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Up-to date Review and Case Report

Management of a patient with osteogenesis imperfecta and trisomy 18

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Abstract – Trisomy 18 and osteogenesis imperfecta are serious diseases with multiple systemic complications. Osteogenesis imperfecta is usually associated with dentinogenesis imperfecta. **Observation**: A young woman consulted for dental care, with the family suspecting multiple caries because of yellow spots on her teeth. Medical history revealed trisomy 18 associated with osteogenesis imperfecta. The patient was quite uncooperative, even with tooth brushing at home. We provided care after the completion of clinical and radiographic examinations. The colorations were due to amelogenesis imperfecta. **Discussion**: The association between osteogenesis imperfecta and amelogenesis imperfecta has not been described in the literature. Moreover, the presence of an extra abnormality in tooth structure was a delicate situation for the family. This case suggests the link between amelogenesis imperfecta and osteogenesis imperfecta. **Conclusion**: This case is the first description of the association of amelogenesis imperfecta and osteogenesis imperfecta.

Introduction

The association of trisomy 18 and osteogenesis imperfecta is rare. Osteogenesis imperfecta (OI) is a type of hereditary congenital osteoporosis, characterized by bone fragility and low bone mass, and is linked to a mutation in the gene encoding type-I collagen [1]. Although the prevalence of this disease is not known with certainty, it is estimated that 3000–6000 individuals in France are affected, which is approximately 1 in every 10 000 inhabitants. The condition affects both genders and all ethnic groups [1,2]. Functional prognosis depends on the severity of the condition and support: administration of bisphosphonates has modified the functional impact of the disease, especially in growing children. Survival is strongly linked to respiratory impairment. Sillence reported a classification in 1979 [3], in which OI patients are classified into 4 categories: light form (type I), unviable form (type II), the most severe viable form (type III), and an intermediate form between types I and III (type IV). Glorieux has refined this classification [2] by subclassifying type IV into types V, VI, and VII, dividing patients according to well-defined clinical and histological characteristics (Tab. I). The OI-associated oral manifestations most often found are Angle class III, infraocclusion and crossbite. Dental abnormalities in the number and position are also reported in the literature, as well as eruptive delays [4,5] (Tab. II). Amelogenesis imperfecta has never been reported in association with OI. Trisomy 18 or Edward's syndrome, which was first described in 1960 [6], is the second most common trisomy after trisomy 21. Its prevalence is estimated at 1 out of 6000–8000 births, but is actually higher because of the high rate of fetal mortality and abortion following prenatal diagnosis. The risk of occurrence increases with the age of the mother, but the risk of recurrence within the same family is very low (approximately 1%) [7,8] (Tab. III). Amelogenesis imperfecta is not part of the clinical picture of trisomy 18. We report a rare case of a patient with amelogenesis imperfecta associated with trisomy 18.

Observation

A 20-year-old patient living with her parents consulted the dentistry department of Albert Chenevier hospital, in Créteil, along with her younger sister (support person). Anamnesis revealed the presence of type-III OI as well as trisomy 18. The

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Table I. OI Sillences classification, completed by Glorieux [9].

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop codon in COL1A1
II	Perinatal lethal	Multiple rib and long-born fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in COL1A1 or COL1A2
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in COL1A1 or COL1A2
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; grey or white sclera; dentinogenesis imperfecta.	Glycine substitutions in COL1A1 or COL1A2
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	Unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	Unknown

* May or may not be detectable in a given patient.

Table II. Dental manifestations in temporary and permanent teeth in patients with OI type III and IV [4].

	Finding	Type III OI ($n = 22$)	Type IV OI ($n = 18$)
Malocclusion	Class I	9.1%	23.5%
	Class II	9.1%	15.9%
	Class III	81.8%	70.6%
Open bite	Anterior	31.8%	17.7%
	Posterior	27.3%	33.3%
	Aged > 9 y	46%	46%
Crossbite	Anterior	27.3%	29.4%
	Posterior	36.4%	47.1%
		$n = 14$	$n = 13$
Dental development*	Advanced (>12 mo)	14.3%	23.0%
	Appropriate	64.7%	69.0%
	Late (>12 mo)	21.0%	8.0%
Ectopic eruption	Upper first molars only	$n = 3$	$n = 4$
	Upper second molars only	$n = 2$	$n = 1$
	Upper and lower second molars	$n = 3$	0
Congenitally missing teeth		$n = 3$	$n = 1$

* Panorex not available for 13 patients.

Table III. Physiopathology, manifestations, diagnosis and management of OI III and trisomy 18 (source author).

	Imperfect Type III osteogenesis (our patient)	Trisomy 18
Pathophysiology	**Molecular level** [9] Autosomal dominant mutation in one of the genes encoding α-1 (chromosome 17) and α-2 (chromosome 7) type-I collagen chains: – Quantitative abnormality (light and intermediate OI) or – Qualitative abnormality (severe and lethal OI). **Tissue level** [1,2] Increased bone remodeling with predominant osteoclast resorption: thinner cortical thickness and fewer and thinner spongy trabeculae.	Chromosomal anomaly due to the presence of an additional chromosome 18 (trisomy 18). The trisomy 18 phenotype appears to be related to the presence of three copies of the 18q11–q12 bands [7].
Clinical manifestations	**Skeletal manifestations** – Frequent prenatal and postnatal fractures – Deformed and shortened long bones: patients are small in stature – Soft skull at birth deforming during the first months of life: triangular face, with macrocephaly, micrognathia, small facial mass – Osteoporotic collapse of vertebrae, resulting in kyphosis and/or scoliosis, – Thoracic deformations, severe respiratory insufficiency Dentinogenesis imperfecta was observed in 80% affected patients [9] **Other extraskeletal manifestations** –Ligament laxity: found at the TMJ level • Joint pain, difficulty in chewing [10] • Developmental anomaly [11] – Bluish discoloration of sclera [1] – Hearing: hearing loss in 58% adults [1] – Cardiovascular system — coagulation abnormalities with uncommon and benign vascular tissue disorders [1] – Renal impairment: hypercalcuria [1] – Neurological impairment: headache, cranial nerve impairment, hyperreflexia [1]	– Intrauterine and postnatal growth retardation, – Increased risk of perinatal or postnatal mortality, – Psychomotor disorders and marked cognitive disorders, developmental delays [7] (language, motor, and social skills [12]) Major malformations are frequent [7,13] – Cardiac (>90% cases): interatrial or ventricular septal defects, persistent ductus arteriosus, or valvular pathologies – Renal: hydronephrosis, unilateral or bilateral renal agenesis – Respiratory: central apnea, upper airway obstruction – Ophthalmic: microphthalmia, coloboma – Labioalveolopalatal clefts are sometimes observed. Craniofacial manifestations are typical: face emaciated and hypertrophied, microcephaly, dolichocephaly, microretrognathism, hypertelorism, pointed ears The hands show overlapping fingers, small fingernails, and underdeveloped thumbs. At the trunk level, the sternum appears smaller [7,13]
Diagnosis	**Diagnostic criteria: essentially clinical; lack of consensus** – Blue sclera – Dentinogenesis imperfecta: mainly found in temporary dentition [9] – Family history of the disease [1,2,9] In case of suspected impairment: mandatory assessment of bone density [2]	May be suspected during pregnancy with ultrasound (growth stunting, malformations, multiple choroid plexus cysts, etc.) and confirmed by the fetal karyotype Serum markers (also used to screen for trisomy 21) may be abnormal [7]
Prognosis Support	**Objective: To help the patient acquire optimum motor and functional skills** [1,9] **Interdisciplinary support** Possible surgical treatement: possible use of bisphosphonates (BP) (inhibition of bone resorption via inhibition of osteoclasts	>95% of affected fetuses die in utero; 50% babies with trisomy 18 live >1 week, 5%–10% live for the first year. The most frequent causes of death are respiratory failure and cardiac arrest as a result of malformations

Table III. (continued).

	Imperfect Type III osteogenesis (our patient)	Trisomy 18
	Action: limiting the incidence of fractures).	
	– Pamidronate administered intravenously (IV) [2]: reduction of bone pain, improvement of quality of life, rapid increase of the bone mineral mass Decreased risk of fractures [14]	Prolonged survival (sometimes up to adulthood) is possible, especially in the case of genetic mosaicism or partial trisomy 21 (by translocation) [7]
	– Alendronate in bones: decreased number of fractures [2]	
	NB: The benefit/risk ratio is to be considered for each patient; regular assessment of patient's oral health is essential to track potential infectious foci and prevent a possible osteoradionecrosis of the maxilla [15]	Medical management is limited to supportive care, the surgical treatment of malformations does not change the prognosis significantly [7]

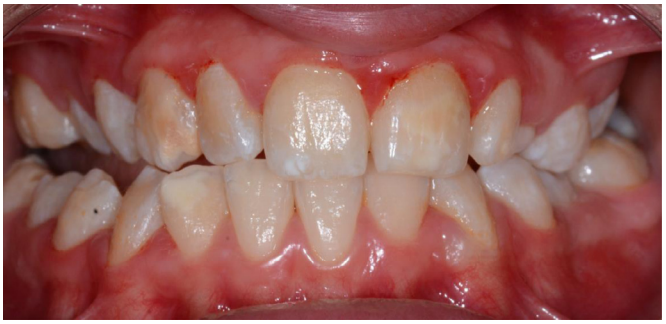

Fig. 1. Clinical perspective: front occlusion (source: author).

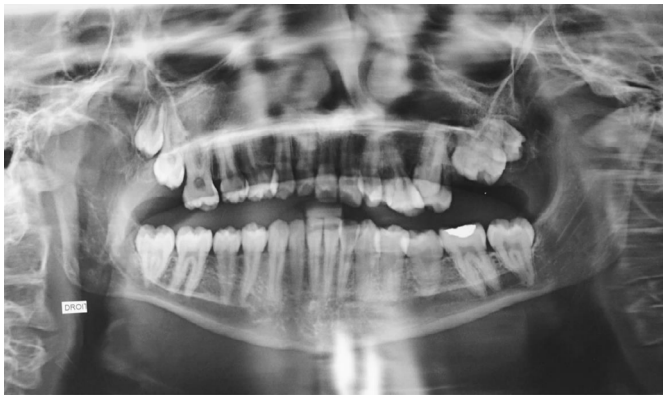

Fig. 2. Panoramic radiograph of the patient (source: author).

patient was currently receiving sodium alginate (Gaviscon®), vitamin supplementation, and oral contraceptive agents. The reason for consultation was twofold: dental pain, located on the left maxillary semiarch, and multiple tooth stains. With regard to the periodontal condition, the patient had severe gingival inflammation associated with a significant amount of plaque and tartar on the day of consultation (Fig. 1). The patient was in the phase of establishing young adult dentition with teeth 17 and 27 being partially below the mucous membrane. Tooth 26 was not visible, tooth 23 was absent, and tooth 63 was persistent on the arcade. Crossbite as well as an infraocclusion were observed between sectors 1 and 4; the mandibular interincisal point was offset by 5 mm to the right. An orthopantomogram (OPT) was prescribed (Fig. 2). It confirmed the presence of tooth 23 impacted in the ectopic position between teeth 24 and 25 (Tab. IV). Residual roots were identified at the left maxillary semiarch level in position 26. A cone-beam computed tomography examination was prescribed. It confirmed the presence of left maxillary first molar residual roots associated with periapical X-ray images corresponding to inflammatory lesions of endodontic origin (Fig. 3). The extraction of the roots of tooth 26 was carried out under local anesthesia and conscious sedation by ENEMO at the rate of 12 L/min. With regard to dental coloring, they were brown and chalky white stains. Enamel was porous and with decreased hardness, but normal thickness. The teeth did not present the characteristic opalescence of dentinogenesis imperfecta (DI) classically associated with OI (Figs. 4 and 5). Eventually, amelogenesis imperfecta was diagnosed. No treatment was implemented because the patient was not cooperative.

Discussion

This clinical case is the first report of an amelogenesis imperfecta case associated with OI, in which the latter caused dental abnormalities. The most widely used classification of dental anomalies is that of Shields, dating back to 1973 [16]: it describes the different types of DI and dental dysplasia. DI is classified into three types [16]: type I: associated with OI; type II: the most common, with an autosomal dominant transmission, unassociated with OI transmission; and type III: very rare,

Table IV. Dental formula.

18	17											23		27	28
		16	15	14	13	12	11	21	22	63	24	25	26		
	47	46	45	44	43	42	41	31	32	33	34	35	36	37	

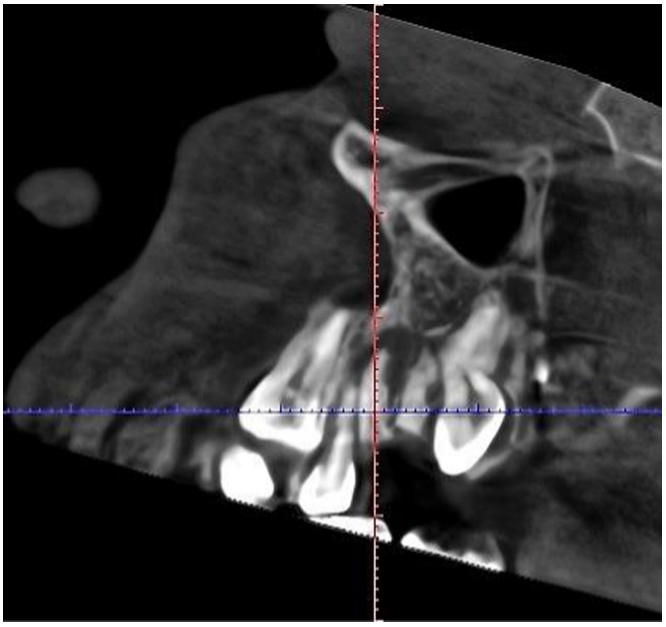

Fig. 3. CBCT (sagittal) focused on the roots of 26 (source: author).

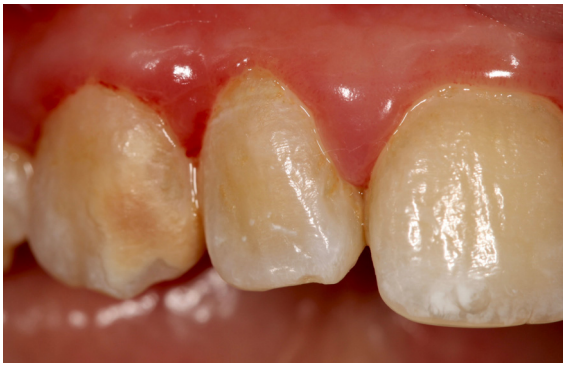

Fig. 4. Clinical view of 11, 12 and 13.

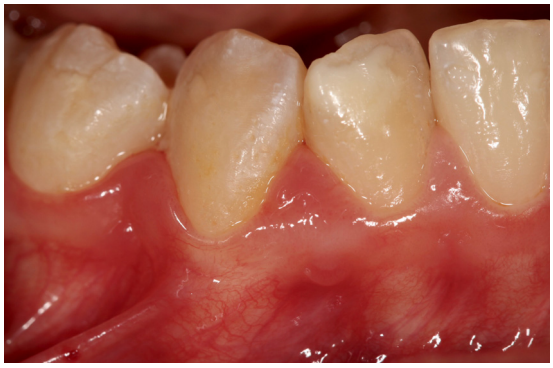

Fig. 5. Clinical view of 41, 42 and 43.

reported only in Maryland, in the United States [17]. Type-I DI has an autosomal dominant transmission [16]. Its degree of impact varies [16] without showing a clear correlation with the nature of the genetic mutation [4,5]. It is more visible in the temporary teeth and is clinically characterized by fragile and crumbly enamel. In affected cases, dentin is quickly exposed and shows attrition. Teeth have a color ranging from amber to bluish grey, associated with an opalescent nature [17]. Impact is less important in the permanent teeth; crowns can be normal, short, globular, abraded, or a combination of these clinical aspects [17]. Nevertheless, frequent enamel fractures and a change in enamel color are observed. Plain radiography shows globular crowns, with marked cervical constriction, short roots, obliteration of the pulp chamber, and a periradicular X-ray image because of early dentin exposure [15–17]. Enamel thickness and mineralization appear normal [17]. In the case of type-III OI, DI is found in 80% cases. However, no clinical or radiographic features characteristic of DI are observed in the patient, whether globular crowns, pulp retraction, periradicular X-ray image, or the opalescent clinical appearance.

The present clinical manifestations (brown/chalky stains, decreased enamel hardness) allowed us to raise several diagnoses: anamnesis revealed no fluorine overdose in childhood, eliminating fluorosis; these stains were present on the incisors and first molars as well as on the canines and premolars which enabled us to exclude the MIH diagnosis. Thus, our diagnosis shifted toward amelogenesis imperfecta. Amelogenesis imperfecta (AI) is a hereditary anomaly of the enamel that affects enamel structure and causes clinical abnormalities in all or almost all teeth, either in isolation or associated with a syndrome [18]. Four types of AI can be distinguished according to Wiktop [19]: hypoplasia (I), hypomaturation (II), hypomineralization (III), and hypomaturation/hypomineralization with taurodontism (IV). We believed the patient had the hypomature form, as the enamel and the dentin did not show the same radio-opacities [20]. There is currently no association between osteogenesis imperfecta and amelogenesis imperfecta in the literature, regardless of the OI or AI type. In the present case, this could be an atypical form of OI,

exceptionally associated with a strictly malformation of the enamel; however, it is more likely that the two pathologies were present concomitantly but without causal connection, such as trisomy 18. To confirm our diagnostic hypothesis, we wanted to conduct a genetic analysis aiming to find the characteristic abnormalities of AI. Unfortunately, despite our explanations, the patient's family refused other medical appointments to make a diagnosis that would not influence the treatment.

Conclusion

Abnormalities in tooth coloring associated with OI are not always related to DI. AI has never been described. The present case highlights the need for a diagnosis offered by an oral cavity specialist to differentiate between these two entities.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to this article.

References

1. Véronique Forin. Ostéogénèse imparfaite [Internet]. Encyclopédie Orphanet – La presse médicale référence, 2007. Available from: www.orpha.net/data/patho/Pro/fr/OsteogeneseImparfaite-FRfrPro654v01.pdf (cited 2015/06/09)
2. Glorieux FH. Osteogenesis imperfecta. Best Pract Res Clin Rheumatol 2008;22: 85–100.
3. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis,nomenclature and severity assessment. Am J Med Genet A 2014;164A:1470–1481.
4. O'Connell AC, Marini JC. Evaluation of oral problems in an osteogenesis imperfecta population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:189–196.
5. Bailleul-Forestier I, Berdal A, Vinckier F, de Ravel T, Fryns JP, Verloes A. The genetic basis of inherited anomalies of the teeth. Part 2: syndromes with significant dental involvement. Eur J Med Genet 2008;51:383–408.
6. Edwards JH, Harnden DG, Cameron AH, Crosse VM, Wolff OH. A new trisomic syndrome. Lancet Lond Engl 1960;1:787–790.
7. Cereda A, Carey JC. The trisomy 18 syndrome. Orphanet J Rare Dis 2012;7:81.
8. Crider KS, Olney RS, Cragan JD. Trisomies 13 and 18: population prevalences, characteristics, and prenatal diagnosis, metropolitan Atlanta, 1994–2003. Am J Med Genet A 2008;146A: 820–826.
9. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet Lond Engl 2004;363:1377–1385.
10. Saeves R, Lande Wekre L, Ambjørnsen E, Axelsson S, Nordgarden H, Storhaug K. Oral findings in adults with osteogenesis imperfecta. Spec Care Dent 2009;29:102–108.
11. Ortega A de OL, Rosa VLM, Zwir LMLF, Ciamponi AL, Guimarães AS, Alonso LG. Anatomic and dynamic aspects of stomatognathic structures in osteogenesis imperfecta: a case report. Cranio J Craniomandib Pract 2007;25:144–149.
12. Baty BJ, Jorde LB, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13: II. Psychomotor development. Am J Med Genet 1994;49:189–194.
13. Ettema AM, Wenghoefer M, Hansmann M, Carels CEL, Borstlap WA, Bergé SJ. Prenatal diagnosis of craniomaxillofacial malformations: a characterization of phenotypes in trisomies 13, 18, and 21 by ultrasound and pathology. Cleft Palate-Craniofacial 2010;47:189–196.
14. Boyce AM, Tosi LL, Paul SM. Bisphosphonate treatment for children with disabling conditions. PM R 2014;6:427–436.
15. Huber MA. Osteogenesis imperfecta. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:314–320.
16. Shields ED, Bixler D, el-Kafrawy AM. A proposed classification for heritable human dentine defects with a description of a new entity. Arch Oral Biol 1973;18:543–553.
17. Rios D, Vieira ALF, Tenuta LMA, Machado MA de AM. Osteogenesis imperfecta and dentinogenesis imperfecta: associated disorders. Quintessence Int Berl Ger 2005;36:695–701.
18. Crawford PJM, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet J Rare Dis 2007;2:17.
19. Witkop CJ. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification. J Oral Pathol 1988;17:547–553.
20. Piette E, Goldberg M. La dent normale et pathologique. De Boeck Université, 2001,pp. 235–246.