion

OI is a rare disorder and is sometimes difficult to diagnose. Dental aberrations are common and may be of diagnostic importance when the diagnosis is uncertain. The major findings in the present investigation of 68 patients were as follows: 1) DI occurred in 42% of the patients; 2) agenesis, apically extended pulp chambers, and impaction of permanent second molars were much more common than in controls; 3) DI was more common in patients with OI type III than in OI types I and IV and also in patients with a more severe form of the disease; and 4) there was a very strong correlation between the prevalence of DI in the parents and offspring.

The prevalence of DI in patients with OI reported in previous studies varies considerably, ranging from 28% to 73% (Table 2). Several factors may contribute to this discrepancy. For example, Lukinmaa et al. (13) reported DI in 22 of 68 patients. However, these patients included more than one member from each family. This may skew the data, as the present investigation indicates a strong correlation between the genotype and the presence or absence of DI. In addition, the material included only two patients with OI type III, possibly leading to a low estimate of the prevalence. Lund et al. (9) reported DI in 25 of 88 patients. In that study only 4 of 50 patients (8%) with OI type I showed DI, compared with 28% in the present study. In several of our patients with OI types I or IV the permanent dentition had no clinical signs of DI, and only on radiographic examination could the typical features of DI be observed (Fig. 4). Notably, Lund et al. did not perform radiographic examinations of patients less than 16 years old, and this may contribute to the low prevalence of DI in their study.

Several findings in the present investigation illustrate the value of extensive dental investigation of patients with OI. In patients with OI types I and IV it was not possible to predict, on the basis of the primary dentition, whether the permanent dentition would be discolored. Radiographic signs of DI were also present in five patients with no clinical signs of the disease (data not shown), and radiographic examination is thus most informative in patients with uncertain diagnosis. It should be noted that normally colored teeth and even absence of radiographic signs of DI do not necessarily indicate absence of DI on histologic examination (26). Parents with OI but without clinical or radiographic signs of DI had tooth fractures in adulthood, and histologic examination might have shown signs of DI.

Fractures and attrition were not common, possibly reflecting effects of early intervention (7). Signs of dental trauma were also rare as compared with data from a normal population (27). This may not be unexpected, as children with OI are more supervised than their healthy peers and are less able to participate in trauma-prone activities.

Impaction was found in nine patients. Two of the impacted teeth were upper canines, whereas the others were second permanent molars. However, only 19 patients were more than 14 years old, which is the normal age at emergence of the second molar. The prevalence of impaction in an older population might be even higher. Putative explanations for the high incidence may be the posterior position of the maxilla or the bulbous shape of the crowns of DI-affected teeth (7). However, patients not affected by DI but with a large apical base also showed impaction (Fig.7).

In contrast to the findings by Lunkinmaa et al. (6), no invaginations were found in the present study. Invagination is often an inherited disorder, and the inclusion of multiple members of the same families in their study may have contributed to an overrepresentation of this finding. In support of this, Lund et al. (9) found no invaginations.

Denticles were found in only 2 of 49 patients, as opposed to 28 of 42 patients investigated by Lund et al. (9). However, denticles may be more common in old than young permanent teeth (10), and less than one third of our patients were more than 15 years old. In one patient there were no denticles at 8 years of age but obvious denticles at 12 years of age. The other patient was 18 years old. In the study by Lund et al. 58 of the 88 patients were more than 15 years old, and this difference in age distribution may explain the apparent discrepancy in the prevalence of denticles.

In the present investigation of young patients with OI the spectrum of disturbances in the tooth development ranged from no detectable abnormalities in 22% to severe abnormalities in 47% of the patients (Table 5). This stresses the importance of a detailed and thorough dental investigation. Among patients with mild forms of the disease, in whom the medical diagnosis may be uncertain, demonstration of disturbances in dental development can be crucial for establishing a correct medical diagnosis.

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