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Review

Primary Failure of Eruption: A Rare but Desperate Condition for Orthodontic Treatment

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Main Points

- Primary failure of eruption has a genetic basis.
- Orthodontic forces cause ankylosis in teeth affected by primary failure of eruption.
- Primary failure of eruption may cause posterior open bite.

ABSTRACT

Tooth eruption is a highly complex mechanism that is controlled by many factors. Various mechanical, systemic, or genetic factors can cause eruption disorders. Primary failure of eruption (PFE) is known as an eruption disorder occurring due to non-syndromic genetic factors. It is frequently seen in the first and second molars and causes posterior open bite. It can be observed unilaterally or bilaterally. Studies show that mutations in many different genes that control the tooth eruption mechanism, mainly the *PTH1R* and *KMT2C* genes, constitute the genetic basis of PFE. Primary eruption disorders are very difficult to treat. It is known that the application of active orthodontic forces causes local ankylosis in the tooth and the failure of the tooth to return to its normal position. For this reason, determining the correct diagnosis and treatment method is very important. Although there are different treatment methods, the results of research about the success of these treatment methods are quite limited. This review aims to explain the etiology, diagnosis, and treatment of PFE in light of current genetic studies.

Keywords: Eruption disorders, orthodontics, posterior openbite, PTH1R, unerupted tooth

INTRODUCTION

In addition to the change in the direction of tooth eruption, there are basically two types of serious eruption anomalies. These anomalies are classified as primary and secondary eruption disorders.[1] Eruption disorders can occur due to a syndrome or develop in a non-syndromic manner. In both cases, it is crucial to differentiate between local or mechanical factors (e.g., adjacent teeth, cysts, lateral pressure of the tongue, or syndromes) and the disorder of the eruption mechanism.[2] If there is no systemic condition or any obstacle in the eruptive path that would prevent tooth eruption, this condition is called primary failure of eruption (PFE).[3] PFE was initially introduced by Proffit and Vig[4] and later redefined by Frazier-Bowers et al.[5,6] It represents a rare genetic anomaly affecting tooth eruption, with a prevalence of 0.06%.[7]

Tooth eruption refers to tooth movements that occur from the time the tooth is in the dentoalveolar structure to the time it begins to function in the mouth.[8] It is a coordinated and complex mechanism, and cellular,

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genetic, and systemic factors can affect this process.[1] The understanding and clinical management of the molecular and genetic mechanisms associated with tooth development and eruption disorders is quite difficult.[9]

Tooth eruption disorders have a wide clinical spectrum, from delayed eruption to the failure of eruption. Different alveolar bone apposition/resorption mechanisms can cause different clinical consequences such as PFE, ankylosis, eruption disorders due to insufficient arch distance, and impaction of the canines.[10]

Tooth eruption and loss are complicated processes that occur through the coordinated work of osteoclasts, osteoblasts, periodontal ligament cells, and dental follicle cells.[10] Before the eruption process begins, osteoclast precursors are organized in the dental follicle, and these cells combine to transform into osteoclasts that then resorb the alveolar bone, creating the pathway necessary for eruption.[10]

The majority of tooth eruption disorders are seen as a result of a change in the eruption direction of the first molars (ectopic eruption). At this stage, early diagnosis and treatment provided by the application of natural forces that will allow eruption are very important in preventing malocclusions. The most common teeth erupting in an ectopic position are the upper permanent molars and canines.

Studies have shown that PFE generally has a genetic etiology.[2] Current studies have revealed that *PTH1R* and *KMT2C* gene mutations cause primary eruption disorders. The currently known genetic etiology of PFE distinguishes it from other eruption disorders. In addition to systemic or syndromic diseases such as Albers-Schönberg Osteopetrosis, Odontodysplasia, and Cleidocranial Dysplasia, a differential diagnosis should be made with other eruption disorders such as mechanical eruption disorder (MFE) and ankylosis with clinical symptoms such as immobility, infraocclusion, and a metallic sound on percussion.[2]

CLINICAL AND RESEARCH RESULTS

Etiology

Typically, local factors such as odontomas, cysts, supernumerary teeth, and jaw fractures which often affect only one tooth and create a physical barrier to the eruption path are the main cause of eruption disorders. Other potential obstacles arise from mispositioned or malformed tooth buds, dilacerations, or ankylosis. While this type of eruption disorders is generally observed in the upper incisors and canines, the first or second molars are rarely affected.[11] Eruptions caused by disorders which are less frequently observed than those caused by physical causes occur in systemic diseases or syndromes such as ectodermal dysplasia, cleidocranial dysostosis, down syndrome, apert syndrome, Gardner's syndrome, hyperpituitarism, and hyperthyroidism. An even more rarely observed eruption disorder is PFE.[11]

Recent studies have revealed that this dental phenotype is genetically linked to mutations in the *PTH1R* and *KMT2C* genes. Additionally, the products of the *Periostin* (*POSTN*), *Ameloblastin* (*AMBN*), and *Amelogenin* (*AMELX*) genes are crucial in tooth development processes and contribute to eruption disorders through various mechanisms. AMELX, an enamel matrix protein, is recognized as a negative regulator of osteoclastogenesis which acts by suppressing the expression of RANKL and M-CSF.[12] Phenotypic variations are based on genetic, epigenetic, and environmental factors, but information about the pathophysiological mechanism leading to PFE is quite limited.[13] Studies have shown that that viral infections in the nerve pathways cause dental anomalies and eruption disorders, but no definitive conclusion can be reached due to various inadequacies in information on this subject.[14] It is anticipated that in the near future, it may become standard practice for orthodontists to collect saliva samples or cheek swabs for genetic testing when necessary. This advancement could lead to more personalized treatment plans and a better understanding of genetic effects on dental and craniofacial development.[15] Interestingly, a relationship between PFE and osteoarthritis was observed in some families affected by PFE, but this does not indicate a direct relationship between the two conditions.[15]

Decker et al.[17] were the first to report that a variant in *PTH1R* is associated with PFE.[16]

PTH1R

PTH1R is located on chromosome 3p21-p22.1.[17] It has been reported that parathyroid hormone (PTH) and PTH-dependent peptide (PTHrP) are the main modulator cells for osteoprotegerin (OPG), which is the osteoclastogenesis inhibitory factor, and RANKL, which is the main modulator cell of osteoclastogenesis.[18]

PFE is an autosomal dominant genetic disease that develops as a result of the heterozygous PTH1R mutation inactivating the functions of PTH1R and shows a phenotype only in the teeth.[19,20]

It is observed that a PTH1R ligand (PTHrP) affects the presence and activity of the dental enamel organ, especially the stellate reticulum of the dental follicle, and the tooth eruption mechanism (Figure 1). A lack of PTHrP production in dental follicle cells which is essential for the physiological root resorption of deciduous teeth and the proper eruption of permanent teeth causes teeth that initially follow a normal development process to be encapsulated by bone.[8,21]

After the link between PTH1R and PFE was established, more than 60 different PTH1R variants have been identified in patients with PFE.[20] Subramanian et al.[19] suggested that these PTH1R variants impair signal transduction in periodontal tissue cells, thereby causing primary failure of tooth eruption. Furthermore, mutations in PTH1R are known to lead to severe growth retardation and skeletal dysplasia.[22]

KMT2C

As a result of detailed clinical and molecular genetic analyses, it was determined that potential pathogenic mutations that may occur in the *KMT2C* gene may form the genetic basis of PFE.[9] The heterozygous splice site mutation in KMT2C causes primary eruption disorder with an autosomal dominant character in humans.[9]

Diagnosis

Since PFE has a family history, the simplest diagnostic approach is to check occlusion status in the parents of suspected patients. The next step is the exclusion of local and systemic causes of eruption failure such as regional odontodysplasia, neoplasms, odontogenic and non-odontogenic tumors, cysts, mucosal barriers-scar tissue, hypothyroidism, and hypoparathyroidism.[16]

Disorders caused by endocrine factors have not been observed in PFE or MFE patients (at least in light of the information we have to date). The main differential diagnosis should be made between mechanical obstruction (ankylosis) in the eruption path of the tooth and disorders in the eruption mechanism. The most accurate way to distinguish these two conditions is to determine the prognosis of the affected teeth.[4]

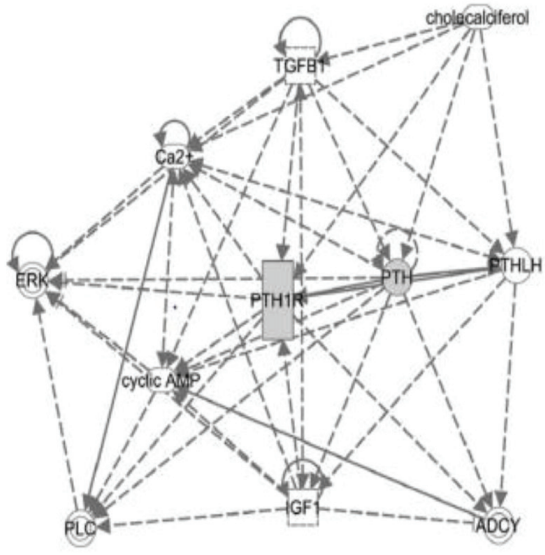

Figure 1. Scheme prepared to investigate the connection between the *PTH1R* gene and the molecular basis of tooth eruption[10]

PFE is mainly characterized by eruption disorders in the posterior teeth and vertical growth retardation in the alveolar process in the affected area. Eruption disorders of the permanent first and second molars are quite uncommon but have a significant clinical impact. Their ability to continue to develop without damage is also important for craniofacial growth.[23] Therefore, the accurate diagnosis and treatment of PFE are important as they will also affect craniofacial growth.

The average age of patients diagnosed with PFE is 13.65 years.[24] Typically, the teeth with the highest PFE rates (excluding the third molars) are the first and second molars in all four quadrants of the mouth.[24]

In a study involving 31 patients who met the inclusion criteria, 15 were diagnosed with PFE. In 100% of the cases, the first permanent molars were affected, while the second molars were affected in 93% of the cases.[25] In another study, 269 teeth were included, of which 87 (32%) were first molars, and 47 (17%) were second molars.[26]

Apart from PFE, other eruption disorders that cause posterior open bite (Table 1) are MFE and indeterminate failure of eruption (IFE). To apply the correct and effective treatment, a differential diagnosis must be made between these two eruption disorders.[4]

Other Types of Eruption Failures That Should Be Considered in Differential Diagnosis of PFE

It has been observed that a single permanent tooth is typically affected in MFE, and this tooth is usually the first or second premolar. Clinical observations have shown that the affected tooth is in infraocclusion, and a metallic sound is heard on percussion. Radiographs typically showed areas of ankylosis on the proximal sides of the teeth, but these could not be distinguished on the labial and lingual surfaces.[27]

Table 1. Table of eruption disorders that cause posterior open bite[4]

Classification	Number of affected tooth	Impact on neighboring teeth	Clinical appearance of ankylosis	Affected teeth visible intraorally	Typical treatment response	Proposed cause of failure
MFE	Usually only first molars	Adjacent teeth normal	Yes	Maybe	Other teeth respond, affected teeth might respond to luxation	Ankylosis, possible other obstruciton
PFE	Unilateral or bilateral, can involve whole quadrants	Distal teeth also affected	No	Usually some portion of at least 1 tooth	No response to orthodontic force	Failure of eruption mechanism
IFE	Too early to determine	Unknown at this stage	No	Maybe	Depends on final diagnosis	Ankylosis or PFE
Other	Any	Unknown	No	Yes	Might respond but tends to relapse	Possible tongue or soft-tissue interference

MFE, mechanical eruption disorder; PFE, primary failure of eruption; IFE, indeterminate failure of eruption

The teeth distal to the most mesially affected tooth are usually normal, and this is the most characteristic feature of MFE in the process of differential diagnosis with PFE. In cases where PFE is suspected based on genetics, genetic screening is recommended for determining the right treatment option.[28] The responses of the affected tooth or teeth to orthodontic forces would also be different.[4]

IFE is a diagnosis made in very young patients, where the distinction between PFE and MFE is not clear, to determine whether the teeth distal to the most mesially affected tooth are affected.[29]

According to a study conducted on 97 patients by Frazier-Bowers et al.[5] (Figure 2), PFE was observed in 39%, IFE was observed in 33%, MFE was observed in 20%, and 8% could not be included in a category.[4] Based on the aforementioned study, the most common eruption disorder causing posterior open bite was PFE.

The frequent involvement of the premolar and molar teeth in both PFE and ankylosis prompts the question of whether these eruption disorders are part of the same spectrum. PFE is more likely to be diagnosed when ankylosis lacks a discernible physical or mechanical cause and is determined to have a genetic origin. The primary distinction in diagnosing ankylosis versus PFE relies on clinical observations. Therefore, accurate clinical assessment leads to an accurate diagnosis.[8,10]

In secondary eruption disorders, the tooth has passed through the bone barrier and erupted but remained in infraocclusion. The situation in which the affected tooth begins to erupt in the mouth but then stops erupting or fails to fully occlude, which is observed in teeth affected by primary eruption disorders, is a characteristic feature that causes confusion in terms of definition with secondary eruption disorders. When teeth with secondary eruption disorders were examined histologically, ankylosed areas were observed at their roots.[1]

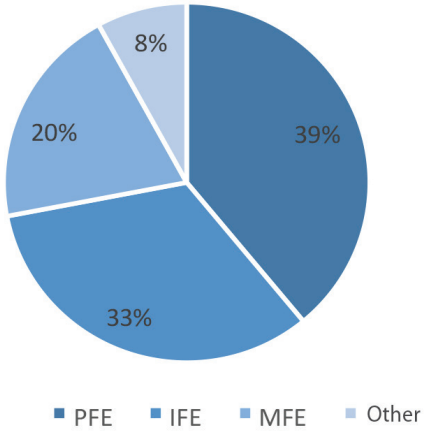

Figure 2. Scatter chart of eruption disorders causing posterior open bite according to percentages[4]
MFE, mechanical eruption disorder; PFE, primary failure of eruption; IFE, indeterminate failure of eruption

Teeth affected by PFE may vary in number, type (deciduous or permanent), and symmetry.[13] PFE has been observed to typically affect multiple posterior teeth. It was determined that all teeth distal to the most affected mesial tooth were also affected and showed similar infraocclusion characteristics.[27] This feature is very important in making a differential diagnosis with MFE. PFE was also reported in cases where other dental anomalies such as peg-shaped lateral teeth and infraoccluded primary molars are present.[6]

Although it is known that posterior teeth are often affected, it was observed that anterior teeth can also be affected. It was stated that in cases where anterior teeth are affected, posterior teeth are also affected.[14] The incidence of PFE did not show a notable difference between the maxilla and mandible.[4] Available clinical findings show that PFE is often observed unilaterally, but it can also be observed bilaterally. This suggests that while PFE affects the teeth on one side of the jaw, it might not cause any eruption disorder in any of the teeth on the other side. It can affect both primary and permanent dentition. The affected permanent tooth may later become ankylosed. It can be observed in a single individual not in other family members of theirs. There is no significant difference in the frequency of observation between the sexes. Dilacerations can be observed in the roots of the affected molar teeth.[11]

In the retrospective comparative study conducted by Avalos-Hernández et al.,[30] CBCT images of 40 teeth affected by PFE and 40 unaffected teeth were analyzed. As a result, the coronal dimensions of molars affected by PFE were smaller, and the mesial and distal root lengths were shorter by approximately 2 mm.[30] Upper molars affected by PFE also showed a characteristic inclination toward the palatal and distal directions, which could be considered diagnostic.[30]

Subtypes of PFE

Studies have shown two subtypes of PFE (Figure 3). It has been reported that in Type 1 PFE, the loss of tooth eruption capacity is related to a certain chronological time, and in Type 2, it is related to a certain root development phase. The eruption potential of teeth affected in Type 2 cases varies. A combination of Types 1 2 was observed in most reported PFE cases.[6]

In Type 1 cases, an open bite progressing from the anterior to the posterior is observed. The eruption defect which is known to be genetically screened for Type 1 is known to be present in all affected teeth at the same developmental stage. A similar and high degree of eruption failure was observed in all teeth from the most mesial tooth to the most distal tooth.[14] For Type 1 cases, a more commonly observed form, teeth distal to the affected first molar exhibit a more severe infraocclusion that causes posterior lateral open bite.[15]

In Type 2 cases, an open bite progressing from the anterior to the posterior is similarly observed. However, various eruption disorders are observed in multiple quadrants.[3] Eruption failure is also observed in the second molar teeth.[10] Although the teeth distal to the most mesially affected tooth have a higher

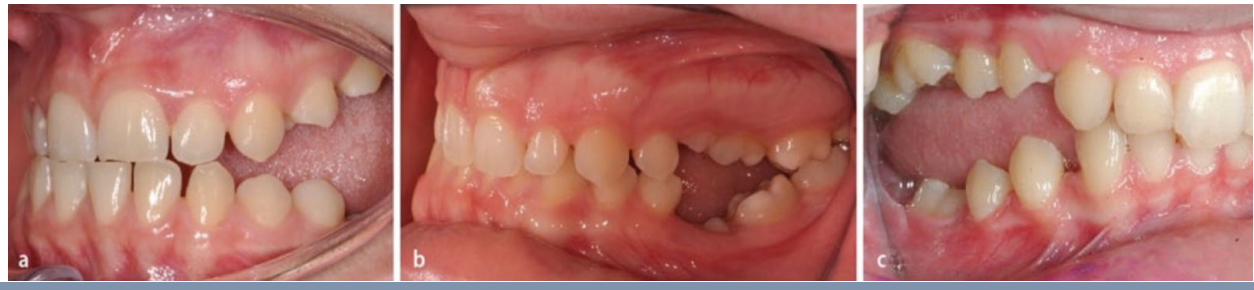

Figure 3. a) Intraoral image of an 18-year-old female patient with PFE Type 1, b) Intraoral image of a 17-year-old female patient with PFE Type 2, c) Intraoral image of a 15-year-old female patient with PFE Type 1 and Type 2 observed together.[11]
PFE, primary failure of eruption

eruption potential, they are still inadequate compared to normal teeth.[14] In a Type 3 case, which can be described as a combination of Type 1 and 2 according to some sources, it has been observed that Types 1 and 2 occur together in different quadrants of the same patient.

Pathogenesis

It is known that several genes including *PTH1R*, *AXIN2*, *MSX1*, and *PAX9* play critical roles in odontogenesis. There is compelling evidence suggesting that PFE is typically an autosomal dominant heterogeneous condition linked to mutations in the *PTH1R* gene and genes involved in the activation of the cAMP/PKA pathway, which are crucial for tooth eruption. However, not all individuals with PFE exhibit mutations in these known genes, and the genetic basis of PFE remains largely unexplored.[31]

Treatment

Although PFE is rare, when it occurs in both the maxilla and the mandible, a severe posterior open bite may occur, which is very difficult to treat and has unpredictable outcomes.[6] Open bite, which occurs as a result of the affected teeth being below the normal occlusal level, can occur unilaterally or bilaterally.

Various multidisciplinary treatment methods are available for the disorders that occur with PFE, especially posterior open bite. Orthodontists and pedodontists are the first to encounter patients with PFE. Still, surgeons and prosthetists will most likely be involved in the management of PFE.[15] Clinicians should consider basic molecular mechanisms when treating simple and complex dental complications resulting from eruption anomalies.[1]

In a study involving 22 cases of teeth affected by PFE, various treatment approaches were reported as follows: unsuccessful orthodontic treatments following extraction (n=6), extraction of affected teeth (n=7), orthodontic extrusion of unaffected teeth (n=1), alignment of upper and lower labial segments (n=1), segmental osteotomy (n=1), and overdentures (n=1). Additionally, 5 patients did not receive any treatment.[14]

Proffit and Vig[4] and Frazier-Bowers et al.'s[5] research suggested that extracting teeth affected by PFE could be a suitable treatment method. For young patients, occlusal stability can be maintained with direct or indirect composite practices until implant placement becomes feasible. Adult patients with mild infraocclusion may not necessarily require treatment but should undergo regular monitoring.[14]

In addition to tooth extraction, surgical interventions or distraction osteogenesis (DOG) may be considered as further treatment options for managing PFE. For example, this is valid in cases where PFE is very severe and where it is necessary to extract the affected teeth and then shift the teeth distal to the first molar into the extraction space (as in cases of Type 2 PFE). One approach to help improve tooth positioning may be to perform single-tooth osteotomies or corticotomies.[15] Since it is known that teeth affected by PFE do not respond well to orthodontic forces, alternative treatment options should be considered. It has not been possible to determine whether the teeth affected by PFE do not respond to orthodontic forces alone and whether the combined surgical and orthodontic approach is quite successful or not due to the lack of studies in this field.[15]

Orthodontic Treatment Methods

In cases where an eruption malfunction is observed in the first molar teeth, this condition can be diagnosed early, and the early extraction of the first molar tooth and the orthodontic mesialization of the second molar tooth can be a good treatment alternative. Nevertheless, for this treatment to be applied, there must be no eruption disorder in the second molar tooth.[10] While orthodontic extrusion, another treatment method, can be an effective method in the presence of MFE in which the eruption mechanism is not impaired, it cannot be a successful treatment method for PFE because it causes immediate ankylosis in the teeth affected by PFE if orthodontic forces are applied.[3] This makes PFE a challenging condition for orthodontists. Therefore, due to the high failure rate of orthodontically assisted eruption in individuals with PFE, it is crucial to conduct a genetic diagnosis before initiating any orthodontic treatment.[13] A genetically confirmed PFE diagnosis will protect both patients and orthodontists from years of unnecessary treatments and the harmful effects of orthodontic forces on the affected area as well as the unaffected area.[32]

A 28-year-old male patient with unilateral posterior open bite secondary to PFE of maxillary molars presented to our clinic (Figure 4). The maxillary right first molar exhibited partial impaction, and the maxillary right second and third

molars were completely impacted (Figure 5). These conditions coincided with the characteristics of PFE. After the extraction of the right first molar, the second molar was erupted with orthodontic forces (Figures 6 and 7).

A case report[33] presented a nine-year-five-month-old female patient who was referred due to the failure of eruption of the maxillary right permanent first molar. A modified Nance palatal arch with a distal extension was fabricated, along with the bonding of an orthodontic button for traction. However, the tooth did not respond to the initial orthodontic forces applied. A follow-up periapical radiograph taken six months later revealed areas indicative of ankylosis. Subsequently, a surgical subluxation was performed, followed by the immediate application of orthodontic forces. Though some initial movement was noted, continuous movement was not achieved, necessitating a second surgical subluxation five months later. Following this intervention, the tooth responded favorably. The orthodontic button was subsequently repositioned to optimize the loading vector. Six months later, the first molar was successfully aligned in its correct position, and the orthodontic appliances were removed. At the end of the 12-month follow-up, radiographic analyses confirmed that the tooth was properly aligned with the occlusal plane of adjacent teeth, preserving the integrity of both dental and periodontal structures. By the end of the four-year follow-up, the tooth remained stable in the desired position, effectively occluding with its antagonist.

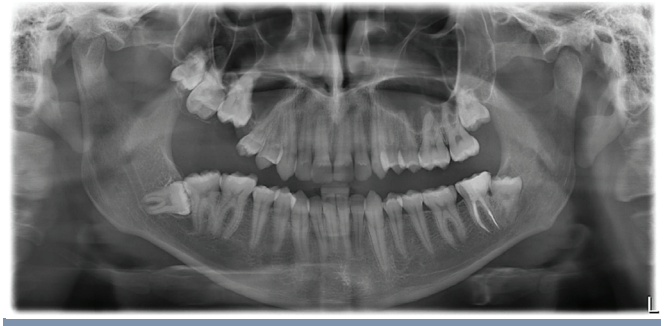

Figure 4. Panoramic radiograph taken before treatment. Right maxillary first molar to third molar positioned below the occlusal plane

Surgical Treatment Methods

The integration of cementum and dentin with the alveolar bone prevents orthodontic tooth movement and necessitates surgical approaches such as vertical DOG or minimal segmental osteotomy for the affected teeth.[34] A segmental osteotomy of the alveolar bone affected by PFE can be performed to reposition the segment and improve the occlusal plane. A bone graft can be placed between the bone segment and the base of the alveolar bone when necessary. There are certain risk factors for both jaws. For the maxilla, the thick and poorly elastic palatal mucosa impedes the movement of the segment, whereas there is a risk of causing damage to the inferior alveolar nerve when performing this procedure in the mandible.[16]

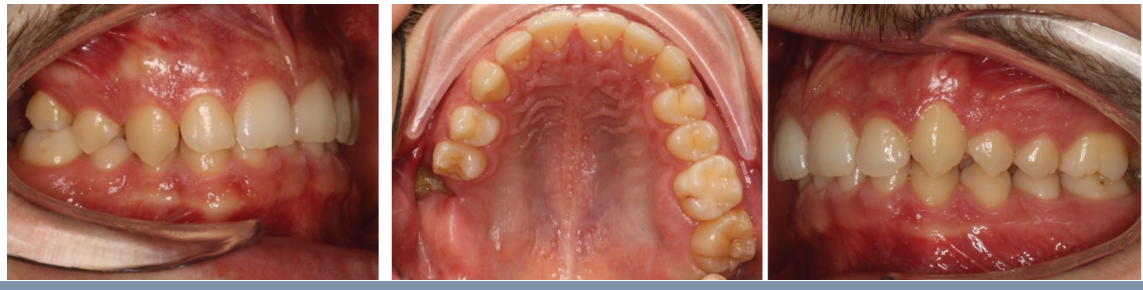

Figure 5. Introral photographs before treatment

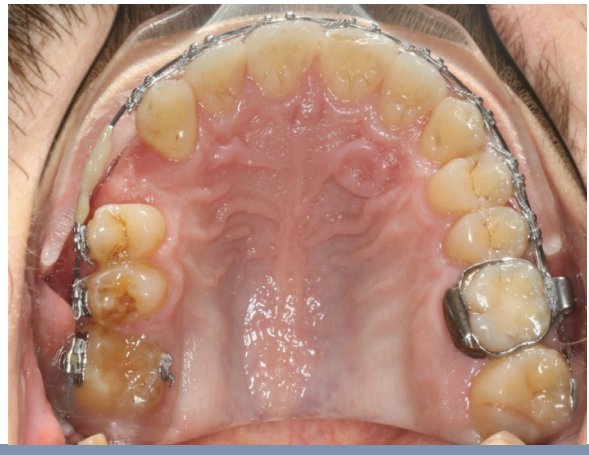

Figure 6. Midtreatment occlusal view

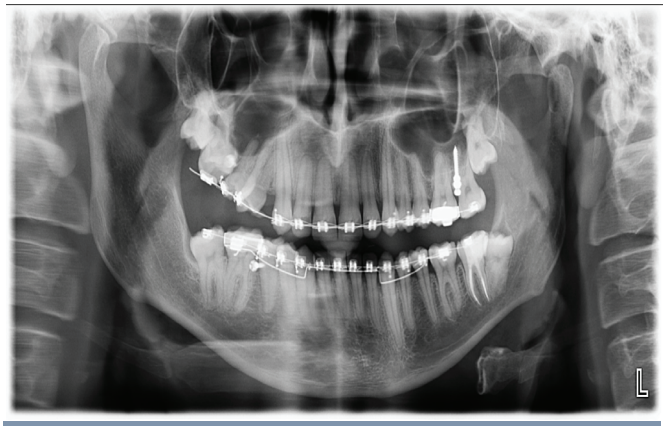

Figure 7. Midtreatment panoramic radiograph

DOG, commonly used in patients with lateral open bite, has some drawbacks in terms of controlling the direction of growth. The linear movement of the distraction device often results in the displacement of the segment towards the palatal side during bone growth. In such cases, the floating bone concept may offer a more effective approach, allowing for the three-dimensional control of the segment's position by continuously applying pressure before complete bone healing. Previously, researchers applied DOG to the maxillary alveolar bone in a PFE case with severe lateral open bite, controlling segment position using elastic traction and removing the device before complete bone healing. This approach successfully improved dental arch morphology and achieved stable occlusion.[16]

Prosthetic Treatment Methods

Prosthodontic treatment is often the only treatment available for these patients. In cases where PFE is milder, a prosthetic approach and the camouflage of the eruption problem with crowns would be a good treatment option.[15]

Depending on the extent of tooth eruption, treatment options such as overlay crowns or overlay removable partial dentures can be considered when the tooth crown is sufficiently visible in the oral cavity. It is generally recommended to not place fixed restorations before vertical growth is completed.[3] This approach ensures that the restoration will properly accommodate any future changes in the tooth's position as vertical growth continues, thereby optimizing long-term treatment outcomes.

CONCLUSION

Since tooth eruption is a multifactorial mechanism, it is known that many different factors can cause tooth eruption disorders. The possibility of PFE comes to mind in cases where eruption disorders are observed despite the absence of any physical disability or systemic disease. The most important feature that distinguishes PFE from other eruption disorders is its genetic etiology. Studies have shown that defects in the *PTH1R* and *KM2TC* genes cause PFE. In addition to these genes, it is known that other genes responsible for regulating the tooth eruption mechanism could also be considered candidate genes for PFE.

It can be stated that the infraocclusion of the posterior teeth is the most distinguishing feature of PFE, especially when it is observed bilaterally. Another important distinguishing feature is that all teeth distal to the most mesial tooth affected by PFE are also affected. Since it is known that orthodontic forces applied for treatment cause ankylosis in teeth affected by PFE, genetic screening is recommended for diagnostic purposes in patients with suspected PFE.

An orthodontic treatment approach to teeth affected by PFE would not be appropriate. Therefore, surgical and prosthetic approaches are recommended, but one may still argue that treatment methods are quite limited since very few cases explaining treatment options have been reported.

Footnotes

Author Contributions: Concept - Y.S., İ.S., S.B., Z.A.A.; Design - Y.S., İ.S., S.B., Z.A.A.; Data Collection and/or Processing - Y.S., İ.S., S.B., Z.A.A.; Analysis and/or Interpretation - Y.S., İ.S., S.B., Z.A.A.; Literature Search - Y.S., İ.S., S.B., Z.A.A.; Writing - Y.S., İ.S., S.B., Z.A.A.

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