Twenty-year follow-up of a familial case of PTH1R-associated primary failure of tooth eruption

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Introduction: Nonsyndromic primary failure of eruption (PFE) is a rare autosomal dominant disorder of dental eruption with no obvious dental or soft tissue interference. The purposes of this study were to genetically and clinically characterize a family with many members affected by PFE and to describe the natural evolution of the disorder. **Methods:** Three generations of a family with 18 members, 10 of them clinically affected by PFE, were evaluated periodically during 20 years of clinical follow-up. PFE was observed in varying degrees of severity in both sexes. Clinical presentation became more severe in adulthood. One patient had spontaneous reeruption of 2 posterior teeth. Cervical root resorptions were observed in 3 members. Genetic analysis showed a deleterious heterozygous mutation in intron 9 of the PTH1R gene (c.639-2A>G) and diagnosed an additional affected member. **Conclusions:** The long-term follow-up of PFE cases in this family permitted the following observations: (1) the onset occurred from the preemergence to the postemergence phases, (2) PFE appeared to be closely related to ankylosis, (3) affected teeth maintained the eruptive potential even in adulthood, (4) the earlier the onset the more severe the open bite, and (5) cervical root resorptions occurred in 3 affected members. (Am J Orthod Dentofacial Orthop 2017;151:598-606)

Nonsyndromic primary failure of eruption (PFE) is a term used to describe a rare disorder in the dental eruption process with no obvious dental or soft tissue interference or associated systemic or syndromic conditions. Although few and isolated cases were reported before 1981, the first definition of the disorder can be attributed to Proffit and Vig.[1] They originally described the condition as a cessation of the eruptive process that affects posterior teeth more severely, rarely in a symmetric pattern. Anterior teeth almost never are affected. Involved teeth may initially respond to orthodontic forces, but ankylosis occurs invariably. In other words, affected teeth seem to fail in the eruption propulsive movement and are not believed to be ankylosed.[2]

The condition was further subclassified into type I, characterized by progressive open bite from the anterior toward the posterior segment, and type II, in which the second molar has some, although inadequate, eruption potential.[3] The timing of type I onset is speculated to occur at the same time as craniofacial development of all affected teeth, whereas type II seems to be related to the stage of root development.[4] Both types may coexist in different quadrants in the same patient,[3] a condition that was further classified as type III.[5]

Although some authors have been reluctant to speculate about the genetic etiology, recent studies have demonstrated heterozygous pathologic mutations in the parathyroid hormone receptor 1 (PTH1R) gene, with a mode of inheritance compatible with autosomal dominant transmission.[5-11]

Differential diagnosis includes mechanical interference with eruption, syndromes associated with eruption defects,[1,12] and long-term sequelae of radiotherapy. Mechanical interference caused by tongue or lip interpositioning leads to an open bite at nearly the same vertical level.[1] Conversely, teeth lay at different vertical levels in PFE. When the eruption ceases after tooth emergence, it may also be diagnosed as secondary retention, which is

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All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.
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Submitted, August 2015; revised and accepted, September 2016.
0889-5406/$36.00

http://dx.doi.org/10.1016/j.ajodo.2016.09.012

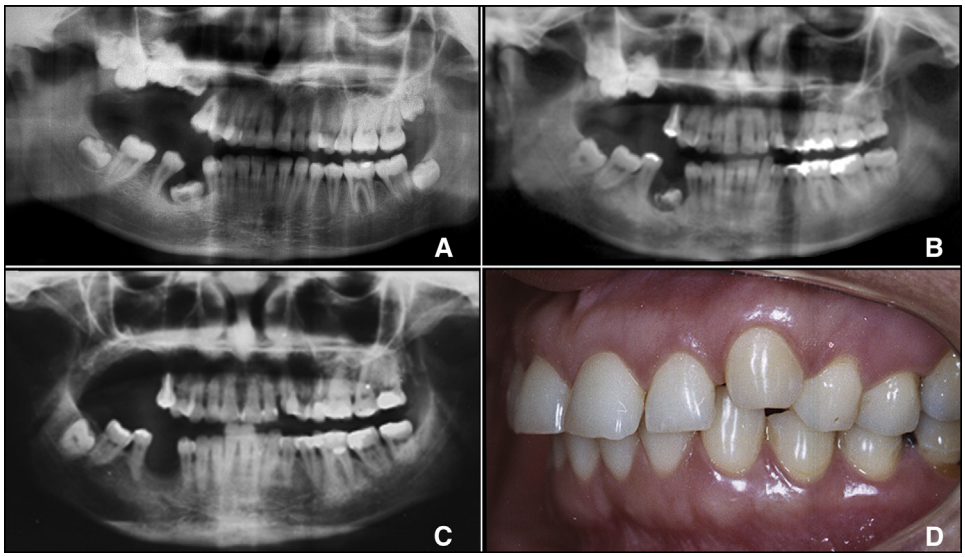

Fig 1. A, Panoramic radiograph of patient II.9 at age 15 years, showing a unilateral open bite with involvement of the deciduous molars, with no mechanical interference. At the ages of **B,** 23 and **C,** 42, progressive intrusive movement of the maxillary left canine and mandibular right third molar can be observed. **D,** Clinical aspect at age 42, with the maxillary left canine in infraocclusion.

attributed to ankylosis.[13] Clinically, it is challenging to distinguish secondary retention from PFE.

Treatment of PFE depends on the degree of clinical severity but usually leads to frustrating results. In severe cases, orthodontic treatment, even associated with surgical procedures, has not resulted in effective establishment of occlusion.[1] Prosthetic techniques are frequently the most feasible treatment option.[1,14]

The rarity of PFE still leads to several gaps in our comprehensive knowledge of its pathogenesis. It is intriguing that a genetically determined condition can result in asymmetrical impairment of the eruptive movements and in various degrees of severity in different segments of the dental arches. Long-term clinical and radiographic studies on the natural course of PFE may provide the basis for determining the prognosis and provide new insights into the pathologic mechanisms. The aim of this study was to genetically and clinically characterize a family with 11 members affected by PFE in 20 years of follow-up.

CASE REPORT

This study was carried out in accordance to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the Dental School of Araçatuba (protocol 00839/2011) in Brazil. Written informed consent was obtained from all family members that permitted blood sampling for genetic analysis.

A 15-year-old girl (patient II.9) was referred to the Oral Surgery Department because of an infectious process caused by the maxillary deciduous first molar of the right side. The tooth was severely submerged, and its position had led to a periodontal pocket and an acute periodontal abscess. Clinically, a unilateral posterior open bite was observed at the right side. The panoramic radiograph showed inclusion of all maxillary permanent molars of the affected side, with no discernible mechanical interference (Fig 1, *A*). The maxillary deciduous tooth was extracted. At the age of 23, the patient returned for extraction of the mandibular deciduous molar of the affected side due to suppuration via periodontal pocket. It was observed that the maxillary canine of the left side was slightly above the occlusal plane (Fig 1, *B*). This infraocclusion was evident at the age of 42, when the mandibular right second molar was completely present in the oral cavity, and all maxillary molars of the same side had already been extracted. The maxillary second and third molars were fused by concrescence. A peculiar finding observed in the panoramic radiographs was the apparent increasing proximity of the mandibular right third molar to the mandibular channel during the follow-up period.

The family was investigated with a follow-up of 20 years, from the time when patient II.9 was 23 years old. Ten of 18 members were clinically affected with different degrees of severity, some of them clearly

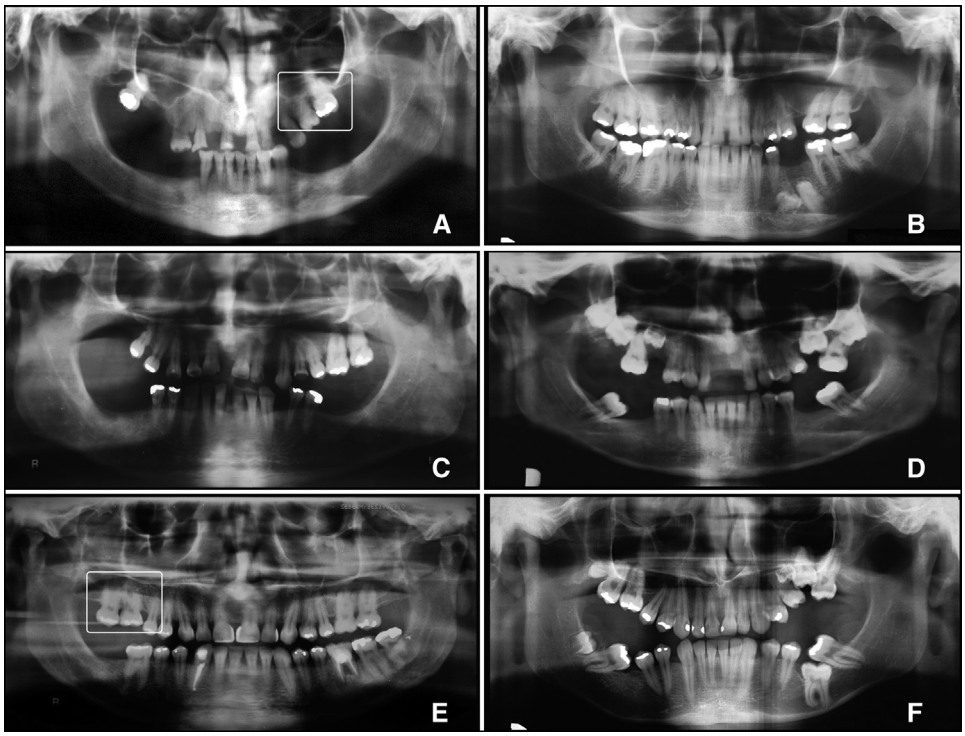

Fig 2. Panoramic radiographs of various members of the family during the follow-up period, showing the phenotypic variability: **A,** patient I.2 (male) at age 62; **B,** patient II.3 (male) at age 32; **C,** patient II.5 (male) at age 47; **D,** patient II.8 (female) at age 21; **E,** patient II.11 (male) at age 37; **F,** patient II.12 (male) at age 20.

bilateral, with no difference between sexes (Fig 2). Patients I.1 and I.3, as well as II.1, II.2, and II.7 were partially edentulous in the posterior segment; this did not permit any clinical conclusions concerning the diagnosis of PFE. Three members had anterior teeth in infraocclusion. Except for third molars, affected teeth had the alveolar bone crest at the level of the cementoenamel junction. There was no evidence of systemic disease in the affected people, and no other features of craniofacial and skeletal malformations or facial asymmetry. Dental arches were well developed, and diastemas were a common finding.

Figure 3 depicts the familial pedigree. During interviews, it was reported that 2 members of the third generation are affected by PFE additionally. However, they were not available for clinical and radiographic examinations and were not included in this report.

During the follow-up period, no treatment was carried out for open-bite correction, except for tooth extractions for periodontal reasons in several members of the family. Dental extractions did not cause any positional modification of adjacent teeth, in vertical direction or in mesial drift. In general, the condition worsened in adulthood, when in some cases PFE became prominent.

Patient II.11 had a peculiar course of development. He was unaware of his condition at age 18, since only the first molars were bilaterally in mild infraocclusion (Fig 4, *A* and *B*). After 20 years, there was a clear open bite at the right side. Surprisingly, the first molars on the left side were in occlusion, and the mandibular right first molar was at the occlusal level. Additionally, the diastemas between the maxillary left and mandibular canines and first premolars were closed (Fig 4, *C* and *D*).

Multiple external cervical root resorptions involving the maxillary posterior teeth were diagnosed in patient II.12 at age 40. External root resorption was initially diagnosed in the maxillary right second premolar, which radiographically had a mottled aspect in an infrabony cavity. The patient reported unspecific and sporadic discomfort. The root canal seemed to be intact. A cone-beam computed tomography image showed further external root resorptions in the maxillary right first molar and the maxillary second molars of both sides (Fig 5, *A* and *B*). Although these resorption lesions were

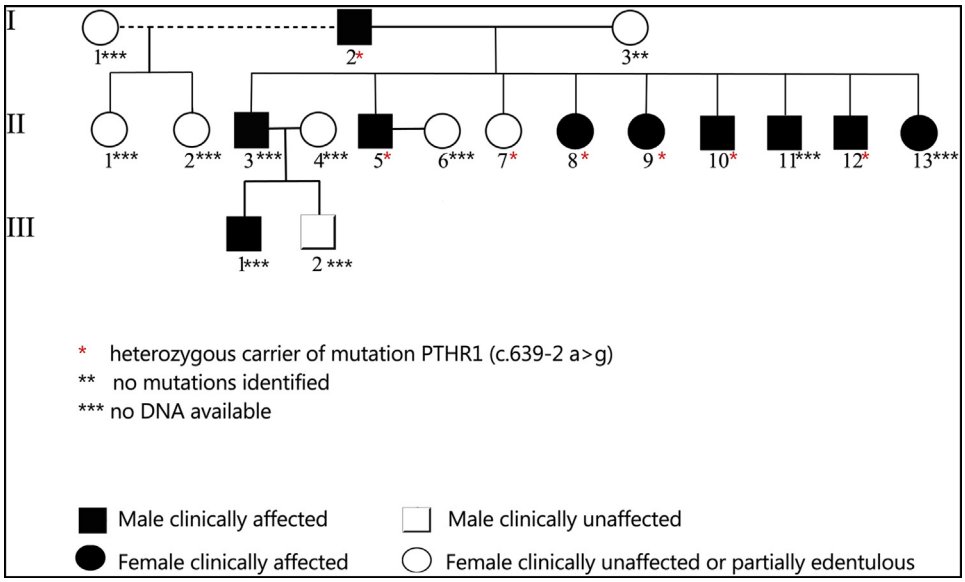

Fig 3. Heredogram showing an autosomic dominant pattern of inheritance.

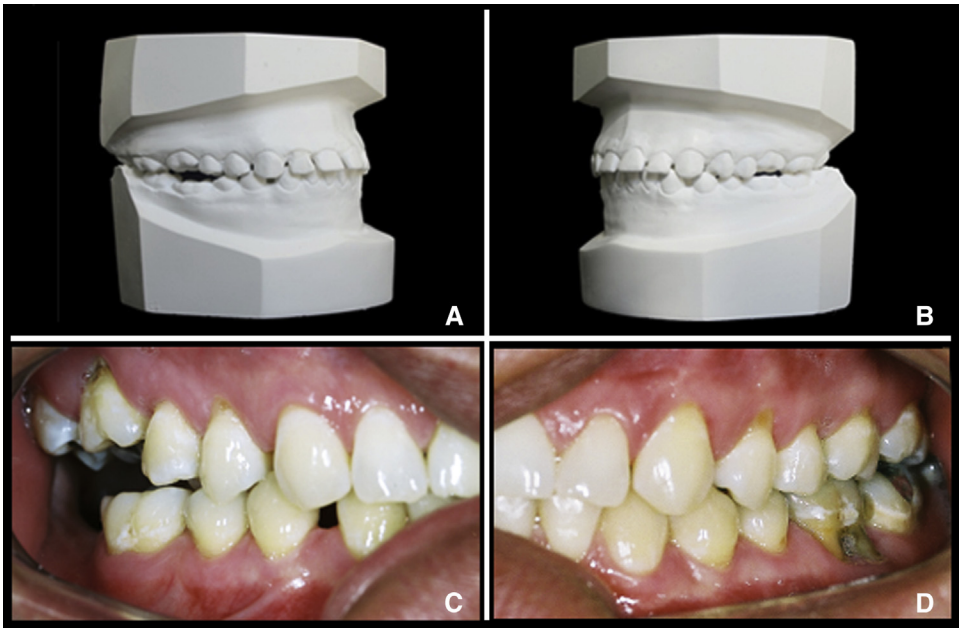

Fig 4. **A** and **B,** Plastic models of patient II.11 when he was 18 years old, showing bilateral open bite at the area of the first molars; **C** and **D,** clinical images taken after 20 years show that the maxillary left first molar and the mandibular right first molar reached the occlusal level.

invasive, they were asymptomatic. Radiographic images compatible with cervical root resorption were also found in the maxillary left first molar of patient I.2 (Fig 5, *C*) and in the maxillary right first molar of patient II.11 (Fig 5, *D*); all were in infraocclusion.

GENETIC ANALYSIS

DNA analysis was carried out in the index patient II.9 by Polymerase Chain Reaction amplification and subsequent didesoxynucleotide sequencing of all coding exons and the immediate flanking exon/intron boundaries

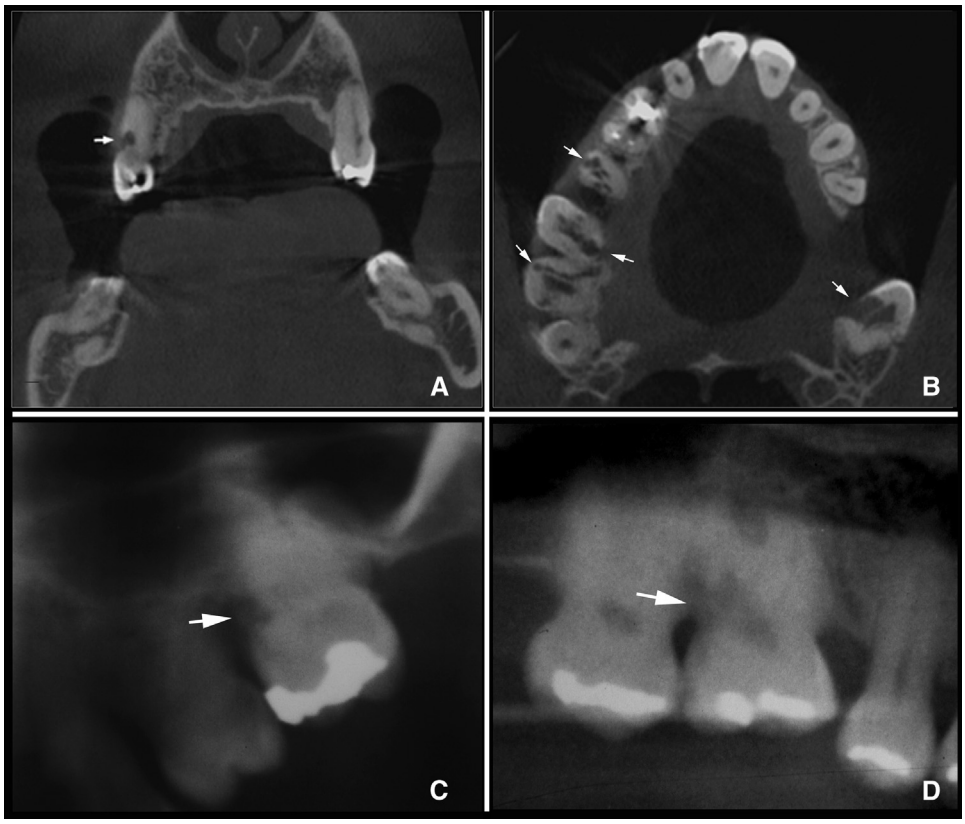

Fig 5. **A** and **B,** Tomographic images of patient II.12 at age 40, showing multiple cervical resorptions in posterior maxillary teeth (*arrows*); note the subgingival position of root resorptions. Details of the panoramic radiographs of **C,** patient I.2 and **D,** patient II.11, showing radiolucencies with scalloped margins at the cementoenamel junction.

(±14 nucleotides) of the PTH1R gene (ref. seq. NM_000316.2), whereby "intron" is defined as a nucleotide sequence within the gene which is removed by RNA splicing during mRNA maturation, and an "exon" is a nucleotide sequence that is still part of the mature mRNA after introns have been removed. The primer sequences were described in a previous study.[11] A heterozygous mutation (c.639-2 A>G) affecting the acceptor splice consensus sequence was found flanking exon 9 of the PTH1R gene. Split eukaryotic genes like PTH1R require the removal of the intronic sequences by the spliceosome and rely on highly conserved sequences at the borders between the respective intronic and exonic sequences. This is particularly true for mutations affecting 1 of the 2 nucleotides at the invariant. AG dinucleotides within the splice acceptor site present at the 3′ end of all known introns or the invariant GT dinucleotide within the splice donor site present at the 5′ end of nearly all known introns.[15] Regarding c.639-2 A>G, this mutation affects the highly conserved adenosine nucleotide at position -2 at the splice acceptor site and thus renders the invariant AG dinucleotide ineffective for the splicing machinery. As a result, the mutation most likely leads to impairment in the mRNA splicing process and is expected to produce a nonfunctional receptor due to protein truncation. The pathogenicity of the mutation is predicted by the splice site prediction suite of the Alamut Mutation Interpretation Software (Interactive Biosoftware, Rouen, France), although the exact nature of the mutational consequences is unknown and would require the sequencing of the mutant transcript ideally in the affected dental tissues. Interestingly, at the same position, a different splice site mutation (c.639-2 A>C) was previously reported and was also predicted to result in an aberrantly spliced transcript.[11] Both mutations are extremely rare and are not present in any of the 4 major public databases on human gene variations, including the dbSNP database (build44), the ExAC database[16], the NHLBI GO Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), and the 1000 Genomes Project.[17]

To confirm segregation of c.639-2 A>G with disease in our pedigree, family members I.2, I.3, II.5, II.7, II.8, II.10, and II.12 were specifically sequenced for the absence or presence of the c.639-2 A>G mutation (Fig 3). Clinically affected family members I.2, II.5, II.8, II.10, and II.12 all were heterozygous carriers of the splice site mutation. Patient II.7 also carried the heterozygous mutation c.639-2 A>G, although not clinically diagnosed because of the edentulous condition, giving a total of 11 affected members in this family. Family member I.3 showed the reference sequence.

DISCUSSION

In this study, PFE was genetically confirmed by identifying a heterozygous deleterious mutation in the PTH1R gene segregating with the disease in 6 persons from 2 generations. The inheritance pattern suggests autosomal dominant transmission, in full accordance with previous studies.[2,3,5-11,18] This mutation in the PTH1R gene is expected to result in failure in the splicing processes of PTH1R pre-mRNA, most likely leading to the truncation of the protein. The PTH1R gene encodes a family B G-protein-coupled receptor that gives rise to several biologic functions when activated by parathyroid hormone or parathyroid hormone-related protein. The former polypeptide ligand regulates blood levels of calcium and phosphate, whereas the parathyroid hormone-related protein acts in developing tissues in a paracrine manner and regulates cell differentiation and proliferation.

Genetically determined malformations have a tendency to be symmetrical. Moreover, tooth eruption is characteristically timely and bilaterally symmetric.[19] Hence, it is intriguing that, although caused by the same PTH1R genetic mutation, the PFE phenotype varies greatly in severity, is asymmetric, and is more severe in posterior areas.[1] A closer analysis of the PFE features may point to temporal and regional-based factors in its pathogenesis.

Regional differences in gene expression have been shown during early stages of tooth development[20] and eruption.[21] As a result, different sets of genes are expressed in anterior and posterior segments, in an overlapping pattern of expression domains of different homeobox genes that, in conjunction, provide regulatory "rules" for the development of dental mesenchyme.[20] Tooth eruption begins after crown formation, in an interdependent sequence of eruption movements, alveolar bone growth, and root formation, but probably these events are governed by different genetic programs. Involved events seem to have a window of opportunity when an eruption pathway must be provided for tooth movement. If such events are not well coordinated, tooth eruption may be compromised, and ankylosis may occur.[19] Fortunately, some compensatory mechanisms exist with variable rates of success to overcome some discrepancies.

The clinical presentation of PFE indicates that tooth eruption is subjected to microenvironmental influences, in addition to epigenetic and local factors.[22] Interestingly, the biologic response to PTH1R stimulation varies according to the structure of the bound ligand, the cell type, and the prevailing homeostatic condition of the organism.[23] As a consequence, PTH1R signaling is determined by microenvironmental factors related to cellular context, resulting in biologic responses specific in temporal and spatial terms.[23] In conjunction, these data may, at least in part, account for the asymmetric phenotype of this genetically determined condition. However, it seems to be unreasonable to state that PFE can be unilateral. The unaffected contralateral side most likely has alterations that are too subtle to be clinically apparent.

There are insufficient data in the literature to provide a plausible explanation for the role of PTH1R gene mutations in the pathogenesis of PFE since there is no observable physical consequence for body or craniofacial development as would be expected. Additionally, PTH1R gene expression may be observed in structures derived from dental follicles, such as osteoblasts in mandibular and maxillary bones,[24] cementoblasts, and inner and outer ameloblasts and odontoblasts.[25] However, there is no dental anomaly that can be diagnosed with clinical and radiographic means in patients with PFE. Enamel and dentin do not seem to be affected in PTH1R knockout mice or in late-term Blomstrand syndrome, a disease caused by a complete loss of function of PTH1R.[24]

The eruption process in PFE may be impaired from the preemergence phase, when the tooth germ moves along its eruption pathway to the oral cavity, until the postemergence phase, when compensatory drifts maintain occlusal and interproximal contacts. Postemergence movement permits the adjustment of tooth position to the increasing height of the jaws, which occurs more actively from age 14 to 18 years,[26,27] and then alveolar growth proceeds at a slower rate and lasts until the fifth decade of life.[19] When eruption ceases before or during puberty, the disturbance halts the development of adjacent alveolar bone, resulting in progressive submergence. Then, the earlier the onset, the more severe the open bite. As a general rule, PFE can be diagnosed during puberty but will be more evident in adulthood, when facial growth is completed and PFE seems to stabilize and acquires its full characterization.[2] The

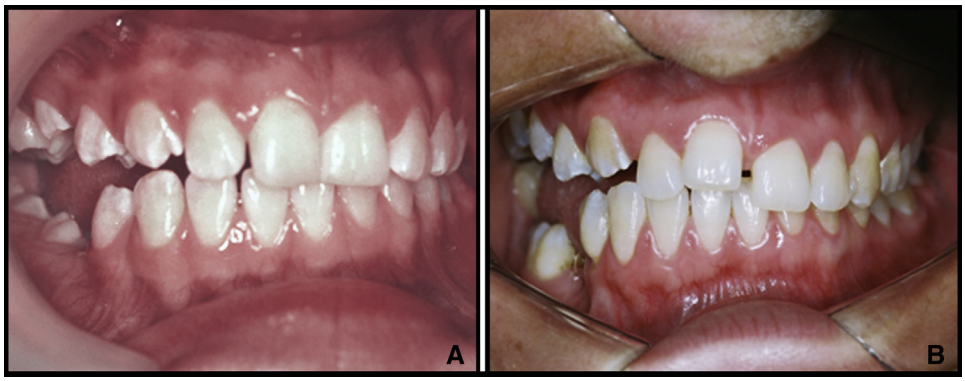

Fig 6. Patient II.13: **A,** at age 13 and **B,** at age 32. The condition became more severe in adulthood with the involvement of anterior teeth of the right side.

resultant clinical outcome is the worsening of open bite in adulthood (Fig 6).

Mild cases of PFE, with localized dental infraocclusion, may be clinically indistinguishable from secondary retention. This last condition is characterized by eruption impairment after the tooth emergence phase. Histologic studies have shown small points of ankylosis in all teeth clinically diagnosed as affected by secondary retention.[13,28] Percussion and radiographs permitted the diagnosis of ankylosis in only 29% and 21% of cases, respectively.[28] Clinical aspects of secondary retention were observed in this study (Figs 1 and 6) and give support for the possibility of secondary retention and PFE sharing the same pathogenic mechanisms.[7]

Ankylosis has been ruled out as an etiologic factor of PFE, since affected teeth may respond initially to orthodontic traction before they become ankylosed.[1,2] Moreover, involved teeth show no sign of ankylosis during extraction.[29] However, it might be speculated that small points of ankylosis could be broken without being noticed during dental extraction or when initial orthodontic forces are applied. To date, no histologic study has ascertained the absence of ankylosis in PFE patients.

Concerning the distribution of small spots of ankylosis in teeth affected by secondary retention, there is a predilection for bifurcation and interradicular surfaces.[28] If the same pattern is extrapolated for PFE, it might explain the greater severity of open bite in molar areas, the teeth with greater interradicular surfaces, as opposed to unirradicular teeth, such as mandibular premolars and anterior teeth. The same rationale may justify the higher number of affected maxillary premolars compared with mandibular premolars, as also observed by Stellzig-Eisenhauer et al.[5]

Another strong indicator of ankylosis as an etiologic factor of PFE is the evolution of patient II.11 from 18 to 38 years. He had spontaneous reeruption of the maxillary left first molar and the mandibular right first molar (Fig 4); this indicated that the PFE-affected teeth maintained their eruption potential during adulthood. Similar occurrences were described in patients in whom ankylosis was diagnosed.[30-32] This spontaneous reeruption may be explained by a continuous and normal process of bone remodeling, which might cause the resorption of small points of ankylosis. In this context, surgical dental luxation might be suggested as a treatment for PFE followed perhaps by orthodontic movement. This approach was already suggested but had limited success.[3] Points of ankylosis are deprived of periodontal ligament. As a result, even if ankylosis points are broken, the long-term tendency is reankylosis, although an unpredictable dental movement might be possible for a short time immediately after dental luxation.[2,3]

Cervical root resorption is a term used to describe an insidious and aggressive form of external root resorption of unknown etiology. When it is found in several teeth, as observed in patient II.12, it is considered a rare condition. The occurrence of this condition associated with PFE has not been described in the literature to date. However, the role of PTH1R in the regulatory pathway of bone formation and resorption seems to make plausible the association between cervical root resorption and PFE. The cervical root resorptions in 3 members of this family indicate that this specific PTH1R gene mutation may predispose to cervical root resorption, or cervical root resorption may be a further manifestation of PFE. This question will remain unanswered until additional studies are completed.

CONCLUSIONS

The long-term follow-up of these familial cases indicates that the primary etiology of PFE is intimately correlated with a disturbance in periodontal ligament metabolism with an increased tendency to genetically determined ankylosis. As a consequence, ankylosis seems to occur at random, leading to great variability in clinical presentations. The manifestation of the disturbance may occur from the preemergence to the postemergence phases; as a general rule, the earlier the onset, the more severe the open bite. However, in this family, affected teeth maintained their eruptive potential even in adulthood. Although rare and unpredictable, small changes in affected tooth position may occur as long as precluding factors are eliminated. Further studies are required to determine whether our findings are the result of the specific genetic mutation or are a further manifestation of PFE.

ACKNOWLEDGMENTS

We thank the members of this family who kindly collaborated with us, Michel Saad Neto for his encouragement in carrying out this study, and Thomas J. Gardella for sharing his views and valuable expertise in the molecular pathways of PTH1R.

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