Craniofacial morphological changes of familial bilateral hypodontia of maxillary premolars

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Abstract
The hypodontia of a permanent tooth from a dental group represents a normal evolution in human dentition morphology. Nevertheless, the hypodontia of two teeth within a dental group is a rare developmental anomaly when not associated to a systemic syndrome. The aim of this study was to report two rare cases of four maxillary premolars hypodontia, not including the third molar, of two white women from the same family. There were presented clinical, radiological and genetic findings. These cases are of interest to practitioners for four aspects: the atypical phenotype of hypodontia, the complexity of craniofacial morphological changes, the autosomal dominant familial inheritance with variable expressivity and the difficult classification of diagnosis.

Keywords: hypodontia, agenesis, craniofacial morphological changes, autosomal dominant inheritance, diagnosis.

Introduction
Permanent teeth hypodontia is the congenital absence of a small number of teeth (1–6 teeth) excluding the third molar. Numerous studies have reported the prevalence of permanent teeth hypodontia ranging between 2.6% and 11.3% in populations among continents and races, with an insignificant predominance in women [1–4]. The white population in the UK had a rate of 4–5% permanent teeth hypodontia [5].

Hypodontia can be isolated (non-syndromic) or associated with other congenital anomalies (syndromic) [1]. The most frequently reported phenotype was the isolated hypodontia. In studies conducted on Caucasian populations, mandibular second premolars and maxillary lateral incisors were the most frequent congenitally absent teeth [6, 7] and for the Asian population were the mandibular central incisors [4]. Population studies on permanent teeth’s hypodontia severity reported a prevalence of over 80% in the cases of 1–2 congenital absent teeth, less than 10% of cases with 4–5 absent teeth and less than 1% of cases with six or more teeth [8, 9].

Hypodontia is associated with around 150 syndromes [10], but the most common are the congenital anomalies associated with lip cleft and/or palate [11, 12].

Hypodontia has a multifactor etiology, a genetic predisposition and environmental aspects also intervene in varying proportions. Rubella, thalidomide and irradiation were reported as the most important environmental factors [13–15]. Family and twin studies were relevant for emphasizing the strong genetic influence [16–18]. Molecular genetic studies have attempted to identify the familial genes involved in the craniofacial and dental development [19–21]. The Msx1 gene mutation was associated to clefts and to non-syndromic form of hypodontia, and the Pax9 gene mutation as well [22–25]. Not being clarified, the mechanisms of congenital absence of teeth, has attracted the attention of specialists on the phenotypic and genotypic variation of hypodontia.

The emergence of new phenotypes of permanent teeth hypodontia has a clinical significance on the changes in the dental-maxillary and craniofacial morphology with multidisciplinary diagnostic implications. The purpose of this article is to report two rare cases of first and secondary maxillary premolars hypodontia, excluding the third molars, on two white females, members of the same family.

Patients, Methods and Results
The study was carried out on two white members of the same family, as volunteer participants, who gave their informed consent. The family selection criterion was the proband (Case No. 1), who presented herself with bilateral upper premolars hypodontia for orthodontic treatment.

Case No. 1
Dental and maxillary assessment
A female patient, white, 25-year-old, presented herself at the Orthodontics Clinic at the Ambulatory of the “St. Spiridon” University Emergency Hospital, Iassy, Romania, for the absence of certain maxillary teeth.

Her dental history included loss of maxillary deciduous molars without being replaced with premolars and therapeutic extractions of permanent posterior mandibular teeth due to complications subsequent to decay.

The maxillary arch presented a mixed dentition, the absence of the premolar group (14, 15, 24 and 25), the persistence of temporary tooth 53, the transposition of 13–53 and closure of remnant free areas (Figure 1). On the mandibular arch, there was observed a permanent dentition interrupted by the post-extraction spaces of 36, 45 and 46. Examining the dental occlusion, there were found mesial canine sagittal relations and distal molar relations, crossbites (13 and 23) and right mandibular lateral
deviation (Figure 2). When the temporomandibular joint was examined a jaw cracking was heard on its left side.

The panoramic radiography examination confirmed the congenital absence of all upper premolars dental buds and the agenesis of third molars 28, 38 and 48 and the root remains of 36 and 46 (Figure 3).

Linear and angular measurements made on the lateral cephalometric radiograph (Steiner and Tweed computer analysis) detected the following abnormal values: S–L=53 mm, S–E=24 mm, ANB=5°, SND=73°, SN–OcP=23°, SN–GnGn=34°, 1U–NA=19°, 1L–NB=27°, Holdaway ratio=3 mm and Z to Merrified=91° (Figure 4).

Medical general assessment

The proband was evaluated at the Office of Medical Genetics, Iassy, and it was observed that she presented normal morphometry (weight, height, and cranial perimeter), declarative precocious puberty, discrete exophthalmia, hypodontia, hypoplastic right thumb inserted proximally (Figure 5), left preauricular operated hemangioma and kyphoscoliotic deformities.

There were conducted a series of additional tests. The thyroid ultrasound revealed four follicles with the diameter of 2/6.3 mm on the left ovary at three follicles with a 3/7.1 mm diameter on the right ovary, the anteversion and right lateral deviation of the uterus and a polycystic ovary was put under observation. The phosphocalcic metabolism was normal, and the right wrist radiography showed that the right thumb is inserted proximally (Figure 6).

Case No. 2

Dental and maxillary assessment

The 27-year-old proband’s sister reported the same lack of maxillary premolars eruption after the exfoliation of deciduous molars.

The maxillary arch presented a mixed dentition, the absence of the premolar group (14, 15, 24 and 25), the persistence of temporary teeth 63 and the migration of posterior teeth on the remaining free spaces (Figure 7). The mandibular arch presented permanent dentition with frontal and lateral mild crowding. Examining the dental occlusion there were found mesial canine sagittal relations and distal molar relations, crossbites (13, 16, 23 and 26) and left mandibular lateral deviation (Figure 8). Examining the temporomandibular joint there was heard a jaw cracking on its right side.

The panoramic radiography examination confirmed the congenital absence of all dental buds of upper premolars, the agenesis of the third molars 18 and 28 and the root remains of 36 (Figure 9).
Linear and angular measurements made on the lateral cephalometric radiograph detected the following abnormal values: \( S-L=60 \, \text{mm}, \ S-E=27 \, \text{mm}, \ SNA=75^\circ, \ ANB=1^\circ, \ SN-\text{OcP}=21^\circ, \ SN-\text{GnGo}=35^\circ, \ 1U-\text{NA}=20^\circ, \ 1L-\text{NB}=14^\circ, \) Holdaway ratio=6 mm and Z to Merrified=62° (Figure 10).

**Medical general assessment**

The proband’s sister clinical genetic examination revealed a normal morphometry, discreet exophthalmia and kyphoscoliotic attitude.

**Family history**

Following the completion of the family’s pedigree investigation was revealed the autosomal dominant inheritance with high penetrance of bilateral hypodontia of first and second superior premolars at II.1, III.12, III.13 and probably II.5. We did not have reliable clinical data or medical records about the II.5 person’s hypodontia, because the person dyed at the age of 43 years from an accident. Declarative data was obtained from the proband (III.13) and her sister (III.12). There were not found any hand abnormalities to other members of the family. It was also noted this family’s concentration of multifactor diseases with genetic predisposition (Figure 11).
Discussion

The normal human dentition morphology of permanent teeth consists of four groups (incisive, canine, premolar and molar) symmetrically arranged in four quadrants, bilateral and bimaxillary. Within a quadrant, the incisive group consists in one central incisor and one lateral incisor, the canine group consists in one canine, the premolar group consists of first and second premolars, and the molar group consists in a first, a second and a third molar.

A meta-analysis of Caucasian populational studies on the natural evolution of human permanent dentition considered hypodontia to be the most common abnormality of growth [26]. Usually, in the non-syndromic hypodontia of permanent teeth, one tooth is congenitally missing from a dental group, unilaterial or bilateral, maxillary or bimaxillary (third molars, second premolars, upper lateral incisors or lower central incisors) [1].

By clinical forms, hypodontia can be unidental, when a bilateral tooth is congenitally missing from a dental group, bidental when a bilateral tooth is congenitally missing from two dental groups of teeth (lateral incisors and second premolars) [27], multidental, when a bilateral tooth is congenitally missing from several dental groups of teeth or monodontal when only one tooth is congenitally missing from the dental arches.

In order to describe the severity of permanent teeth hypodontia, Dhanrajani used the term mild to moderate hypodontia for the agenesis of 2–4 teeth and the term severe hypodontia for the agenesis of six or more teeth [28]. The first premolars, first permanent molars and the canines are rarely congenitally absent and only in association with severe hypodontia or oligodontia [29].

Both of the presented cases were diagnosed with bilateral hypodontia of first and second maxillary premolars based on interview, clinical examination and panoramic radiograph analysis. None of the clinical forms could classify the hypodontia, because the two teeth were congenitally missing from a dental group, namely the premolar maxillary group. The hypodontia’s severity was classified as mild to moderate because of the congenitally absence of four teeth, except the third molars.

The natural migration of maxillary posterior teeth into the remaining hypodontia spaces produced the shortening of the maxillary arch and a series of changes in teeth positions, occlusal and joint relations. The persistence of temporary teeth on the maxillary arch and the dental transposition were signs associated with the hypodontia. The canine and molar abnormal sagittal occlusal relations were considered false, inconclusive for classifying the diagnostic of malocclusion, because the maxillary teeth did not maintain their positions on the dental arches and could not be considered references in relation to the mandibular teeth. Crossbites formed due to changes of the teeth axis. Crossbites produced the mandibular lateral deviation and caused temporomandibular joint dysfunction.

By analyzing the two sisters’ side lateral cephalograms, it was observed an increased length of the skull base (distance S–E and S–L), which was not reported previously in the study of hypodontia. Consecutively to the teeth migration and the number of maxillary teeth reduction, the upper incisors retroinclined in both cases (1U–NA angle). The latter is more relevant than the former, because the mandibular arch was integer and presented maxillary retrognathia (SNA angle).

In a study conducted on 189 side lateral cephalograms of Caucasian patients with hypodontia and oligodontia, aged up to 16 years, Créton et al. reported retrusive maxillary position in 33 cases, retroinclined upper and lower incisors in 15 cases and proclination of the lower incisors with retrusive mandible in 61 cases [30].

In both of the presented cases, the sagittal discrepancy between the skeletal bases (ANB angle) amended the maxillary relations with facial soft tissues (Z to Merrifield angle) in an individualized manner, depending on the mandibular dental clinical situation. On the first case, the absence of posterior mandibular teeth, due to extraction was beneficial to the compensation of the maxillary dental discrepancy and it was observed a Class II skeletal pattern, while the proclination of the lower incisors (1L–NB angle) has formed as a dental compensation due to the mandibular dental arch shortening. Consecutively to this skeletal pattern, the soft tissue profile changed, the upper lip being tangent to the Z to Merrifield line. The second case presented a Class III skeletal pattern, while the lower incisors retroinclined as a dental compensation to the maxillary bone shortening. Following this skeletal pattern, the soft tissue profile has modified, the lower lip being tangent to the Z to Merrifield line.

Previous studies conducted on side lateral cephalograms whose purpose was to detect skeletal effects associated to hypodontia, reported the predominance of Class I skeletal pattern, but also of Class II or III, these tendencies varying depending on the severity of hypodontia [31, 32].

According to the ANB angle, the first case was classified as a Class II Angle skeletal malocclusion, and the second case as a Class III Angle skeletal malocclusion. These forms of malocclusions represent sagittal skeletal severe discrepancies with changes in the facial aesthetics profile.

Previous studies have concluded that the non-syndromic form of permanent teeth hypodontia is occasionally caused by environmental factors, but the most common hypodontia is monogenic, the inheritance being autosomal dominant [25, 33]. Some authors have reported autosomal recessive [1, 34], X-linked [35] and polygenic transmission patterns [36].

The family’s pedigrees analysis revealed that maxillary premolars hypodontia of the studied family had an autosomal dominant inheritance with complete penetrance and variable expressivity. The upper limbs abnormalities were not observed in another family members and it was considered random the association between hypodontia and thumb hypoplasia. The risk of hypodontia recurrence in this family depends on the consulting couples. Thus, for a couple composed of a sick and a healthy person, the risk of recurrence is 50%.

In our cases, the association of hypodontia with other congenital anomalies led to the hypothesis of a syndromic hypodontia. Thus, there were suspected the syndromes that presented the association with autosomal dominant inheritance and hypodontia. In Table 1, there are displayed the McCune–Albright syndrome, the Book syndrome,
cleidocranial dysplasia and the lachrymo-auriculo-dento-digital syndrome [37–40], which have been identified to support the diagnosis of the proband. The syndromes with autosomal recessive transmission, the X-linked and those associated with mental retardation and other birth defects that were not present in the proband’s family were excluded.

Table 1 – Differential diagnosis of the proband III.13

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Present abnormalities</th>
<th>Missing abnormalities</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCune–Albright syndrome</td>
<td>Sceliosis</td>
<td>Fibrous dysplasia of bone</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Possible endocrinopathies</td>
<td>Café-au-lait skin spots</td>
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<td></td>
<td>Precocious puberty</td>
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<tr>
<td>Book syndrome</td>
<td>Premolar aplasia</td>
<td>Hyperhidrosis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Premature graying of hair</td>
<td></td>
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<tr>
<td>Cleidocranial dysplasia</td>
<td>Delayed eruption of teeth</td>
<td>Delayed fontanel closure</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Sceliosis</td>
<td>Hyperplasia of bone</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hypoplastic clavicles</td>
<td></td>
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<tr>
<td>Lachrymo-auriculo-dento-digital</td>
<td>Hypodontia</td>
<td>Obstruction of nasal lachrymal ducts</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Digitalized thumb</td>
<td>Sensorineural hearing loss</td>
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<td>Dry mouth</td>
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The proband’s general abnormalities were not identified with any syndrome that was taken into consideration, which disproves the hypothesis of a syndromic hypodontia. Nevertheless, there were not performed molecular genetic evaluations.

Both of the presented cases were diagnosed with non-syndromic hypodontia of maxillary premolar group, one of them associated with proximally inserted hypoplastic thumb, a previously unreported clinical manifestation. This phenotype is atypical to permanent teeth isolated hypodontia and difficult to classify into a pre-existing diagnostic classification.

Preferably, patients and direct family members should be counseled about such implications when a diagnosis of rare hypodontia is made, to allow the family to prepare for these matters and reduce their potential impact.

Conclusions

We have described this as a rare phenotype of bilateral maxillary first and second premolars hypodontia, which we classified as mild-to-moderate, non-syndromic hypodontia which has an autosomal dominant inheritance and an increased risk of recurrence in the studied family. The hypodontia was associated with an abnormality of the thumb in one of the presented case. The absence of four maxillary posterior teeth caused severe harm to the dental status, with serious consequences on the craniofacial morphology. The diagnosis and the late, multidisciplinary and complex treatment of this hypodontia phenotype, represent challenges for practitioners at the expense of the economic benefits of the patient and the public health system. The early detection of these cases would be appropriate, in order to establish a therapeutic interceptive management to prevent further disorders in the skeletal growth, and maintaining a facial balance.

References


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