Genetic syndromes with premature loss of teeth: a retrospective study and a suggested classification

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Aim
The aim was to identify some of the disorders that feature premature loss of teeth (PLOT) and categorize them in a classification that might help in the diagnosis of these syndromes.

Patients and methods
In this study, the authors investigated the presence of PLOT in a cohort of patients over a 6-year period. The authors searched the files for PLOT as a chief complaint and then as a feature. The authors used the London Dysmorphology Database and Online Mendelian Inheritance in Man to find disorders that feature PLOT to review their files if present. Children who had no teeth at the primary evaluation were recalled as well as children on replacement therapies. Criteria for PLOT involved looseness, early loss, and remaining roots. In primary dentition, PLOT was from 2 to 5 years, whereas in permanents, it was at 6 years.

Results
Of 2044 patients, 57 had PLOT. They constituted 19 disorders, which are cherubism, Coffin-Lowry syndrome, congenital insensitivity to pain with anhidrosis, Fanconi–Bickel syndrome, Hajdu-Cheney syndrome, hypophosphatasia, hypophosphatemic rickets, kyphomelic dysplasia, lacrimoauriculodentodigital, Langerhans cell histiocytosis, mandibuloacral dysplasia, microcephalic osteodysplastic primordial dwarfism, Oculodentodigital dysplasia , osteogenesis imperfecta, osteopetrosis, juvenile Paget, polyostotic fibrous dysplasia, vitamin D-dependent rickets 1A, and vitamin D-dependent rickets 2A. Only three cases remain under investigation. The classification was constructed according to the dental findings.

Conclusion
PLOT due to genetic disorders could occur owing to caries, trauma, jaw lesions, and short roots and not only aggressive periodontitis. Both mandibuloacral dysplasia and nail–patella syndrome are probably not PLOT syndromes.

Keywords:
aggressive periodontitis, classification, premature teeth loss, syndromes

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Introduction

Teeth development that ultimately ends with primary teeth eruption, shedding, and then eruption of the permanent successors, is a timely intricate process. It can be used to assess a person's age in relation to their alveolar bone level starting from 30 weeks *in-utero* till 24 years of age (AlQahtani *et al.*, 2010). It is an accurate process that fails considerably in case of their premature loss.

Among the famous causes of premature loss of teeth (PLOT) is early-onset periodontitis, which is currently classified under aggressive periodontitis, a condition characterized by rapid progression of bone loss that exceeds the amount of plaque and calculus to be found (Papapanou *et al.*, 2018). Clinically, it may show mild gingival erythema (Devi *et al.*, 2015).

Aggressive periodontitis is a feature in several genetic syndromes. The most famous of those is Papillon-Lefevre syndrome and its phenotypic variant Haim-Munk syndrome, which are hyperkeratosis disorders (Sulák *et al.*, 2016). Other syndromes include immunologic disorders such as Chediak-Higashi, leukocyte adhesion deficiency, and congenital neutropenia (Rezende *et al.*, 2013; Devi *et al.*, 2015; Abu Karaky *et al.*, 2017). The list also includes several skeletal disorders such as Coffin-Lowry syndrome, which is associated with cementum hypoplasia (Koehne *et al.*, 2016). Paget's disease when affects

the facial bones causes the teeth to become loose and lost (Campolongo *et al.* 2018).

In addition, there are metabolic bone disorders such as hypophosphatasia (alkaline phosphatase deficiency) and hypophosphatemic rickets (excessive loss of phosphates through the kidney; used to be termed vitamin D-resistant rickets) (Al-Jundi *et al.*, 2011; Whyte, 2017). Periodontal diseases are common in hypophosphatemic rickets and vitamin D-dependent rickets (affection of enzymes responsible for vitamin D metabolism or affected vitamin D receptors), though it is more severe in the latter (Japaridze *et al.*, 2015). Some bone disorders could show PLOT due to periodontal affection as well, such as Hajdu-Cheney syndrome (HC) (Dokou *et al.*, 2016).

PLOT is not exclusive to early-onset periodontitis but could be found in conditions such as cherubism (Stoor *et al.*, 2017). It could also be owing to traumatic injuries as in congenital insensitivity to pain where a child can playfully extract their tooth without feeling any pain (Mostafa *et al.*, 2017). Extensive carious lesions due to abnormal enamel in syndromes like epidermolysis bullosa has been reported to be the cause of PLOT (Leal *et al.*, 2016).

Usually the diagnosis of these cases is not straightforward. In some instances, it could be even a 'dilemma' with no final diagnosis (Sharma and Whatling, 2011). Moreover, because these conditions are not usual in everyday dental clinics, yet if faced with one, a list of 100 entries appeared on OMIM (2019) when consulted, and 62 entries in the London Dysmorphology Database (Winter and Baraitser, 2014). This study aims to include the most common syndromes with PLOT.

Patients and methods

Orodental records of the patients from the outpatient clinic of the skeletal dysplasias and limb malformation clinic over a period of 6 years (2014–2019) were reviewed. Records with the entry 'PLOT' were included. The diagnoses were reviewed as well, and reevaluation by follow-up of patients who might show PLOT after eruption was arranged. Moreover, patients who should have been on medications for treatment of their conditions, particularly hypophosphatemic rickets and vitamin D-dependent rickets type IA (VDDR IA), patients were reassessed. This study followed the declaration of Helsinki guidelines for retrospective studies.

Results

The total number of patients examined was 2044. Patients with PLOT as a chief complaint were four patients, whereas as a manifestation found on examination were 57. The patients' ages at the time of presentation ranged from 1 to 29 years old. The list included 19 disorders, and three cases are still under investigation, where two of them had PLOT as a chief complaint, as shown in Table 1.

Table 1 The studied disorders exhibiting premature loss of teeth as a manifestation

Disorders	OMIM number	Number of patients	Number of patients with PLOT
Cherubism	118400	1	0
Coffin-Lowry syndrome	303600	1	0
Congenital insenstivity to pain with anhidrosis	256800	6	4 (1 had it as a chief complaint)
Fanconi-Bickel syndrome	227810	1	1
Hajdu-Cheney syndrome	102500	1	1 (aged 29)
Hypophosphatasia	241500	7	1 (1 had it as 1ry chief complaint)
Hypophosphatemic rickets	241520	30	10
Kyphomelic dysplasi	211350	9	1
Lacrimoauriculodentodigital	149730	1	1
Langerhans cell histiocytosis	604856	1	1 (with mild gingival erythema)
Mandibuloacral dysplasia	248370	2	0
MOPD	210720	2	1
Oculodentodigital dysplasia	257850	2	2
Osteogenesis imperfecta	166200	200	21 (OI type I)
Osteopetrosis	259710	8	3
Juvenile Paget	601080	1	1
Polyostotic fibrous dysplasia	174800	1	0
Vitamin D-dependent rickets 1A	264700	2	2
Vitamin D-dependent rickets 2A	277440	10	3
Under investigation		3	3 (2 have it as a 1ry chief complaint)
Total number of patients with PLOT		289	56

MOPD, microcephalic osteodysplastic primordial dwarfism; PLOT, premature loss of teeth.

The age range of the patients who were diagnosed with syndromes that feature PLOT according to the literature but not listed in the files was 1 month to 15 years of age. This list included additional seven syndromes (Table 2). Patients who were recalled amounted to 295 patients from both lists. Patients who complied to the reevaluation were 289, whereas three patients were deceased. Two patients had congenital insensitivity to pain and one had osteopetrosis. The remaining three patients could not be reached.

Patients on replacement therapy were the two patients with VDDR IA; one of them had shown improvement, and the other one has just started his regimen. As for the 30 patients with hypophosphatemic rickets (Fig. 1a and b), only 10 patients had PLOT, and only one showed improvement in their dental condition after eruption of the successors.

The results aided in the formulation of the suggested classification in Table 2. The dental features were used as the base for the classification. It aims to aid the general practitioner dentist to categorize the condition at hand and hopefully reach the diagnosis, which could be then confirmed by molecular analysis if possible.

Table 2 Suggested classification of premature loss of teeth syndromes according to causation of loss

I. Periodontitis	II. Abnormally short or absent roots
	Dentin dysplasia
	MOPD
Metabolic diseases of bone	III. Caries
Decreased mineralization	Epidermolysis bullosa
Hypophosphatemic rickets	LADD syndrome
Hypophosphatasia	
VDDR type I and II	
Osteogenesis imperfect	
Fanconi-Bickel syndrome	
Increased mineralization	
Juvenile Paget	
Osteopetrosis	
Skeletal dysplasias and Limb anomalies	
Coffin-Lowry syndrome	
Hajdu-Cheney syndrome	
ADULT syndrome	
Blood disorders and immunologic disorders	
Chediak-Higashi syndrome	
Leukocyte adhesion deficiency	
Congenital neutropenia	
Hyperkeratosis	
Papillon-Lefevre syndrome	
Haim-Munk Syndrome	
Collagenopathies	
Ehlers-Danlos Types IV and VIII	
Poikilodermatosis	
Kindler syndrome	
Metabolic disorders	
Acatalasemia	
	IV. Trauma
	CIPA
	V. Lesions
	Cherubism
	Fibrous dysplasia (monostotic or polyostotic)
	Familial expansile osteolysis

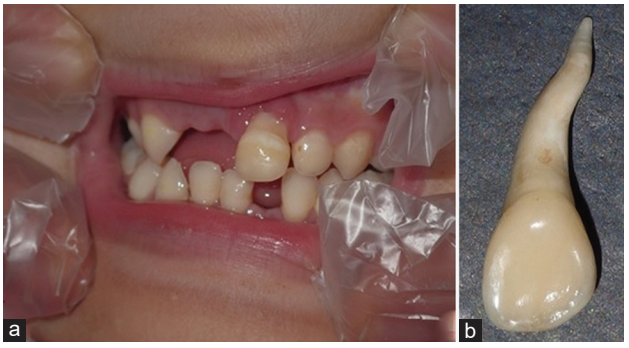
Discussion

PLOT in a population of normal children is caused chiefly by caries and its subsequent events, and trauma comes in the second place (Olatosi and Sote, 2012; Eigbobo *et al.*, 2014). Nevertheless, in a population of children with skeletal and limb disorders, these causes may take a later ranking. This study shows that the prime cause of early teeth loss is periodontal affliction caused by the genetic disorders, and this is similar to a population of normal adults in certain communities (Danielson *et al.*, 2011).

Periodontal health is defined as the absence of periodontal disease signs and symptoms in a functional dentition which entails absence of a biofilm, inflammation, attachment loss, bone loss, pain, and mobility (Mariotti and Hefti, 2015). Aggressive periodontitis is a type of periodontal disease characterized by its rapid progression irrespective of the scarcity of the biofilm on the teeth. It usually affects children and adolescents and it could be localized or generalized. The disease is multifactorial, yet a linkage with chromosome 1 has been established owing to its familial tendencies (Fine *et al.*, 2018). The study at hand included no case of aggressive periodontitis, but it was present as a feature in several cases.

The absence of an isolated case of aggressive periodontitis herein could be explained by the type of flow of patients to the limb malformation and skeletal dysplasia clinic where the patients were recruited from, as these patients are likely to consult orodental genetics clinics. The type of patients' flow also explains the absence of cases of epidermolysis bullosa in the pool presented.

Figure 1



(a–b) A presentation of a girl with hypophosphatemic rickets. (a) Oral condition of the 5-year-old girl with premature loss of teeth; (b) the lost tooth with a complete root.

Early loss of teeth at a young age could be a mark of hypophosphatasia, particularly odontohypophosphatasia or the childhood type (Haliloglu *et al.*, 2013; Yokoi *et al.*, 2019). For the patients with hypophosphatasia in this study, 50% were under 12 months of age, which could be the reason they had not lost their teeth yet, but PLOT remains a key feature of the disorder as they have affected mineralization of acellular cementum, leading to root detachment from the alveolar bone (Foster *et al.*, 2012; Whyte *et al.*, 2015).

Other metabolic bone disorders that feature early teeth loss are hypophosphatemic rickets and VDDR. One-third of the patients with hypophosphatemic rickets showed PLOT which is in accordance with the literature, where PLOT represents an occasional finding, whereas dental caries and unprompted dental abscesses are the most common oral features in this disorder. According to Rabbani *et al.* (2012), dental manifestations can be detected in 23–67% of the cases with hypophosphatemic rickets. The affection is thought to be caused by periodontal affection secondary to an abnormal dentin matrix protein 1 (Al-Jundi *et al.*, 2011).

Although both cases of VDDR IA in this study have shown PLOT which disappeared in the newly erupted successors of one patient after taking the replacement therapy, it is not always the case for all patients with VDDR IA, as reported by Zambrano *et al.* (2003), where the reported patient experienced enamel hypoplasia, gingivitis, periodontitis, and malocclusion clinically and thin dentin and large pulp chambers radiographically.

It is the general understanding that periodontitis is less severe in VDDR types (Japaridze *et al.*, 2015). In contrast, this study proves that both conditions could amount to PLOT. In addition, in the report by Nishino *et al.* (1990), the patient with VDDR II presented no PLOT, which explains the seven patients of the 10 who have shown no PLOT in the study at hand. This reinforces the probability of PLOT being an additional feature in these disorders. All types of rickets affect tooth development, eruption, and attachment; however, teeth morbidity does not occur in all cases, an area where further studies are warranted.

Fanconi-Bickel syndrome is a rare but well-defined clinical entity, inherited in an autosomal recessive disorder. It is mainly characterized by failure to thrive, distended abdomen, hepatomegaly, renal tubular disease, reduced bone density, rickets, hypophosphatemia, sparse subcutaneous fat, thin limbs, developmental delay (in some patients), and recurrent fever. The oral findings as described by Jomaa *et al.* (2015) were delayed eruption of teeth, hypocalcification, rapidly progressive periodontal disease, and premature loss of primary teeth. These dental findings of Fanconi-Bickel Syndrome are similar with variable degrees of hypophosphatemic vitamin D-resistant rickets, renal tubular acidosis, and hepatomegaly resulting from glycogen storage disease type XI. Our patient was a female aged 2.5 years old; her oral evaluation showed microstomia, PLOT, and enamel hypocalcification, which coincide with the oral findings described by Jomaa *et al.* (2015), who recommended that a dentist should collaborate during the early ages of the affected children to lessen the orodental morbidity.

Another disorder of decreased bone mineralization is the collagen disorder osteogenesis imperfecta (OI). Dentally, OI is a disorder of abnormal dentin, which occurs in some OI types, presenting as dentinogenesis imperfecta, and at instances, it may show teeth agenesis (Malmgren *et al.*, 2017). PLOT on the contrary, was reported only once, and it is thought to be owing to other mutations in association with OI type I (Lu *et al.*, 2014). This probable association was observed in twenty one cases of OI out of 200 in the current study. These cases of OI with PLOT are candidates for exome sequencing to identify the causation of the dental phenotype.

On an opposite note, disorders of increased mineralization that may show PLOT are Paget disease of bone the juvenile type and osteopetrosis (Antoniades *et al.*, 1993; da Silva Barbirato *et al.*, 2017). These disorders usually show delayed eruption of teeth (Oosterkamp *et al.*, 2014; Whyte *et al.*, 2014). PLOT on the contrary is an uncommon finding. The exact cause of the teeth loss in both disorders is still unclear. It is said that in certain types of osteopetrosis, it could be owing to affection of the teeth attachment apparatus due to defective bone metabolism. The only case of juvenile Paget provided in this study showed PLOT as well as two out of the eight cases of osteopetrosis.

Among the bone dysplasias that have periodontitis as their key feature is HC. It is a disorder of acro-osteolysis and abnormal facial features together with the dental affection. The exact cause of periodontitis provoked PLOT in these cases is still at large. An early account by Chawla (1964) describes the ridges of these patients to be atrophic and osteoporotic. Although atrophy of the ridges might at first be a good cause for teeth loss, it is usually an event that follows tooth loss not precede it (Reich *et al.*, 2011). The fact that these patients are candidates for implant placement is proof that their bone condition is not that severe as to cause tooth loss (Dokou *et al.*, 2016). On the contrary, abnormal

dentine and cementum could explain why these patients may have PLOT (Grant *et al.*, 1995).

It was difficult to judge the reason for PLOT in the patient with HC herein, as she was 29 years old with difficulty to maintain proper oral hygiene owing to her condition; it was then correlated with the clinical geneticists that HC is the cause of PLOT in her case.

Another bone disorder that affects the cementum is the Coffin-Lowry syndrome. An X-linked disorder characterized by abnormal facies, fusiform fingers, deafness, and intellectual disability. PLOT could be an early diagnostic sign of this disorder, but it is not common in all patients, as it is the case in the study at hand (Hartsfield *et al.*, 1993).

It is unlikely to find PLOT in patients with kyphomelic dysplasia (KD), a disorder of bowing and short limb bones. The oral manifestation often mentioned with it is micrognathia, and there is an account that reports cleft lip and palate (Temple *et al.*, 1989). To our knowledge, this is the first study to associate PLOT with KD. The probability of having a different gene at work in this isolated case from 9 could not be dismissed, though the causative gene for KD is still unknown (OMIM, 2019).

In contrast to KD, mandibuloacral dysplasia (MAD), the progeria-like disorder, is mentioned in the literature twice as one associated with PLOT, but the case reevaluated in the current study had none. It is worth noting that the only photograph provided in the first report by Zina *et al.* (1981) had no mandibular hypoplasia. The mandible was rather steep and the chin was long, whereas in the second report by Al-Haggar *et al.* (2012), it is not stated whether a dentist evaluated the orodental manifestations. However, according to Hennekam *et al.*(2010), they assert that patients with MAD have absent cellular cementum and hypoplastic roots (Danks *et al.*, 1974). Our findings agree with Afifi and El-Bassyouni (2005) that PLOT is not a key feature in MAD.

Cherubism and polyostotic fibrous dysplasia (PFD) are among the syndromes that might show PLOT according to the literature. Both disorders are among the many fibro-osseous lesions that can affect the jaws, where bone is replaced by fibrous and immature calcified tissue (Suarez-Soto *et al.*, 2013). It is said that premature loss of deciduous teeth occurred in a case of cherubism secondary to the lesion (Stoor *et al.*, 2017). This might be the case for PFD as well. The only reference to PLOT with PFD is as a differential diagnosis in a case of familial expansile osteolysis, which is another disorder that may show PLOT, but to our knowledge, there has been no reports of PLOT with PFD (Crone and Wallace, 1990).

The theory of PLOT being secondary to the fibro-osseous lesion could be supported by the fact that in both disorders the lesion causes loss of the lamina dura, resorption of roots, and displacement of teeth, a group of features that might contribute to PLOT. Both cases in this study have shown no PLOT. In PFD, it was because the craniofacial complex was spared, whereas in cherubism, tooth agenesis and displacement was only found as reported before (Temtamy *et al.*, 2012).

Lacrimoauriculodentodigital syndrome is a type of ectodermal dysplasia characterized by a high hair line, sparse eyebrows, xerostomia, lacrimal affection, and radial defect (Hajianpour *et al.*, 2017). The patient in this study experienced PLOT secondary to the effects of xerostomia.

Another disorder that could appear on electronically generated lists when searching for syndromes with PLOT is nail–patella syndrome, a disorder mainly characterized by aberrant nails, patella, elbow joints, renal problems, and eye problems. There is a single account by Sweeney *et al.* (2003), where they mentioned the probability of these patients to have thin enamel, which may be the cause for their teeth fragility, but there was no mention of PLOT as a feature. In the cases herein, the patients could not be reached, but at the time of presentation, they had normal dentition. This is still an area for further investigation and for that it is not categorized in the classification, but if it will be, it should go under disorders that might show PLOT owing to caries, but there was no sufficient evidence to do that.

Several immunologic disorders manifest with PLOT. Among them is Langerhans cell histiocytosis. Oral manifestations occur in 77% of the cases, which makes this disorder, despite its rarity, essential to the awareness of the dentists as they might be the first to examine these patients. The manifestations of the disease with all its types are owing to the invasion of the tissues by macrophages and dendritic cells. This could be in the soft tissue and the bone. Affection of the alveolar bone ultimately ends in PLOT in an aggressive periodontitis like manner (Devi *et al.*, 2015). The case in the study at hand was a case of chronic diffuse Langerhans cell histiocytosis (Hand-Schuller-Christian disease), and it showed PLOT with mild gingival erythema.

Congenital insensitivity to pain with anhidrosis is an example of PLOT owing to trauma. The patients luxate their teeth intentionally as these patients exhibit self-mutilating behavior, as they have inability to sense

pain, intellectual disability, and no sweating. These patients also experience tooth agenesis, which should not be mistaken for PLOT (Xue *et al.*, 2018). Proper history taking would unwind the confusion.

Finally, there are other syndromes that can show PLOT, but were not included in this study either owing to their rarity or on account of the type of the flow the clinic receives. These disorders have among them those that may present with aggressive periodontitis such as Ehlers-Danlos syndrome, Kindler syndrome, and the metabolic disorder acatalasia (Delgado and Calderón, 1979; Wiebe *et al.*, 1996; Abel and Carrasco, 2006). There are syndromes that affect root length and morphology such as dentine dysplasia and microcephalic osteodysplastic primordial dwarfism type II (Kantaputra *et al.*, 2011; Ye *et al.*, 2015). There are disorders that would feature PLOT, but the exact cause of the loss is still unclear, such as Acro–Dermato–Ungual–Lacrimal–Tooth (ADULT) syndrome (Avitan-Hersh *et al.*, 2010).

Conclusion

To conclude, it is customary practice to review PLOT syndromes that feature aggressive periodontitis in the dental literature rather than presenting those that occur due to caries and trauma (Sharma and Whatling, 2011), a routine that has been broken in the study herein to address comprehensively the PLOT manifestation and put to the awareness of the dentist all possible causes of such an alarming symptom for both the patients and their families. It also served to clear the misconception about certain syndromes where they are found on electronically generated lists of disorders as syndromes of PLOT whereas they seldom show that as it is the case with MAD. Yet, it is fair to say that the practice of reviewing aggressive periodontitis syndromes is justifiable, as the diagnosis of these groups of disorders is somewhat challenging. We suggest that the classification at hand might help with this dilemma. We assume it could be durable to time as it can accept additions. It is also based on the dentist's findings, which could prove to be a helpful tool.

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Conflicts of interest

There are no conflicts of interest.

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