Annual Issue of the Greek Association for Orthodontic Study & Research

Greek Journal of Orthodontics

«Tooth agenesis»

- Radiographic imaging for implant placement
- Epidemiology of dental agenesis in Greece
- Genetics of tooth agenesis
- Congenitally missing upper laterals. Clinical considerations: Orthodontic space closure
- Congenitally missing maxillary laterals. Restorative and prosthetic options
- Prosthetic intervention with implants
- Unilateral congenitally missing second mandibular premolars: Treatment options following diagnosis

www.eogme.gr

Issue 1

Athens 2012
Table of contents

- Introduction of the Board of Directors of G.A.O.S.R. ................................................................. 57

- Introduction of the Issue Editor ..................................................................................................... 58

- Radiographic imaging for implant placement .............................................................................. 59
  Demetrios J. Halazonetis,

- Epidemiology of dental agenesis in Greece .................................................................................. 66
  Marina Karamolegkou

- Genetics of tooth agenesis ............................................................................................................. 71
  Heleni Vastardis

- Congenitally missing upper laterals. Clinical considerations: Orthodontic space closure ........ 77
  Marina Karamolegkou, Panagiotis Prevezanos, Panagiotis Christou

- Congenitally missing maxillary laterals: Restorative and prosthetic options ............................... 81
  Efstratios Papazoglou, Panagiotis Christou

- Prosthetic intervention with implants .......................................................................................... 89
  George Papavasiliou

- Unilaterally congenitally missing second mandibular premolars: Treatment options following diagnosis 94
  Gerassimos Angelopoulos, Arfoditi Kouli

Greek Journal of Orthodontics
Annual Issue of the Greek Association for Orthodontics Study and Research
Introduction of the Board of the Directors of G.A.O.S.R.

It is with great pleasure, that we welcome you to the first edition of the “Greek Journal of Orthodontics” as is the name of our journal according to the bylaws of the G.A.O.S.R. With over 6,000 languages and 192 countries in the world, a global language becomes absolutely necessary as a tool of communication with the rest of the world, but without the English language being able to replace our native language. Therefore, it was decided that the Journal is published bilingual, both in Greek and English and be issued once a year. With dozens of scientific journals published in the field of orthodontics to establish another Journal with the form of collection of diverse subject articles was rightfully considered by the Board of Directors of G.A.O.S.R. as unnecessary. Instead, through consultation with our Greek colleagues of high academic level, found that there is a need for the creation of a Journal that will cover in the best possible way a single topic with clinical orientation. Each issue, will be assigned to an issue editor, who will assume the responsibility to choose the authors that would give him/her, the best possible coverage of the selected topic.

This project, is a challenge and an opportunity of expression, for all those who produce both in research and in the clinical field new data, new insights or new techniques or introducing in Greece new information that will help us maintaining and further the rendering of excellent Orthodontic services in our country.

The first issue of “The Greek Journal of Orthodontics” was unanimously decided by the Board of Directors to be entrusted to Professor and Head of the Orthodontic Department of University of Athens Dr Margaret Makos.
Introduction of the Issue Editor

It is with great honor that I accept the Boards’ of Directors of G.A.O.S.R. decision, to entrust to me the publication of the first issue of “The Greek Journal of Orthodontics”.

This issue of the “Greek Journal of Orthodontics” is dedicated to “Dental Agenesis”. In particular, treatment regimens are presented for persons with dental agenesis with emphasis on the combination of Orthodontics and Restorative Rehabilitation.

Modern treatment of persons with oligodontia requires cooperation of Orthodontics and Prosthetics. A special treatment approach is imperative for people with dental agenesis of lateral incisors or premolars in the maxilla as well as in cases with unilateral dental agenesis of second mandibular premolars. Because of the location of the agenesis in the anterior esthetic zone and the possibility to create asymmetry in the lower dental arch, the treatment regimen should consider patients’ expectations, the essentials of modern aesthetics, and include all aspects that will improve the prognosis of the treatment result.

The purpose of this issue is, to present the basic principles of dealing with these cases and to identify the specific elements important for drawing up the plan of treatment, such as orthodontic preparation, the optimal age for placement of implants, site of insertion and selection of the most appropriate prosthetic rehabilitation.

Nine colleagues ask questions and attempt to answer briefly the following:

Associate Professor of the Department of Orthodontics of University of Athens, Demetrios Halazonetis, launches this issue presenting the basic prerequisites for locating missing teeth with imaging techniques. What are the advantages and limitations of each imaging technique and especially of Cone Beam CT scan? Finally, adhering to the Supreme command of “Hippocrates” “To treat and not harm”, a detailed reference is presented to the radiation emitted by each imaging technique.

The orthodontist, graduate of the Orthodontic Department of University of Athens, Marina Karamolegkou presents the epidemiological data with respect to the frequency that these problems are found in our country. What is hypodontia and what oligodontia? What are the most common congenital missing teeth that appear in our clinics? Assistant Professor Heleni Vastardis of Oral Biology of the University of Athens, is presenting the genetic background of agenesis. How is the genetic determination of agenesis done? What we know today about the genes involved in the formation of the tooth? In which stage are we, in regard to gene mapping of dental agenesis? What we know and how far are we, from creating teeth from scratch?

The orthodontist Marina Karamolegou in collaboration with the dentist Panagiotis Prevezanos and Lecturer of the Department of Orthodontics of University of Athens, Panagiotis Christou present different clinical regimens. Specifically, they describe space closure by moving canines and premolars in the place of laterals and canines. What are the six points which should be given particular attention to?

The Assistant Professor of the Department of Operative Surgery of the University of Athens, Efstratios Papazoglou together with Lecturer Panagiotis Christou, present subsequently space maintenance and the prosthetic rehabilitation. What are the signs that need special attention? How should we deal with the problem of size and color of canines? How is the gingival outline? What are the advantages and disadvantages of implant placement in the premolar region? When the space between adjacent clinical crowns and roots is sufficient? When the width and height as well as the morphology of alveolar crest are judged sufficient? What alternative conservative restorations are there?

The Assistant Professor of the University of Athens, Department of Prosthetics George Papavasiliou presents a treatment regimen that includes, preserving spaces in the anterior region for implants with emphasis on both the advantages and the disadvantages. What are the six points which should be given particular attention to? When the space between adjacent clinical crowns and roots is sufficient? When the range of the height and the morphology of alveolar crest are sufficient?

Finally, Associate in Dentistry of the Department of Orthodontics of Athens University Gerassimos Angelopoulos together with the dentist Afroditi Kouli present the different treatment options for unilateral congenitally missing second mandibular premolars. When the definitive diagnosis can be performed? Which factors should be considered before we decide whether to extract or maintain the primary molar? Can the primary molar be kept and what should we do to avoid a compromise in the occlusion? How should we deal with ankylosed primary molars? If the decision is to close the space, what choices are available to achieve efficient and controlled space closure?

Have an enjoyable reading,

Margaret Makos

Professor and Head of the Orthodontic Department of University of Athens, Greece
Radiographic imaging for implant placement

Demetrios J. Halazonetis

Introduction
Radiologic examination of the area that will accept dental implants is considered essential in order to evaluate the quality of bone, the width and height of the alveolar process, the space between the roots of adjacent teeth, the location of anatomical structures that could get injured during placement as well as the presence of any pathology in the area. The most common imaging modalities are the periapical radiograph, the panoramic radiograph and computed tomography (CT). Selecting the best choice is a matter of comparison between the capabilities of each, mainly regarding their diagnostic value, and the dosage incurred to the patient. This assessment is more challenging between the panoramic radiograph and computed tomography, and this is where the emphasis will be placed.

Periapical Radiography
Periapical radiography is the most common type in dentistry, giving an image of high definition with a small dosage and low cost. Provided the radiograph has been acquired with the proper technique, measurements have good accuracy and validity, similar to that of CTs. Repeatability of measurements is better than CTs, probably due to higher resolution and clarity of the image. A disadvantage of periapical radiographs is their limited field of view, thus potentially excluding structures that would be of interest in placing implants, such as the mandibular canal and neighbouring teeth (e.g. impacted third molars). Furthermore, like all conventional radiographic imaging methods, it does not provide information regarding the width of the alveolar process along its bucco-lingual dimension.

Panoramic Radiography
A panoramic radiograph is the first choice for evaluation of implant sites. Among its advantages are ease of acquisition and lower dosage compared to a full-mouth series of periapicals, but what it really stands out for is its comprehensive overview of the whole dentition, the jaws and the implant sites. However, panoramic radiographs have significant disadvantages, including a) uneven magnification, especially in cases of errors in the positioning of the patient or incorrect adjustment of the tomographic zone (focal trough), leading to distortion, b) incorrect depiction of the mesio-distal

Figure 1.
Vertical magnification depends on the relative distance of the object from the focal spot and the radiographic film.
angulation of teeth, resulting in misleading evaluation of the space between roots, c) failure to image the bucco-linual dimension, and the 3-dimensional structure in general, a common problem of conventional radiography.

**Magnification – Distortion**

Magnification is the change in size of the image relative to the original object. In panoramic radiography magnification occurs due to the following factors:

**Divergent beam**

The source of the x-rays, the focal spot, is small in size (smaller than 1 mm) relative to the image. Therefore, the beam diverges resulting in magnification of the object. The magnification factor mainly depends on the ratio of the distance of the object and the film from the focal spot (Figure 1). Common magnification factors range between 20% and 30%\(^3\).\(^4\). It is important to note that magnification due to divergent rays occurs on the vertical dimension only, because the x-rays are restricted to a thin vertical beam by a vertical metal slit diaphragm.

**Circular motion**

Horizontal magnification is produced by the motion of the x-ray tube and the film. The x-ray tube rotates around a center of rotation which is positioned inside the patient’s head. Because this center is closer to the film than the distance between the focal spot and the film (Figure 2), the horizontal magnification would be larger than the vertical magnification\(^3\).\(^4\). However, following the principles of tomography, the film moves as well, so that the anatomical structures that lie in a narrow zone at a pre-defined distance from the center of rotation – the focal trough – are imaged clearly. The rotary movement of the film is opposite that of the x-ray tube, resulting in compression of the image along the horizontal direction. Mathematical analysis of the combined movements shows that the optimum speed that will produce a clear rendering of the objects in the focal trough is equal to that which will result in equal horizontal and vertical magnification\(^5\).\(^6\). Thus, the objects in the focal trough are depicted larger in both dimensions, but without distortion. Objects that lie outside the focal trough experience un-equal magnification in the horizontal and vertical dimensions and are therefore shown distorted, the amount of distortion depending on their distance from the focal trough\(^6\).\(^7\). Horizontal magnification is more sensitive to object position than vertical magnification. If an object is outside the focal trough and closer to the film it will experience smaller vertical magnification but appreciably smaller horizontal magnification, thus appearing narrower. Conversely, if it lies closer to the center of rotation it will appear wider. It should be noted that the focal trough is an area without clear boundaries, mainly defined subjectively, as that area wherein objects are imaged with sufficient clarity and little blurring. The only area that is ideally imaged is a cylindrical surface of zero thickness at a fixed distance from the center of rotation\(^7\).

The magnification of objects on this surface is given by the manufacturer and can be compensated for during printing, so that the image has the same dimensions as the objects. Magnification, even for objects in the focal trough, is not constant at every point of the panoramic radiograph, because it depends on the relative distance of the focal trough to the film. This distance changes for different anatomical regions and is determined by the relative speed of the film and the x-ray tube. However, this factor is of lesser importance than the distortion caused when objects lie outside the focal trough.
Nishikawa et al. report that even after compensating for magnification, based on the manufacturer’s recommendations, measurements appear systematically smaller (by approximately 1 mm) and with large random error (above 10%). Reddy et al. studied the magnification when the mandible is inadvertently not positioned at the ideal location but more forward, backward, or with inappropriate inclination. Although at ideal mandibular position the magnification was within the expected range (approximately 30% and equal in the vertical and horizontal direction), when the mandible was positioned 5 or 10 mm from the ideal, horizontal magnification ranged from 4% to 237%, with the larger discrepancies appearing at the incisal region. These values show the sensitivity of the technique to errors in patient positioning and reflect how important it is to respect the focal trough area. In contrast to horizontal magnification, vertical magnification does not show large variability.

**Discussion**

The above problems raise doubts as to the validity of the panoramic radiograph for diagnosis and treatment planning of implant placement. Regarding the anterior maxillary area, and in cases of agenesis of maxillary lateral incisors, various factors seem to operate, frequently in opposition, hindering a confident evaluation:

1. In cases of maxillary lateral incisor agenesis, especially if accompanied by agenesis of other maxillary teeth, the maxilla is often in a retruded position. Thus, the anterior area, including the roots of the canines and premolars, may lie at the interior border of the focal trough, or even behind it. This would result in larger horizontal than vertical magnification, giving the false impression of a wider mesio-distal space between the roots for implant placement than actual. In contrast, validity of the measurements in the vertical dimension is considered acceptable and the space for implant placement in this direction can be assessed with confidence.

2. The apparent mesio-distal angulation of the canine may be misleading. Because the central beam does not usually fall perpendicular to the dental arch, the apex of the canine is depicted more mesial than actual, giving the

---

**Tooth inclination**

During the machine’s rotation movement, the central beam seldom falls perpendicular to the dental arch. The beam falls at an angle, especially in the area of the canines and premolars, its direction being more posterior-anterior than linguo-buccal. This results in a misleading mesio-distal angulation of teeth. For example, if a tooth has its root palatally inclined, the apex will be projected at a more mesial position than the crown, making the tooth appear to have a mesial root angulation. Conversely, teeth with buccal root inclination will appear to have their roots distally inclined (Figure 3).

The above phenomenon has been extensively studied because the panoramic radiograph has been proposed as a diagnostic tool for assessing root parallelism during the final phases of orthodontic treatment, and is used as such for case evaluation by the American Board of Orthodontics. The consensus is that a panoramic radiograph does not record the mesio-distal angulation of teeth with high validity. The incisal area suffers the least, whereas the largest errors occur at canines and premolars. Discrepancies between depicted angulations and actual values may exceed 10 degrees; more than 60% of the measurements seem to exceed the clinically acceptable (arbitrary) limit of 2.5 degrees. Non-ideal positioning of the patient in the machine exacerbates the problem.

**Discussion**

The above problems raise doubts as to the validity of the panoramic radiograph for diagnosis and treatment planning of implant placement. Regarding the anterior maxillary area, and in cases of agenesis of maxillary lateral incisors, various factors seem to operate, frequently in opposition, hindering a confident evaluation:

1. In cases of maxillary lateral incisor agenesis, especially if accompanied by agenesis of other maxillary teeth, the maxilla is often in a retruded position. Thus, the anterior area, including the roots of the canines and incisors, may lie at the interior border of the focal trough, or even behind it. This would result in larger horizontal than vertical magnification, giving the false impression of a wider mesio-distal space between the roots for implant placement than actual. In contrast, validity of the measurements in the vertical dimension is considered acceptable and the space for implant placement in this direction can be assessed with confidence.

2. The apparent mesio-distal angulation of the canine may be misleading. Because the central beam does not usually fall perpendicular to the dental arch, the apex of the canine is depicted more mesial than actual, giving the
Figure 4.

a) Panoramic radiograph of a case of agenesis of maxillary lateral incisors (detail). Root approximation and available space between the roots are not reliably shown. The labio-palatal dimension of alveolar bone is not depicted.

b) CBCT 3-dimensional imaging of the same case. All distances can be measured accurately and reliably.

c) Virtual placement of an implant 3.5 mm in diameter. Lack of space is evident on the right side, as the implant is in contact with adjacent roots. In contrast, on the left side, there is sufficient space (more than 1.5 mm) on either side of the implant for the periodontal ligament to cover the roots and alveolar bone between implant and natural teeth.

d) Axial slices at two levels along the roots of the teeth - at the middle of the root and at the root apex - showing the labio-palatal width of alveolar bone, which can be evaluated for implant placement.

Computed Tomography

Computed tomography (CT) entered the field of dentistry after the advent of cone beam computed tomography (CBCT), due to the significant advantages of ‘dental’ machines over medical CT machines. Lower dosage to the patient played a decisive role, but other practical matters, such as the relative small size of the machines, lower cost, capability of installation in a private office and ease of use, also helped and led to widespread adoption by maxillofacial surgeons, orthodontists and implantologists. The obvious difference from all conventional radiographic techniques is the 3-dimensional representation. In contrast to periapical and panoramic radiographs, CT also provides cross-sectional images (axial slices) and allows evaluation of the bucco-lingual dimension of the alveolar process at any height level. In addition, there is no superposition of structures, no distortion, and all dimensions are equal to their actual values. Therefore, implant site assessment can be accomplished with high validity.

Experimental studies have shown that all measurements performed on CT images are clinically identical to their actual values. However, it should be noted that the resolution of CT images is lower than that of most conventional techniques and anatomical structures that are small in size, such as spicules of bone and thin bony surfaces may not be discernible. The resolving power of CT depends mainly on the signal to noise ratio and voxel size. In CBCTs, voxel size depends on the extent of the field of view. A small field of view is usually accompanied by small voxel size, high resolving power and smaller radiation dosage, and vice versa. In cases where we are interested in evaluating areas of alveolar bone that are very thin (e.g. labially to incisor roots), it is advisable to select a small voxel size, otherwise the bone may not be visible and we may falsely conclude that a dehiscence or fenestration is present.

Taking full advantage of CT requires training in the new imaging technique and the artifacts that may accompany the images. The images can be studied either in the printed form that is provided by imaging laboratories, or by dedi-
Radiation dosage

An important factor for selecting a radiological examination is the radiation dosage to the patient. Panoramic radiography incurs significantly lower dosage than CBCT, but the specific values depend heavily on the machine and the protocol that is used. Table 1 shows representative values, as reported in the literature.

Effective dose is calculated by multiplying the absorbed dose with a coefficient proportional to the biological sensitivity of the tissue being irradiated. The coefficients for each tissue type have been estimated by the International Commission on Radiological Protection (ICRP) and were last updated in 2007. The new guidelines include coefficients for the salivary glands, for which there were no separate values previously. Compared to the calculations based on the ICRP 1990 guidelines, the new values show that panoramic radiographs have a higher risk than previously considered, mainly due to their high radiation of the salivary glands. For this reason, the dosage ratio between panoramic and CBCT radiography has improved in favour of the second, but CBCT still holds the worst position.

Conclusions

Selection of the pre-surgical radiographic technique for implant placement should be based on the specific needs and characteristics of each case, and always under the general principle of As Low as Reasonably Achievable (ALARA).

Table 1. Effective dosage from a CBCT, a panoramic and a full-mouth periapical examination.

<table>
<thead>
<tr>
<th>Cone beam computed tomography</th>
<th>Effective dosage (μSv)</th>
<th>Equivalent panoramic dosage</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NewTom 9000</td>
<td>41 – 91*</td>
<td>2.0 – 4.5</td>
<td>Ludlow et al. 2003*48</td>
</tr>
<tr>
<td>NewTom 9000</td>
<td>64*</td>
<td>3.2</td>
<td>Tsiklakis et al. 2005*49</td>
</tr>
<tr>
<td>NewTom 3G</td>
<td>59**</td>
<td>2.9</td>
<td>Ludlow et al. 2006*50</td>
</tr>
<tr>
<td>NewTom 3G</td>
<td>30 – 57*</td>
<td>1.5 – 2.8</td>
<td>Loubele et al. 2009*41</td>
</tr>
<tr>
<td>i-CAT next generation</td>
<td>74 – 87*</td>
<td>3.7 – 4.3</td>
<td>Ludlow, Ivanovic 2008*42</td>
</tr>
<tr>
<td>i-CAT</td>
<td>193**</td>
<td>9.6</td>
<td>Ludlow et al. 2006*43</td>
</tr>
<tr>
<td>i-CAT</td>
<td>34 – 82*</td>
<td>1.7 – 4.1</td>
<td>Loubele et al. 2009*41</td>
</tr>
<tr>
<td>i-CAT</td>
<td>36 – 182</td>
<td>1.8 – 9.1</td>
<td>Roberts et al. 2009*44</td>
</tr>
<tr>
<td>Panoramic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22*</td>
<td>5 – 15*</td>
<td></td>
<td>Ludlow et al. 2003*48</td>
</tr>
<tr>
<td>23*</td>
<td>14 – 24*</td>
<td></td>
<td>Giibelis et al. 2005*44</td>
</tr>
<tr>
<td>Full-mouth periapical</td>
<td>35 – 170*</td>
<td>1.7 – 8.5</td>
<td>Palomo et al. 2008*45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ludlow et al. 2008*46</td>
</tr>
</tbody>
</table>

† Based on a panoramic dosage equal to 20 μSv.
* ICRP 1990 including dosage to salivary glands.
** ICRP 2005 provisional recommendations, similar to ICRP 2007.
* ICRP 2007
American Academy of Oral and Maxillofacial Radiology suggests that an axial slice image of the implant site should be taken in all cases, either by conventional or computed tomography. This proposal was published in 2000 and perhaps should be updated to more recent data. The European guidelines of 2004 that concern radioprotection in dental radiology suggest periapical radiographs in combination with a panoramic radiograph, in cases of a single implant, or, with CBCT, in cases of multiple implants. The European initiative SEDENTXCT, with its main aim to "develop evidence-based guidelines on use of CBCT in dentistry" has issued guidelines that include implant placement. In the guidelines it is stated that "CBCT is indicated for cross-sectional imaging prior to implant placement as an alternative to existing cross-sectional techniques where the radiation dose of CBCT is shown to be lower". As to when cross-sectional imaging is indicated, one can follow the advice of the European Association of Osseointegration (EAO), which devised consensus guidelines on imaging for implant dentistry. It should be noted that if CBCT images are taken, the clinical assessment of the images should be performed by a specially trained maxillofacial radiologist, especially in wide field of view images.

Bibliography

22. Fatemitabar SA, Nikgoo A. Multichannel computed tomography versus cone-beam computed tomography:
Epidemiology of dental agenesis in Greece

Marina Karamolegkou

Abstract
Dental agenesis is common among orthodontic patients. There are plenty of reports for the prevalence and the patterns/phenotypes of dental agenesis existing among different populations. The present study refers to the prevalence of dental agenesis among Greek orthodontic patients, as well as the observed patterns. Patients from three orthodontic centers in Athens, Greece participated in the study. The results are compared to similar studies on other populations. Finally a short report for the influence of dental agenesis on the facial skeleton is presented.

Introduction
Dental agenesis is defined as the failure of formation of a permanent or primary tooth. It is separated into oligodontia, when one up to five teeth are missing, and hypodontia, when more than six teeth are missing. There are reports for dental agenesis even among prehistoric populations.

There are many studies and reports in the foreign literature that refer to the prevalence and phenotype, according to the race. Europeans have the highest prevalence, 11.3%, followed by Asians, 9.4%, Americans, 7.4% and Arabs, 4.0%. A dispute for the prevalence of dental agenesis among males and females exists up to nowadays. Earlier reports claimed that females had a higher prevalence against males. Egermark-Eriksson & Lind refer that the ratio between males and females is 2:3. In later reports that ratio seems to change in 1:1.

Tooth agenesis is one of the most common developmental anomalies in humans. Tooth agenesis appears a familial or a sporadic trait. When familial, it is transmitted as an autosomal dominant, recessive or X-linked type. Comparing the incidence of dental agenesis between twins and siblings, there seems to appear no statistical difference.

Dental agenesis is a common finding in many syndromes, such as ectodermal dysplasia. In that particular syndrome besides agenesis, there is microdontia and anomalies at the morphology of teeth. Plenty of other syndromes are related to tooth agenesis, and a high incidence is reported among people with oral clefts.

Although in the primary dentition the prevalence of dental agenesis is very low, from 0.5% up to 0.9%, there seems to be a high correlation between agenesis in primary and permanent dentition. Persons having agenesis in their primary dentition, always have agenesis in the permanent dentition, as well. Many other tooth anomalies are combined to tooth agenesis, such as canines’ impaction, microdontia of upper lateral incisors, infraocclusion of primary molars and distoangularation of mandibular second premolars.

Environmental and genetic factors are associated to dental agenesis. Young children that have accepted high-dose chemotherapy and body irradiation appear higher incidence of dental anomalies and tooth agenesis. After the dioxin accident in Seveso, Italy, in 1974, people with higher levels of dioxin in their blood also had a higher incidence of problems in tooth morphology and dental agenesis.

Genetic factors are under research the two last decades. The first report was in 1996 for a mutation in the homeobox gene MSX1, in a family appearing a familial trait of tooth agenesis. Two other genes referred to cause dental agenesis, named PAX9 and AXIN2.

In the present study the prevalence of dental agenesis among Greek orthodontic patients, the pattern of dental agenesis, the incidence between the two sexes as well as the incidence between, maxilla and mandible and right and left side are examined. A first estimation for the heritage trait, familial or sporadic, is reported. There is also a small mention for the impact of dental agenesis on facial skeleton.

Incidence of dental agenesis
For the calculation of dental agenesis an epidemiologic study took place, with the participation of three orthodontic centres in Attica, Greece. The subjects were selected by the files of the Orthodontic department of Athens Dental School, the Orthodontic Department of the Military Dental Clinic of Athens and the Orthodontic Department of the Naval Hospital of Athens.

A total of 2350 files were examined. Patients with syndromes, craniofacial deformities and developmental anomalies were excluded. Files with inaccurate information or diagnosis were excluded, too.

Finally, 2061 files of orthodontic patients were selected (1171 women and 890 men). Patients were between the age of 7 and 47 years old, with average age of 13.5 years old. All files included dental and medical anamnestic data, study models, initial and final panoramic radiographs and photographs. Furthermore, all patients were clinically examined. To ensure the accurate diagnosis of dental agenesis in patients younger than 12 years old, a later orthopantomogram
incisors have the highest incidence of missingness (12, 22) (Fig. 4) followed by the second mandibular premolars. A special observation was made for that subgroup; persons with agenesis of one lateral incisor always had the other lateral incisor missing, in contrary to agenesis of any other tooth.

When agenesis of three or four dental units occurs, the most was examined, because the maxillary second premolars are the teeth that may be mineralized even after the age of 1227. Through the 2061 patients, 202 of them have at least agenesis of one tooth. The highest number of missing teeth in one person is 20 dental units (Table 1). The prevalence of tooth agenesis is 9.7% for males and 9.8% for females. Univariate logistic regression was used in order to assess the effect of sex on missingness and indicated that there is no difference in the odds between males and females. Sex has no impact on the phenotype of agenesis.

Most patients with dental agenesis belong to the hypodontia group, presenting a percentage of 88.6%. The percentage of patients that belong to the oligodontia group is 11.4%. The tooth most often missing is the left second mandibular premolar (35), followed by the left upper lateral incisor (22), the right second mandibular premolar (45) and the right upper lateral incisor (12). The rest teeth appear lower incidence of missingness, in the following order: 31, 41, 15, 25, 14, 42, 17, 32, 37, 24, 27, 47, 13, 23, 16, 34, 43, 46, 26, 33, 44, 11 and 21 (Fig. 1). As far as it concerns the number of missing teeth per person, the highest incidence was found for the agenesis of two dental units (Fig. 2), which are most often the upper lateral incisors and the lower second premolars.

If patients with agenesis get separated into subgroups, according to the number of missing teeth, the incidence of missingness changes. For example among patients with one missing tooth, the left second mandibular premolar has the highest incidence of missingness (Fig. 3).

Among patients with two missing teeth, the upper lateral incisors have the highest incidence of missingness (12, 22) (Fig. 4) followed by the second mandibular premolars. A special observation was made for that subgroup; persons with agenesis of one lateral incisor always had the other lateral incisor missing, in contrary to agenesis of any other tooth.

Most patients with dental agenesis belong to the hypodontia group, presenting a percentage of 88.6%. The percentage of patients that belong to the oligodontia group is 11.4%. The tooth most often missing is the left second mandibular premolar (35), followed by the left upper lateral incisor (22), the right second mandibular premolar (45) and the right upper lateral incisor (12). The rest teeth appear lower incidence of missingness, in the following order: 31, 41, 15, 25, 14, 42, 17, 32, 37, 24, 27, 47, 13, 23, 16, 34, 43, 46, 26, 33, 44, 11 and 21 (Fig. 1). As far as it concerns the number of missing teeth per person, the highest incidence was found for the agenesis of two dental units (Fig. 2), which are most often the upper lateral incisors and the lower second premolars.

If patients with agenesis get separated into subgroups, according to the number of missing teeth, the incidence of missingness changes. For example among patients with one missing tooth, the left second mandibular premolar has the highest incidence of missingness (Fig. 3).

Among patients with two missing teeth, the upper lateral incisors have the highest incidence of missingness (12, 22) (Fig. 4) followed by the second mandibular premolars. A special observation was made for that subgroup; persons with agenesis of one lateral incisor always had the other lateral incisor missing, in contrary to agenesis of any other tooth.

When agenesis of three or four dental units occurs, the most

<table>
<thead>
<tr>
<th>Number of missing teeth</th>
<th>Males</th>
<th>Females</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>41</td>
<td>33.6%</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>40</td>
<td>36.1%</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>11</td>
<td>8.9%</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>8</td>
<td>7.4%</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>3</td>
<td>5.9%</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5</td>
<td>3.4%</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1.98%</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0.9%</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>0</td>
<td>0.9%</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>1</td>
<td>1.48%</td>
</tr>
</tbody>
</table>

Table 1: Agenesis per sex. The incidence is referred to the sum of tooth agenesis.

Fig 1: Incidence of agenesis per tooth (third molars are not included).

Fig 2: Number of missing teeth per person.

Fig 3: Agenesis of 35 in a person with one dental unit missing.

Fig 4: Agenesis of 12, 22 in a person missing two dental units missing.
usual phenotype is agenesis of the upper and lower second premolars (Fig. 5). When five dental units are missing they are usually the four second premolars and one more tooth from the frontal or the distal area of the dental arch (Fig. 6). When grouping the persons that belong to the group of hypodontia, it is observed that the most often missing tooth is the left second mandibular premolar, followed by the right second mandibular premolar and the upper lateral incisors (Fig 7).

In the group of oligodontia the observed phenotype is different. There is not a specific phenotype but, generally, the highest incidence of missingness belongs to the upper lateral incisors, followed by the central mandibular incisors, the upper second premolars and the mandibular second premolars (Fig 8). In the group of oligodontia a different phenotype is observed, in comparison to the group of hypodontia, where the mandibular second premolars and the upper lateral incisors are most often missing. In the group of oligodontia the mandibular lateral incisors have a high incidence of agenesis, but in the group of hypodontia that incidence is very low (0.6%). Comparing the groups of hypodontia and oligodontia, there is a statistically great difference the percentage of agenesis of the second mandibular premolars (35, 45) and the lateral maxillary incisors (12, 22). All the other teeth have almost the same percentage of agenesis in both groups (Fig. 9).

Comparing the right and the left side there is not a statistical difference.

The effort to define the sporadic or familial trait of dental agenesis was really difficult because most parents of children belonging to the hypodontia group, didn’t know if they, or someone else in the family had a missing tooth, too. In the oligodontia group, due to the seriousness of the situation, most patients knew about the familial or sporadic trait of heredity. Through the 23 persons, 12 of them had a familial trait, 9 of them a sporadic trait and 2 did not know if there was another member of the family having agenesis (Fig. 10).

Discussion

Plenty of theories exist about dental agenesis. As reported, the second mandibular premolar has the highest incidence of missingness. The results of the present study come into agreement with most of previous studies concerning the Greek population and other populations. On the contrary, Davis PJ (1987) 28 and Niswander & Sujaku (1963) 29 report
that the most often missing tooth in Chinese and Japanese people, is the central mandibular incisor. Other investigators report that the tooth with the highest incidence of agenesis is the upper lateral incisor. According to Clayton JM (1956) the above teeth, with the third molars, are under evolutionary pressure. Such a fact cannot explain agenesis of mandibular central incisors.

In 1988, Svinhufvud et al. tried to give another theory based on anatomical sights. They assumed that some regions of the jaws are under the influence of epigenetic factors during embryogenesis. Those areas are: the region of fusion of the middle and lateral nasal processes, which are the areas containing the central and lateral upper incisors, and the region of fusion of the mandible, which contains the mandibular central incisors. As far as it concerns the second premolars, the explanation for their high incidence of agenesis is their position at the distal end of the primary dentition, which is a fragile point, according to Stritzel et al. (1990).

Plenty of reports exist for the impact of dental agenesis on the facial skeleton. There are many studies with cephalometric values of persons with dental agenesis. Most of them conclude that the maxilla is reduced compared to the maxilla of persons without dental agenesis. As a result is the retrognathism of the maxilla.

Conclusions
The participation of the three orthodontic centers gave the ability of a great number of patients. The results of the present study are:

- The prevalence of dental agenesis is 9.8%
- There is not a statistic difference between sexes
- The pattern/phenotype does not seem to be influenced by the sex
- The percentage of hypodontia is 88.6% and of oligodontia is 11.4%
- The highest incidence of dental agenesis, in a total of 592 missing dental units, belongs to the left second mandibular premolar (35)
- Most persons with dental agenesis, miss two dental units
- According to the number of missing dental units, there are different patterns of dental agenesis
- In the hypodontia group the highest incidence of agenesis belongs to the second mandibular premolars (35, 45)
- In the oligodontia group the highest incidence of agenesis belongs to the upper lateral incisors
- There is no statistic difference when comparing the maxilla and the mandible, or the right and left side
- 52.2% of person belonging to the oligodontia group had a familial trait of inheritance and the rest 39.1% had a sporadic trait of inheritance.

Acknowledgements
This study was supported in part by a eea grant (Norway, Iceland, Lichtenstein) and the Hellenic Ministry of Finance Grant # EL0069.

Bibliography


Genetics of tooth agenesis

Heleni Vastardis\textsuperscript{a,b}

Dentists must understand genetics to provide accurate information to patients and be able to discuss benefits and limitations of the biological, clinical, and ethical issues related to genomic-based health care.

J Dent Educ. 68(8): 809-818, 2004

Evidence supporting the genetic basis of human familial tooth agenesis is being established through the identification of mutations that result to the condition. Although the over 300 genes identified to play a role in mouse odontogenesis could potentially be candidates for tooth agenesis in humans, only three of them have they been associated with the familial non syndromic, autosomal dominant tooth agenesis. Two of them\textsuperscript{1-2}, \textit{MSX1} and \textit{PAX9} seem to be critical for premolar and molar development as the phenotype of affected family members points out. The third one\textsuperscript{3}, another dental -and more- gene, \textit{AXIN2} is associated with a less tooth-specific agenesis type involving almost any permanent tooth except for the upper central incisors along with predisposition to colorectal cancer. During the last fifteen years several mutations were identified on the \textit{MSX1}, \textit{PAX9} and \textit{AXIN2} genes and effort is being made towards linking the genotype to the dental phenotype and explaining human heterodonty.

This report aims to review the latest developments in the field of human molecular genetics relatively to tooth agenesis, to comment on possible obstacles in the way of identifying defective dental genes and to emphasize the need for genotype to phenotype associations in order to speed up the process of understanding human tooth development.

Introduction

Tooth agenesis or the developmental failure of certain teeth is the most common anomaly of the human dentition. Other terms such as hypodontia, partial anodontia or oligodontia are being used interchangeably in the literature to describe numeric dental anomalies. Tooth agenesis occurs as part of a genetic syndrome or as an isolated sporadic or familial finding. Familial tooth agenesis (FTA) is transmitted as an autosomal dominant, autosomal recessive or X-linked trait although there are cases of FTA with no clear segregation pattern. The condition presents interfamilial and intrafamilial variation in its expression\textsuperscript{4}.

Maxillary lateral incisors, second premolars, and third molars are the most frequently targeted teeth of the permanent dentition with an incidence that varies among 2.2%, 3.4%, and up to 30% respectively. Primary dentition is less frequently affected (0.1%) (Figure 1, reviewed\textsuperscript{4}).

Tooth agenesis often presents with associated findings such as atypical or smaller teeth and delay of development and eruption of certain teeth\textsuperscript{5-6}. Unfavorable pathway of eruption or impaction of certain teeth such as distal inclination (distoangulation) of second lower bicuspids and palatal impaction of upper canines are established microforms of the dental syndrome that accompanies dental agenesis\textsuperscript{5-6}. Tooth has been used as a model for understanding organogenesis for years as a typical example of an organ undergoing complex morphogenesis regulated by epithelial-mesenchymal interactions. Although considerable information has been accumulated –more than 300 genes have been identified to play a role in mouse odontogenesis- and the elucidation of the molecular events of odontogenic induction is a work-in-progress, the molecular basis of human tooth development and patterning remains largely undefined. The Human Genome Project has given fresh impetus to the experimental investigation of odontogenesis providing the art and science of locating genes on chromosomes. Naturally, gene mapping reflects gene defect mapping via identification of human mutations that cause conditions such as tooth agenesis.

Pinpointing human defective dental genes-Three genes for the "odontogenic code"

Genetic defects causing tooth agenesis have recently started to be emerging. Genetic linkage studies in a family with autosomal dominant agenesis of second premolars and third molars identified a locus on chromosome 4p, where the homeobox gene, \textit{MSX1} (muscle segment homeobox 1), resides\textsuperscript{1}. \textit{Msx1} is a transcription factor expressed in several embryonic structures including the dental mesenchyme. Targeted inactivation of \textit{Msx1} in transgenic mice leads to arrested tooth development at the bud stage\textsuperscript{7}. \textit{Msx1}\textsuperscript{-} deficient mice...
exhibit multiple craniofacial abnormalities including cleft palate, whereas the heterozygotes appear completely normal. The dental phenotype of the Msx1 deficient mice, the expression assays in murine teeth, and the availability of the human genomic sequence of MSX1, the candidate gene residing in the locus we identified by genetic linkage analyses, have prompted us to MSX1 mutation screening. Sequence analyses have detected a missense mutation (Arg196Pro) in the homeodomain of MSX1 in all affected family members providing evidence of the involvement of the human MSX1 in tooth development. Although the pattern of agenesis in this family is bilateral and symmetric and involves second premolars and third molars, some affected members, also presented phenotypic variability by lacking flanking teeth such as maxillary first premolars or mandibular first permanent molars. The Arg196Pro MSX1 mutation results in a protein containing an Arginine to Proline substitution at position 31 of the homeodomain of the MSX1. The homeodomain consists of 60 amino acids and is the most well conserved area through evolution of MSX1. To investigate the consequences of this substitution on the structure and function of the gene, we performed biochemical and biological analyses. These analyses have shown that the single point mutation renders MSX1 inactive. Such data point to haploinsufficiency - insufficient amount of the functional protein - as the mechanism causing tooth agenesis in this family. The selective effect of a single amino acid change in a protein, presumably present in all teeth, on only certain teeth can be best explained in terms of a threshold active during odontogenesis. For a complete tooth to develop this threshold needs to be overcome. Since tooth agenesis in this family segregates as an autosomal dominant trait, inactivation of one copy of MSX1 deprives tooth primordial of its odontogenic potential, and highlights the importance of dosage for mediating the biological actions of MSX1. Apparently the reduced dosage of MSX1 in other teeth, is better tolerated, suggesting that morphogenesis of the affected teeth requires a greater amount of MSX1. The idea of an individualized need for MSX1 amongst different types of teeth is also supported by the clinical observation that while individuals with MSX1 defects always fail to develop second premolars and third molars, flanking teeth are more variably affected. Alternatively, tooth morphogenesis in the affected family might be particularly susceptible to a reduced MSX1 dosage because of specific effects on genetic background. Interestingly, all affected members reported a complete primary dentition suggesting functional redundancy of homeoprotein signals and/or that other genetic mechanisms are involved in the development of the primary teeth. Such state can also be explained by a reduced need of MSX1 in
the primary dentition or could even be in accordance with the lack of defects in heterozygous mice. MSX1 has also been associated with syndromic forms of tooth agenesis. A nonsense mutation (Ser105Stop) in the MSX1 gene, in a family with autosomal dominant tooth agenesis and combinations of cleft palate only and cleft lip and palate has been identified, providing additional evidence for the importance of this gene in craniofacial development.

The clinical profile of the affected individuals in this family resembles the phenotype of the Msx1 knockout mice. The MSX1 effect on tooth, lip and palate development offers an appreciation of the associations between different organs in the developing body.

Another nonsense mutation (Ser202Stop) in the homeodomain of MSX1 has been found to cosegregate with the phenotype of Witkop syndrome - also called tooth and nail syndrome - suggesting that MSX1 controls the fate of both nail and tooth buds.

The dental phenotypes associated with the Ser105Stop and Ser202Stop mutations are typical for MSX1 mutations. In both cases, second premolars and third molars were the teeth at stake.

Another mutation, (Met61Lys) upstream of the homeodomain of MSX1 has been identified in a family, presenting a tooth agenesis profile similar to that of the Arg196Pro mutation.

Based on the clinical information provided in the literature, these two MSX1 mutations (Arg196Pro and Met61Lys) appear responsible for a specific pattern of severe tooth agenesis that involves second premolars and third molars but, not maxillary molars. On the contrary, the autosomal dominant orofacial clefting and tooth agenesis, and the Witkop syndrome nonsense mutations are capable of producing a variable degree of maxillary molar agenesis. Whether the severity and/or extent of the phenotype depend on the location of the genetic defect (complete absence of the homeodomain for the Ser105Stop, non-involvement of the homeodomain for the Met61Lys mutation etc) or tissue-specific genes compensate for MSX1, modifying its expression remains to be investigated. The variation observed suggests that other factors modulate the effects of MSX1 mutations.

Table 1: Reported MSX1 mutations

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>PHENOTYPE</th>
<th>MUTATION TYPE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>R196P</td>
<td>FTA</td>
<td>MISSENSE</td>
<td>Vastardis et al., 1996</td>
</tr>
<tr>
<td>S105X</td>
<td>FTA + cleft lip and palate</td>
<td>NONSENSE</td>
<td>van den Boogaard et al., 2000</td>
</tr>
<tr>
<td>S202X</td>
<td>FTA + NAIL DYSPLASIA Witkop Syndrome</td>
<td>NONSENSE</td>
<td>Jumlongras et al., 2001</td>
</tr>
<tr>
<td>M61K</td>
<td>FTA</td>
<td>MISSENSE</td>
<td>Lidral and Reising, 2002</td>
</tr>
<tr>
<td>G187X</td>
<td>FTA</td>
<td>NONSENSE</td>
<td>De Muynck et al., 2004</td>
</tr>
<tr>
<td>G22RhsX168</td>
<td>FTA</td>
<td>FRAMESHIFT</td>
<td>Kim et al., 2006</td>
</tr>
<tr>
<td>A194V</td>
<td>FTA</td>
<td>MISSENSE</td>
<td>Mostowska et al., 2006</td>
</tr>
<tr>
<td>A219T</td>
<td>FTA</td>
<td>MISSENSE</td>
<td>Chishti et al., 2006</td>
</tr>
</tbody>
</table>

It has been suggested that tissue-specific differences in the expressivity of the MSX1 mutations, resulting from a comparable loss of MSX1 function, can be explained by modifier genes’ actions.

More known MSX1 mutations are summarized in Table 1.

Many cases of tooth agenesis have not been explained by MSX1 defects. Five additional families presenting different types of missing teeth (incisal, premolar or canine agenesis) were evaluated for linkage to MSX1. None of these families was linked to MSX1 demonstrating that defects in different genes contribute to the clinical variation of this disorder and therefore, tooth agenesis is characterized by genetic heterogeneity.

Two additional independent groups failed to associate MSX1 with familial or sporadic tooth agenesis. In particular, studies in Finnish families have shown recombinations between MSX1 and hypodontia. The pattern of hypodontia in these particular families is a non-uniform one, ranging between numerical and morphological dental malformations i.e., incisor agenesis and premolar agenesis and conically-shaped teeth. Additionally, gene carriers exhibit no dental phenotype suggesting a model of reduced penetrance for these families.

PAX9 (paired box 9) is another defective gene found to cause human tooth agenesis in a family with agenesis of mainly permanent molars and sporadic agenesis of second premolars and lower permanent lateral incisors. Via genome-wide linkage analyses and candidate gene sequencing a frameshift mutation of the PAX9 gene was reported.

Pax9 is a member of the Pax-family of homologous genes that code for the paired-box containing transcription factors. Pax9 is expressed in neural-crest derived mesenchymal cells in the craniofacial region. The need for functional Pax9 gene was shown by the creation of Pax9 null mouse. Homozygote knockouts have secondary cleft palate and other abnormalities in the craniofacial skeleton and they lack all teeth and derivatives of the third and fourth pharyngeal pouches. The heterozygotes with one functional allele appear completely normal.

Another nonsense mutation in the PAX9 gene has been as-
associated with autosomal dominant molar tooth agenesis in a Finnish family\textsuperscript{19}. The A340T transversion creates a truncated PAX9 protein at the end of the DNA-binding paired-box. The tooth agenesis phenotype involves all permanent second and third molars and the majority of the first molars and resembles the previously reported PAX9 phenotype. Haploinsufficiency of PAX9 has been proposed as the likely mechanism for such a phenotype\textsuperscript{19}.

In a small nuclear family, in which a father and his daughter are affected with agenesis of all primary and permanent molars, evidence has been provided supporting that deletion of the entire PAX9 gene is the cause of molar agenesis\textsuperscript{20}. These data support a model of haploinsufficiency for PAX9 as the underlying mechanism for tooth agenesis\textsuperscript{21}.

More known PAX9 mutations are summarized in Table 2\textsuperscript{22}, \textsuperscript{23}, \textsuperscript{24}, \textsuperscript{25}, \textsuperscript{26}, \textsuperscript{27}, \textsuperscript{28}, \textsuperscript{29}, \textsuperscript{30}.

In another Finnish family with molar tooth agenesis, similar sequence changes in PAX9 have not been found\textsuperscript{19}. Attempts to detect more participants in the human odontogenic code have given two more dental loci\textsuperscript{31}, \textsuperscript{32}. A family with autosomal recessive hypodontia associated with various dental anomalies, such as enamel hypoplasia and failure of eruption has been linked to a region on chromosome 16q\textsuperscript{31}. There is no report on the specific genetic defect responsible for this type of hypodontia, as yet\textsuperscript{31}. Another locus on chromosome 10q11.2 has been recently identified causing agenesis of permanent teeth\textsuperscript{32}.

Studies in a Finnish family with severe familial tooth agenesis who did not present with mutations in MSX1 or PAX9, the two genes that when mutated can lead to oligodontia, disclosed the presence of a mutation (R656X) in the axis inhibition protein 2 (AXIN2) gene\textsuperscript{3}. The medical records of the family revealed a history of familial adenomatous polyposis. The possibility of establishing a dental clinical marker to screen for colorectal cancer brings additional interest to the studies of the genetic regulation of tooth agenesis. AXIN2 is a negative regulator of the Wnt signaling pathway. Axin2 is expressed during mice odontogenesis in the dental mesenchyme, enamel knot, dental papilla mesenchyme, and in mesenchymal odontoblasts. There is also extensive evidence of the expression of AXIN2 in colorectal tissues leading to carcinomas\textsuperscript{3}.

At least 8 permanent teeth were missing in 11 members of the family and 2 of them developed only 3 permanent teeth. Colorectal cancer or precancerous lesions of variable types were found in 8 of the patients with tooth agenesis\textsuperscript{3}. The association with AXIN2 and tooth agenesis was independently investigated in 55 Polish dental patients and an association was found between tooth agenesis and markers in the gene\textsuperscript{33}. On the other hand, germline AXIN2 mutations were found to be rare in patients with multiple polyposis\textsuperscript{34}. Work from Callahan et al., further supports a role of AXIN2 in human tooth agenesis and suggests AXIN2 is involved in sporadic forms of common incisor agenesis. Future studies should identify which specific tooth agenesis subphenotypes result from AXIN2 genetic variations\textsuperscript{35}.

Recent work by van den Boogaard et al., identified WNT10A mutations in 19 (56%) of 34 unrelated patients with non-syndromic tooth agenesis and concludes that WNT10A is a major gene in the etiology of isolated hypodontia\textsuperscript{36}.

### Table 2: Reported PAX9 mutations

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>PAX9 mutations</th>
<th>AA change</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frameshift - Nonsense</td>
<td>218,219insG</td>
<td>G73fsX243</td>
<td>Oligodontia</td>
<td>Stockton et al., 2000</td>
</tr>
<tr>
<td>Nonsense</td>
<td>A340T</td>
<td>Lys114stop</td>
<td>Oligodontia</td>
<td>Nieminen et al., 2001</td>
</tr>
<tr>
<td>Frameshift – Nonsense</td>
<td>792,793insC</td>
<td>V265fsX315</td>
<td>Oligodontia</td>
<td>Frazier-Bowers et al., 2002</td>
</tr>
<tr>
<td>Missense</td>
<td>A271G</td>
<td>Lys91Glu</td>
<td>Hypodontia</td>
<td>Das et al., 2003</td>
</tr>
<tr>
<td>Missense</td>
<td>G151A</td>
<td>Gly51Ser</td>
<td>Oligodontia</td>
<td>Mostowska et al., 2003</td>
</tr>
<tr>
<td>Missense</td>
<td>T62C</td>
<td>Leu21Pro</td>
<td>Hypodontia</td>
<td>Das et al., 2003</td>
</tr>
<tr>
<td>Frameshift – Nonsense</td>
<td>175,183del/ins288bp</td>
<td>R59fsX177</td>
<td>Oligodontia</td>
<td>Das et al., 2003</td>
</tr>
<tr>
<td>Missense</td>
<td>C76T</td>
<td>Arg28Tyr</td>
<td>Oligodontia</td>
<td>Lammri et al., 2003</td>
</tr>
<tr>
<td>Missense</td>
<td>G83C</td>
<td>Arg28Pro</td>
<td>Oligodontia</td>
<td>Jumlongras et al., 2004</td>
</tr>
<tr>
<td>Transition</td>
<td>A1G</td>
<td>Met1Val</td>
<td>Oligodontia</td>
<td>Klein et al., 2005</td>
</tr>
<tr>
<td>Missense</td>
<td>A259T</td>
<td>Ile67Phe</td>
<td>Oligodontia</td>
<td>Kapadia et al., 2006</td>
</tr>
<tr>
<td>Nonsense</td>
<td>C175T</td>
<td>Arg59stop</td>
<td>Oligodontia</td>
<td>Tallon-Wolton et al., 2007</td>
</tr>
<tr>
<td>Missense</td>
<td>C139T</td>
<td>Arg47Tyr</td>
<td>Oligodontia</td>
<td>Zhao et al., 2007</td>
</tr>
<tr>
<td>Missense</td>
<td>G16A</td>
<td>Gly6Arg</td>
<td>Hypodontia</td>
<td>Wang et al., 2008</td>
</tr>
<tr>
<td></td>
<td>G128A &amp; C129A</td>
<td>Ser43Lys</td>
<td>Oligodontia</td>
<td></td>
</tr>
<tr>
<td>Frameshift mRNA instability</td>
<td>321,322insG</td>
<td></td>
<td>Oligodontia</td>
<td>Suda et al., 2011</td>
</tr>
</tbody>
</table>
Conclusions

MSX1, PAX9 and AXIN2 mutations can explain a fraction of tooth agenesis cases and particularly, the familial and the most severe ones where multiple posterior teeth are missing. So far, gene defects responsible for anterior teeth i.e., incisal and canine agenesis have not been uncovered in humans. Experimental animal models have given clear indications of patterning in the mouse dentition. To mention a few, Dlx-1 and Dlx-2 null mutant mice are missing maxillary molars whereas maxillary and mandibular incisors and mandibular molars are normal. The opposite phenotype can be seen in the activin βA, activin receptor IIA and IIB, and Smad2 mutant mice. Therefore, it becomes clear that understanding dental anomalies is impossible using solely a monogenetic model, but rather, genetic, epigenetic and environmental interactions operate towards development of a pathological phenotype. As knowledge of tooth agenesis genes expands, a deeper understanding of the condition will be obtained in terms of the relation between clinical characteristics - severity and complexity of the phenotype- and sequence features. Interpretation of the genomic data will help in reconstructing odontogenesis in the laboratory and relate protein function to new treatment modalities. The identification of mutated genes will help to evaluate how other factors modify the phenotypic appearance of these anomalies. Gene function analyses would further assist to understand the most common ones. Finally, the identification of the pathogenic mechanisms of non-syndromic teeth anomalies would also clarify the role of teeth in craniofacial development, and would contribute to the diagnosis, treatment and prognosis of congenital malformations, and the eventual association with other severe diseases (e.g., oligodontia and colorectal cancer). Knowledge gained would lead to the development of simple tests for doctors to make an early diagnosis of severe health problems.

Bibliography

Congenitally missing upper laterals. Clinical considerations: Orthodontic space closure

Marina Karamolegkou a, Panagiotis Prevezanos b, Panagiotis Christou c

Introduction
Discrepancies in the number of permanent teeth is a common finding varying from total absence of the teeth (anodontia) to congenital absence of only a few teeth (hypodontia or oligodontia in congenital absence of six teeth or more). As a general rule, if only one or a few teeth are missing, the absent tooth will be the most distal tooth of any given type. If a molar tooth is congenitally missing, it is almost always the third molar; if an incisor is missing, it is nearly always the lateral; if a premolar is missing, it almost always is the second rather than the first. Lower incisors are an exception of this rule. One or more third molars are missing in 20-25% of the population. The prevalence of congenital absence of the other teeth varies in different populations. Prevalences around 6% are given for the Scandinavian population with about two per cent each for mandibular premolars, maxillary premolars and maxillary lateral incisors.

The treatment options include space opening or closure of the spaces which are a result of the congenitally missing lateral incisors. The present review refers to the orthodontic space closure. This treatment approach includes orthodontic treatment with fixed appliances for closing of the spaces and replacing the congenitally missing maxillary lateral incisors by the canines and the canines by the first premolars, respectively. It is a common and popular approach which can lead to very esthetic and satisfying results nowadays with the aid of esthetic and restorative dentistry. The most difficult task in substituting canines for missing lateral incisors is the achievement of an excellent esthetic and functional outcome that resembles an intact natural dentition.

Indications and contraindications
Orthodontic space closure may be indicated or contraindicated, after the evaluation of the factors below:
Important considerations are:
- Profile
- Malocclusion
- Size, shape and color of the teeth
- Bilateral or unilateral absence
- Smile line

Particularly, these factors are:
Profile. A careful examination must be done so the profile type is evaluated, apart from the occlusal type. In general, a balanced, relatively straight profile does not influence the decision of the appropriate treatment plan. A patient with mildly convex profile with no contraindications for space closure is preferred to be treated by canine substitution. Especially, when there is a little growth potential and overjet reduction by retraction of the central incisors will be used to camouflage a skeletal problem. However, space closure in a patient with moderately convex profile may not be the best option. A better alternative may be one that addresses not only the dental malocclusion but the facial profile as well, such as orthognathic surgery. Patients with concave profile type present midface deficiency and/or mandibular prognathism. If the treatment plan is canine substitution of the missing maxillary lateral incisors, this may increase profile concavity and maxillary deficiency. So, these patients should be treated by space opening for prostheses.

Malocclusion. Angle Class II malocclusion with maxillary prognathism is considered as an obvious indication for space closure. In this occlusal pattern, the molar relationship remains Class II and the first premolars are located in the traditional canine position. A Class I malocclusion with sufficient crowding where mandibular extractions are required is also an indication for space closure (Fig. 1). Generally, whenever teeth of the mandibular arch need to be extracted for orthodontic reasons, such as severe crowding or protrusion, space closure is the suitable option (Fig. 2). Another indication is a patient with full-lip profile when anterior teeth are severely protruded, or tipped labially or a patient with a balanced profile with normally inclined anterior teeth and minimal or no space available in the maxillary arch. When there is generalized spacing in the arch, closing the spaces is not indicated, but on the contrary, when crowding is present, space closure is the suitable option. The congenital absence of lateral incisors in Class III malocclusions is generally considered as a contraindication for
orthodontic space closure, especially in patients with retrognathic profile type. These cases usually have an edge-to-edge or negative overjet which may be worsened if the spaces are closed as the maxillary arch contracts.

**Size, shape and color of the teeth.** Normally, the canine is a longer and larger tooth, mesiodistally and labiolingually, than the lateral incisor it is to replace 6, and the first premolar is shorter and narrower than the canine. These differences can create an unattractive periodontal profile with too long and too large mesiodistally 'lateral incisors', and too short and too small 'canines', respectively. Moreover, the natural canine is usually darker and more yellowish than the intact central incisor and its color should be addressed and approximate that of the central incisor, which can be achieved by at-home or in-office vital bleaching 3,4,7,9.

**Unilateral absence.** These cases seem to be more difficult to manage than the bilateral absence because it is not easy to achieve a midline symmetry which contributes to better dental harmony. In addition, the contralateral incisor is often peg-shaped or diminutive with a thin and short root which causes size discrepancy between the anterior teeth 10. In such circumstances, extraction of the contralateral incisor and normal space closure may be a better option as it facilitates the maintenance of midline and dental symmetry of the maxilla 3,4,7,11.

**Smile line.** In a patient with a high smile line, the demand on esthetic result is enhanced as the gingival levels are more visible. These patients should be treated with orthodontic space closure, as it results to an esthetically more attractive outcome, and should not be treated with space reopening and lateral incisor implant placement, especially young patients. It is unconceivable that such a technique can achieve the long-term occlusal, gingival, and periodontal results in the esthetic zone that are seen with space closure 3,4,7,12.

**Advantages**

The major advantage of space closure is the permanence of the finished result. This is a one-shot therapy, which means that the overall treatment can be completed by the end of orthodontic treatment at an early age with a permanent result and long-term stability. The alveolar bone height in the actual region is maintained by the early mesial movement of the canine. The individual keeps his natural dentition which means that lifelong prosthetic restorations, that are likely to need repairs or replacements in the future, are avoided. Thus, the total cost of treatment is reduced for patient’s benefit 12-14. In addition, clear and natural gingival margin is achieved which will change in synchrony with the patient’s own teeth over a lifetime and any change due to the normal aging or for other reasons (mechanical, including tooth-brushing, or periodontal) will take on a natural look 7,12,15.

The esthetic result of space closure as a treatment option in patients with congenitally missing maxillary lateral incisors is generally preferred by general dentists, orthodontists, combined dental specialists, and laypeople. An interesting point was that a significant percentage of general dentists would restore the missing lateral incisors with implants for esthetic reasons but, even those professionals who felt the missing teeth should be restored, many did not prefer the esthetic result of a restored option 13,14.

In another study, Robertsson and Mohlin 16 evaluated the satisfaction of fifty treated patients with lateral incisor agenesis. They have shown that (a) patients treated by space closure were more satisfied with the treatment results than the prosthesis patients, (b) there was no difference between the 2 groups in prevalence of signs and symptoms of temporomandibular joint (TMJ) dysfunction, and (c) patients with prosthetic replacements had impaired periodontal health with accumulation of plaque and gingivitis.

**Disadvantages**

The tendency of the anterior teeth to reopen and relapse, after the orthodontic treatment is completed, is considered as the main disadvantage 3,7,12,17. However, this can be overcome with long-term fixed retention with a palatally bonded flexible spiral wire retainer on the palatal surfaces of the six anterior teeth.

Another disadvantage of this treatment option is the enameloplasty which is required usually on both the canine and premolar in order to resemble the teeth they substitute 13,14. Moreover, the color difference between incisors and canines, can cause esthetic problems and requires restoration. In addition, the fact that canine-protected occlusion is not feasible with space closure is considered as a disadvantage by certain authors, due to the stress placed on the premolars 5. Though, long-term occlusal and periodontal studies have shown there is no evidence for establishment of Class I canine relationship and space closure with premolar substitution for canines can lead to an acceptable functional relationship with modified group function on the working side 16.

**CONCLUSIONS**

Orthodontic space closure is a valid treatment option in cases of congenitally missing maxillary lateral incisors and depends on the evaluation of profile, state of occlusion, and the available space.

- Mildly convex profile
- Class II malocclusion
- A tendency towards maxillary crowding in a patient with a well-balanced profile and normally inclined anterior teeth
- Marked maxillary crowding or protrusion
- Canines and premolars of similar size
- Dentoalveolar protrusion
Fig. 1. A. Patient with congenitally missing upper laterals and class I malocclusion. Mandibular extractions to resolve the lack of space were decided. B. Treatment outcome after orthodontic space closure.

Fig 2. A. Patient with congenitally missing 22 and conoid 12. Cephalometric analysis revealed upper and lower bimaxillary protrusion. Mandibular extractions with extraction of the conoid 12 were decided. B. Final result after orthodontic space closure.
Bibliography


11. Savarrio L, McIntyre GT. To open or to close space-That is the missing lateral incisor question. Dent Update 2005; 32:16-25.


Congenitally missing maxillary laterals. Restorative and prosthetic options

Efstratios Papazoglou\textsuperscript{a} - Panagiotis Christou\textsuperscript{b}

Introduction
When a patient with agenesis of maxillary lateral incisors visit an orthodontist, then he faces a therapeutic dilemma: closure of the spaces due to agenesis of the lateral incisors or space opening for prosthetic restorations. Important difference of the restorations in the anterior region of the upper jaw is the high esthetic demands, making the selection and performance of the most appropriate type of restoration difficult, while an additional factor is the conservation of tooth structure. Therefore, create-space management for prosthetic restorations in the region of missing lateral incisors is needed. By this option, all the teeth are maintained in their natural position in the dental arches and the lateral incisors are replaced by prosthetic restorations.

INDICATIONS AND CONTRAINDICATIONS
The following factors have to be evaluated in a patient with congenitally missing lateral incisors so as to proceed to space opening or closing procedures (Table).

Profile: Patients with concave profile type usually have an edge-to-edge or a negative overjet and present midface deficiency and/or mandibular prognathism. If upright maxillary incisors need to be protruded, or tipped labially, to correct anterior crossbites or to gain upper lip support, space opening is indicated as this will improve the midface deficiency.\textsuperscript{1,2}

Occlusion: Class III malocclusion is regarded as an inarguable indication for space opening and prosthetic restorations for the missing lateral incisors as this can camouflage the existing malocclusion. This will effect also in the possible midface discrepancy that usually co-exists in this type of malocclusion. Where the skeletal discrepancy is not severe, the space opening procedure may produce a stable Class I incisor relationship at the end of treatment, if sufficient overbite is present.\textsuperscript{1,3,4} Orthodontic space opening is also indicated when there is no significant malocclusion or normal intercuspation of the posterior teeth, as it will maintain an Angle Class I occlusal type.\textsuperscript{1} Finally, when pronounced spacing is present in the maxilla, space opening is the treatment of choice.\textsuperscript{1,3,4}

Advantages
Space opening for missing maxillary incisors favors an ideal intercuspation of canines through first premolars and as a result this is marked as an advantage both functionally and occlusally.\textsuperscript{1,3,4} These teeth are maintained in their natural position within the dental arch with their natural morphology. In addition, if the treatment plan includes a single tooth implant, the natural teeth remain totally untouched. Finally, the orthodontic treatment is generally shorter in contrast with orthodontic space closure.\textsuperscript{1,7,8}

Disadvantages
The major disadvantage of this treatment option is that it commits the patient to a lifelong prosthesis in the most visible area of the mouth where tooth shade and transparency, gingival color, contour and margin levels are critical and difficult to control, particularly in the long term.\textsuperscript{1,7,8} Furthermore, the overall treatment is not complete when the orthodontic treatment ends. This means, particularly in adolescent patients, that the patient needs long-term retention of the spaces with temporary retainers until all skeletal growth is complete and tooth eruption has ceased, so he or she is eligible for permanent restoration. In addition, all the additional expenses for the permanent restoration and its lifelong maintenance are marked as a disadvantage.\textsuperscript{7-10}

RESTORATIVE AND PROSTHETIC OPTIONS
Closing diastema and tooth shape modification with direct composite resin
This restorative option is considered the most conservative since it maintains the adjacent teeth intact. If closing the diastema is selected as a therapeutic option, usually it is necessary to modify the shape of the tooth. The simplest and most conservative way of modifying the shape of canine to lateral incisor is with the use of composite resin and adhesive systems. The shape change may be realized with laminate veneers too (partial coverage restorations) using ceramics or composite resins. In both occasions it is necessary to fabricate a diagnostic wax up followed by transfer of all the changes to the oral cavity. In the case of direct restorations we transfer the diagnostic wax up to the mouth with the aid of an anatomic guide made out of silicone (silicone index) that covers the palatal surface of all adjacent teeth.
along with their incisal edge. Enamel is prepared for adhesion first by superficial grinding. By grinding the outermost layer, the aprioristic enamel is removed and is ready for etching with phosphoric acid. Enamel grinding is realized with a fine diamond or intraoral sandblasting. Composite resin masses are selected for the restoration that have such optical properties that the restoration: a) mimics the adjacent teeth, b) the margins of the restoration are indistinguishable and c) the restoration gives a satisfactory esthetic result (Pictures 1a-f).

**Shape modification with indirect partial coverage restoration**

Alternatively shape change can be done with indirect restorations of full or partial coverage. In all cases that we plan to implement many changes a diagnostic wax up should be accomplished first followed by a mock up or provisional restorations (Pictures 2a-f) to try the new functional and esthetic situation. If all elements of the restoration are satisfactory then we advance to the fabrication of the definitive restorations.

**Resin bonded bridge**

When we select to create the space for the prosthetic rehabilitation of the missing tooth with resin bonded bridge (RBB) we maintain the adjacent teeth intact or we remove minimum amount of tooth structure to create space for the “wings” when occlusion is tight or to create path of withdrawal. Historically, these restorations have a metallic frame made out of base metal alloy and porcelain coverage of the pontics. Today there are modern materials for the construction of these restorations. Instead of feldspathic porcelain, laboratory composite resin can be used (Pictures 3a-d). Additionally, there is the possibility of construction of all ceramic RBBs covering a high strength ceramic core with feldspatic porcelain. Finally, the RBB can be fabricated with a glass-fiber frame, covered with laboratory processed composite resin (Pictures 4a-e). The 5-year success rate reaches 67.3% with fracture or decementation of the bonded wing as the main reason.\(^{12}\) The parameters that must be considered for the placement of such restoration include location in the mouth, abutment mobility, thickness and translucency of abutments, as long as the occlusal situation. Parafunctional habits are a contraindication for placement of this type of restoration due to the high risk of decementation.\(^{12-18}\) They can be distinguished to those bonded on one side (Pictures 5a-h) and those bonded bilaterally (Pictures 3c, 4d).

**Cantilevered fixed partial denture**

Cantilevered fixed partial denture is the second most conservative restoration and in contrast with the resin-bonded fixed partial denture, the success of this type of restoration is not dependent on the amount of proclination or mobility of the abutment teeth. The 5-year survival rate is 92.3%.\(^{12}\) The canine is an ideal abutment for such a restoration due to its root length and crown dimensions (Pictures 7 a-g). Long-term success of the cantilevered fixed partial denture can be achieved if all contacts in excursive movements are removed from the cantilevered.\(^{4,12,13,18,20}\)

**Conventional full-coverage fixed partial denture**

This is the least conservative of all tooth-supported restorations and it is considered as the treatment of choice when replacing an existing fixed partial denture or when the adjacent teeth require restoration for structural reasons or to alter the facial esthetics (Pictures 6a-f). The control of the occlusion and occlusal forces is an advantage of this prosthetic option but, on the other hand, the amount of tooth preparation needed is the main disadvantage, especially in young patients.\(^{14,18}\)

**Single-tooth implant**

Single-tooth implant has become a very popular restoration nowadays as it is the most conservative prosthetic option. One of the main advantages is the ability to leave the adjacent teeth totally untouched. In addition, such restorations have shown high success rates with successful osseointegration but maxillary lateral incisor implants are challenging aesthetically. However, there are some thoughts to be evaluated if implant-supported crowns are to be placed.\(^{51,23}\)

**Implant site development**

When agenesis of maxillary lateral incisors is diagnosed in a young patient, usually primary maxillary lateral incisors are retained. In such cases, it may be necessary to selectively extract the primary lateral incisors to encourage the permanent canine to erupt mesially, adjacent to the central incisor. The canine will influence the thickness of the edentulous alveolar ridge due to its large buccolingual width; otherwise the osseous ridge will not fully develop due to the absence of the lateral incisor.

As the canine is moved distally to open space for the lateral incisor implant and crown, the root movement creates an increased and adequate alveolar ridge which allows proper implant placement. However, the time of implant placement should be relative close to the orthodontic treatment. This procedure is called “Implant site development”\(^{21,24}\) If inadequate alveolar ridge is present, ridge augmentation may be necessary using bone grafts.\(^{4,15,21,22,25}\)

**Clinical aspects**

Adequate implant space: The amount of space needed for the implant and crown is generally determined by the contralateral lateral incisor. However, if both lateral incisors are missing or the contralateral one is peg-shaped, the amount of space should be determined by one of the methods below:

1. The golden proportion or a recurrent esthetic proportion
2. The Bolton analysis
3. A diagnostic wax-up\(^{22}\)
4. Mean values\(^{26,27}\)

The small size of the maxillary lateral from 5.5-8.0 mm\(^{26}\) requires careful planning for an implant to be placed. Is important that orthodontic movement has distanced not only the
crows, but the roots of the adjacent teeth too. Generally, the adequate coronal space should be no less than 6.3mm whereas the interradicular space no less than 5.7mm.\textsuperscript{29} At least, 1.5 mm between of the implant and adjacent roots is desirable as it is cited that narrower distances between them are more likely to show a reduction in bone height over time.\textsuperscript{19,21,29} In addition, fixed retention is suggested rather than removable appliances to prevent relapse.

When the orthodontist opens space for the missing lateral incisor with fixed appliances, he should be very careful so the central incisor and the canine are moved bodily and not to tip them apart, because this is likely to make implant placement impossible. Thus, the orthodontist must confirm the ideal root position with a periapical or a panoramic radiograph, before the fixed appliances are removed.\textsuperscript{19,21}

In certain patients, it may be impossible to achieve acceptable interradicular spacing, even though the coronal spacing may be ideal. Particularly, in a patient with a Class III tendency malocclusion who requires proclination of the maxillary central incisors, when the crowns are tipped labially, the roots tend to converge toward each other resulting in a “wagon-wheel” effect. In such cases, an alternative restoration option is required.\textsuperscript{21}

\textbf{Time of implant placement.} Generally, implants must not be placed until the patients have completed their facial growth and the majority of their tooth eruption.\textsuperscript{30-32} As the face grows and the mandibular rami lengthen, teeth must erupt to remain in occlusion. However, the implant behaves like an ankylosed tooth and will not follow the changes of the alveolar processes due to the eruption of adjacent teeth.\textsuperscript{30-31}

This may result in clinical infraocclusion of the implant-supported crown and cause a discrepancy in the occlusal plane and between the gingival margins of the implant and the adjacent natural teeth.\textsuperscript{31,33} Thus, evaluation of the completion of facial growth by cephalometric radiographs must be done and subsequently, the patient should be informed for the optimal time of implant placement.\textsuperscript{14,15,21,22} However, even mature adults can exhibit major vertical steps after anterior restorations with implants to the same extend as adolescents.\textsuperscript{33}

\textbf{AUTOTRANSPLANTATION}

Autotransplantation is an interesting treatment alternative in patients with congenitally missing maxillary lateral incisors where the developing premolars are mainly used as autotransplanted teeth. Esthetic improvement of the transplants is necessary.\textsuperscript{34-37}

The optimal time for autotransplantation of premolars in the maxillary lateral incisors region is when the root development has reached two thirds to three fourths of the final root length. Possible complications refer to ankylosis, failure of the transplant, and pulpal necrosis. The root growth continues and the prognosis for complete periodontal healing at this stage of root development is better than 90%.\textsuperscript{26} After the transplantation of the tooth, a normal periodontal ligament is established and it can be moved orthodontically like any other tooth that has erupted into occlusion.

An interesting alternative includes anterior closure of the spaces, with the canines into the lateral incisors’ position, and posterior space opening for single-tooth implants in the premolars’ region, where restorations do not need to meet the same strict esthetic requirements.

\textbf{CONCLUSIONS}

The two most common treatment options in patients with congenitally missing maxillary lateral incisors are space closure by canine substitution and space opening for reconstruction. The main points are:

\begin{itemize}
  \item Both treatment alternatives have advantages and disadvantages as well as indications and contraindications for each one.
  \item Orthodontic space closure has become a more popular treatment choice as it seems to be more acceptable by patients and periodontically better.
  \item When space opening for prosthetic replacement is selected the esthetic result is difficult to achieve and to maintain long-term without further intervention.
  \item The choice of autotransplantation has a good esthetic result and it is feasible only in young patients where the roots of premolars are still developing.
\end{itemize}

The choice of the appropriate treatment plan should be a result of careful examination, where each individual is evaluated as a separate case without personal opinions and biases, and should meet the individual expectations which can lead to the desired aesthetic, functional and biological effects.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Orthodontic space closure} & \textbf{Space opening and rehabilitation} \\
\hline
- Convex facial profile & - Convex profile \\
- Angle Cl II occlusal relation & - Increased intercusption of upper and lower jaw and minor occlusal disturbances \\
- Orthognathic profile and tendency for crowding on the upper arch with minimal irregularity on the upper dental arch & - Excess of space on the upper dental arch \\
- Increased crowding or vestibular tipping of incisors & - Angle Cl III occlusal relation retruded maxilla \\
- Similar vestibular crown dimensions between canine and first premolar & - Great discrepancy in vestibular crown dimensions between canine and first premolar \\
- Protruded maxillary dentoalveolar base & \\
\hline
\end{tabular}
\caption{Factors determinants of the treatment of choice : Orthodontic space closure vs. Space opening and rehabilitation}
\end{table}
29 year old patient with bilateral agenesis of lateral incisors in the maxilla (Picture 3a). The patient declined orthodontic therapy. She had favorable shape of canines and free gingival line (Picture 3b). The treatment plan that was discussed and realized included enameloplasty of the incisal edge of #11, closing the interproximal spaces between 11 and 21 and shape change with composite resin of 13 and 23 to resemble lateral incisors. A diagnostic waxup was done first (Pictures 3c-d). It is important in cases like this that the canines and premolars have such a buccal profile to resemble lateral incisors and canines respectively11 and the occlusal scheme should be group function so there is no single premolar overloaded. The changes that had been planned with the diagnostic wax up were transferred to the mouth with the aid of a silicone index and the result presented in pictures 3e-f was achieved immediately.

23-year old patient with bilateral agenesis of permanent canines in the maxilla. The patient had primary canines with substantial root resorption but no mobility. In the patient smile (Picture 4a) and the intraoral view (Picture 4b) diastemas existed between all anterior teeth and the laterals and canines did not show in the smile. The patient declined orthodontic therapy. The treatment plan proposed involved extraction of primary canines and placement of two osseointegrated implants. For the esthetic improvement of incisors coverage with all ceramic crowns was proposed. The patient preferred to maintain in the mouth his primary teeth for as many years as possible and restoration with indirect laboratory processed composite resin restorations. The differentiation of restorative material between incisors (ceramic) and canines (laboratory processed composite resin) was decided since composite resin has lower hardness and wear resistance than ceramics and we would prefer these teeth to wear with a higher rate than ceramics, therefore to accept the lowest amount of lateral forces possible. Provisional restorations were fabricated (Picture 4d) to try the new functional and esthetic situation. All elements of the restoration were judged satisfactory before fabrication of the definitive restorations (Pictures 4e-f).
Picture 3
16 year old patient with a peg lateral #22 agenesis of #12 and external resorption of #21 (Pictures 5a-b). #11 was extracted, #22 was crown lengthened and the shape of #22 was modified with composite resin (Picture 5c). Finally a resin bonded bridge with metal frame and laboratory composite resin coverage was fabricated (Pictures 5d-e).

Picture 4
A 21-year old patient with agenesis of maxillary lateral incisors. Radiographic examination (Picture 6c) showed that there was not enough space for implant placement especially on the left side. Resin bonded bridges with a frame made of glass fibers and coverage of laboratory composite resin were constructed (Picture 6d).
22-year old patient after orthodontic therapy (Picture 7a). Radiographic examination showed the available edentulous spaces were marginally acceptable for implant supported restorations (Pictures 7b-c). Unilaterally supported etchable all ceramic resin bonded restorations were constructed (Pictures 7d) and they are shown on the cast (Picture 7e) and bonded on the patient mouth (Pictures 7f). Finally we see the smile of the patient (Pictures 7g-h).

Patient with agenesis of maxillary lateral incisors and malposition of adjacent teeth (Pictures 8a-b) decided to have them restored with full coverage metal ceramic restorations (Pictures 8e-f). Surgical management of soft tissues was accomplished to create appropriate space for the pontics (Pictures c-d).
23 year-old patient with agenesis of maxillary lateral incisors after the end of orthodontic therapy (Pictures 9a-b). Radiologic examination showed marginally enough space on the right side (5mm) and not enough space on the left side (<5mm) (Pictures 9c-d). It was decided to place an implant and a screw-retained restoration on the right side and restoration with full coverage cantilever bridge supported on the canine on the left side (Pictures 9 e-f).

Bibliography

4. Savarrio L, McIntyre GT. To open or to close space—That is the missing lateral incisor question. Dent Update 2005; 32:16-25.
Prosthetic intervention with implants

George Papavasiliou

In cases of anterior or posterior agenesisias, dental restoration with osseointegrated implants can often be described as the most conservative intervention. The main reason for this is to avoid preparation of the adjacent teeth. This is a particularly important element in planning the therapeutic approach since most of the patients are young people.

Possible problems include shortage of soft and hard tissues that occur due to the agenesisia of the specific tooth. Their treatment is mandatory prior to placement of the implant in order to achieve both functional and aesthetic restoration of the area. Treatments vary depending on the extent and severity of the defect. They include bone grafts through guided tissue regeneration methods (guided bone regeneration, GBR), soft tissue grafts or a combination of techniques.

Important to the success of restoration are malpositioned adjacent teeth, as they appear before or even after orthodontic intervention. Such problems are easier to be addressed when they occur without prior orthodontic intervention, as appropriate treatment in consultation with the dentist who will perform the prosthetic rehabilitation leads to the solution of the problem. Following orthodontic treatment, the most common problems relate to less than ideal locations of teeth adjacent to the edentulous area and relapse of orthodontic treatment outcomes. Difficult to solve are problems created by the proximity of the roots of teeth to an edentulous area as a consequence of orthodontic treatment. This can make placement of an implant, impossible. An important role in solving such problems, plays the willingness of the patient to undergo new or corrective orthodontic treatment.

According to the above, patients with agenesisias that can be restored using osseointegrated implants are classified into the following categories.

1. Patients that will not receive orthodontic or prosthetic intervention.
2. Patients that will be restored only with prosthetic intervention.
3. Patients that will be rehabilitated with prosthetic intervention in conjunction with orthodontic treatment.
5. Multidisciplinary treatment of patients using a broader range of specialties.

* Assistant Professor, Department of Prosthodontics School of Dentistry, National and Kapodistrian University of Athens
of these patients with implant supported restorations often outweighs other prosthetic solutions, since single dental units can be placed giving the opportunity to create small spaces between the teeth. This is particularly difficult to achieve with the use of fixed partial dentures, both conventional and resin bonded ones.

For the rehabilitation of patients in this category it is particularly important the fabrication of transitional restorations from the diagnostic waxing, so the patient can visualize the expected outcome. In figure 3a Rochete type temporary FPD’s have been placed, restoring the edentulous areas with a second canine and a lateral on the right side and only one lateral incisor on the left side. As the result was cosmetically and functionally acceptable, three implants were inserted in the edentulous areas (Fig. 3b), and were restored with single unit crowns. Both central incisors were restored with ceramic veneers for the elimination of the gap (Fig. 3c, d).

**Patients who will be rehabilitated with prosthetic intervention in conjunction with orthodontic treatment.**

Many of the problems regarding tooth position and asymmetry of edentulous areas that occur in patients with agenesis, which are difficult to be solved only with prosthetic intervention, can be resolved with very good results in case orthodontic treatment is done first. As the diagnosis of agenesis is usually done at an early age when the patients can not receive permanent prosthetic restorations or implants, it is important that coordination with the dentist who will do the rehabilitation is done simultaneously with the start of orthodontic treatment. This way is set a common treatment plan, which because the treatment period is often extensive, should be checked at regular intervals. In addition to what was mentioned above, adult patients often need to repeat or modify previous orthodontic treatment when there has not been a treatment plan with common goals.

In the clinical example of figure 4 the space that was maintained for the restoration of the lateral incisor due to agenesis of the permanent tooth is ideal. In the overall picture (Fig. 5) of the dental arch it is obvious that following careful planning, the existing teeth have been moved to completely different from their normal positions. In the diagnostic waxing (Fig. 6) the shape of the teeth is redefined to simulate the tooth normally in the position which it occupies. The aesthetic and functional result is tried on the patient (Fig. 7) through simulation (mock up) with special resins and the feasibility of the restoration is defined. The implant is placed by means of three dimensional navigation using stereo-
lithographic surgical guides (Fig. 8) and a flapless procedure. The final ceramic mechanical abutment is mounted immediately on the implant as well as the transitional restoration (immediate temporization). After the necessary period of osseointegration the adjacent teeth are prepared and the final ceramic crowns are made (Fig. 9). The final cosmetic result should be attributed to the initial planning and the cooperation of specialists for a long time so any action taken was serving the construction of the final restoration.

**Modification of the prosthetic intervention for highly aesthetic restorations.**

In patients with agenesias (Fig. 10) without any position problems of the teeth adjacent to the edentulous area, combined prosthetic and orthodontic intervention should be designed to maintain the existing spaces and the architecture of soft and hard tissues in order to achieve highly aesthetic restorations. From an orthodontic point of view the conservation of the space with a prosthetic tooth (Fig. 11) of suitable shape and size, bonded to the adjacent teeth, helps the patient to reach an appropriate age for implant restoration. For the final restoration there are surgical and prosthetic techniques that help to achieve an aesthetic outcome. Very small size flaps were used. Transitional abutments were immediately placed on the implants in conjunc-
Suturing of the flaps was done around the transitional restorations (Fig. 11) in order to create the appropriate contour during gingival healing.

In cases where it is particularly important to achieve optimal aesthetics and the periimplant tissues have been modified adequate time should be given to the surgical field in order to achieve complete stabilization of the shape and position of the gums. The difference is evident one week (Fig. 12), three months (Fig. 12 b) and seven months (Fig. 13) after surgery when healing of tissues is complete. The next step is the construction of the final restorations which in this case were metal ceramic. The final cosmetic result (Fig. 14) depends largely on the design of the therapeutic treatment and the use of aesthetic rehabilitation techniques.

Multidisciplinary treatment of patients using a broader range of specialties.

In patients with agenesis where several teeth are missing (Fig. 15), there is a need for cooperation of many experts to achieve full rehabilitation. Orthodontic intervention precedes and aims to settle the few existing permanent teeth in positions suitable for the construction of a prosthetic restoration. Maintenance of the teeth is very important until the age (18-19 years) where restoration with implants can be done. At the time of restoration, initially any existing deciduous teeth are extracted (Fig. 16) and temporary restorations are made supported by the permanent teeth (Fig. 16) solving functional and aesthetic problems of the patient, as the recovery period is very long.

The next stage involves the surgical augmentation of bone defects of the ridge which in many cases is very extensive due to the agenesis of permanent teeth. The surgery involves simultaneous regeneration of many areas (Fig. 17) and the volume of necessary grafts often requires harvesting of bone from the iliac crest. After the required healing period the implants (Fig. 18) are placed to prosthetically driven positions through a surgical guide. Achieving this
The goal is made possible because of the preliminary work that has been done during the orthodontic and surgical intervention. If there is not good coordination of the rehabilitation team then the result would be less than desirable. The final restorations are made after the osseointegration period and consist of crowns and bridges both on permanent teeth and implants (Fig. 19). In this particular patient they were made of zirconia. The design and manufacture of restorations were controlled by computer (CAD-CAM). To achieve the final result (Fig. 20) it took 20 months (not counting the years of orthodontic treatment). The patient in the last four years is on a six-month recall program and the expected long-term outcome seems to be very good.
Unilateral congenitally missing second mandibular premolars: Treatment options following diagnosis

Gerassimos Angelopoulosa - Afroditi Koulib

ABSTRACT:

Four case presentations are utilized to review the treatment options in patients with unilateral congenitally missing second mandibular premolars (UCML5s). Once diagnosed, the dentist can either preserve or remove the respective primary molar (PM5). Preservation will lead to a tooth-size discrepancy. To limit the size of the PM5 to the dimension of the contralateral premolar, and to allow the preservation of alveolar bone, reproximation of its mesio-distal aspect should be undertaken. Later on PM may become infra-occluded or lost, necessitating coronal built-up or a prosthetic replacement, respectively. In the latest case, autotransplantation, replacement by an implant after the completion of growth or orthodontic closure of the space are well-accepted solutions.

PM5 removal may be performed by:

A) Immediate removal to allow adjacent teeth to close the space and deal with the orthodontic aspects later on.

B) Extraction and closure of the space by means which will prevent the deviation of the lower midline and the lingualization of the lower anterior.

C) Controlled slicing of the PM5 and subsequent bisection and removal of the distal part utilizing the mesial root as bookend, while the first molar freely moves mesially. To permit the unimpeded movement of the molar, the premature contacts of the upper second molar should be removed.

In conclusion, aiming the ideal occlusion and profile, the clinician should take into account other orthodontic problems, the possible agenesis of the third molar, as well as pre-existing disparities in lower midline, and accordingly propose the most appropriate treatment plan for each patient.

INTRODUCTION:

Congenitally missing second mandibular premolars (CML5s) are the second most frequent type of agenesis, after the third molar, with an incidence of 2.5% to 5% of the population in the USA and Europe. Unilateral versus bilateral lower second premolar (L5) agenesis has been reported to consist up to 60% of the agenesis cases.

The objectives of this review are to direct the clinician through a diagnostic sequence of recognition and decision-making in planning treatment for a unilaterally CML5 in the most appropriate time and cost effective way.

The first step to formulate a treatment plan is to confirm a definitive diagnosis of the agenesis.

1. DIAGNOSIS OF CML5:

The time of the L5 eruption may vary from the normal values established for different sexes and races. A permanent tooth should not erupt later than 6 months to 1 year after the natural exfoliation of its predecessor. The congenital absence of teeth in the primary dentition is almost always associated with congenitally missing permanent teeth. According to Haavikko, the calcification of L5 starts at around 3.6 years of age for both sexes.

In the literature, several cases of delayed mineralization and slow development of L5 have been reported. Alexander-Abt (1999) reported a case of a 12-year old girl whose panoramic radiographs revealed an apparent agenesis of the left L5, whereas 13 months later (at the age of 13 years), the progress radiograph showed initial crown formation. Daugaard et al. showed that delayed development of the L5 is observed in women but not in men. Nevertheless, Röling (1980) and Bergström (1977) advised that a reliable diagnosis of a CML5 is possible in most cases around 9 years of age, although radiographic evidence of their mineralization is visible as early as 5 years of age. To diminish the chance of misdiagnosis, radiographs that indicate developmental absence should be examined carefully by magnifying glass for the presence of a tooth germ. The spontaneous absorption and disappearance of the follicle may occur in the initial stages of tooth development but always prior to mineralization. The definite diagnosis of a tooth as congenitally missing is based upon the presence of various radiographic signs, including the significant de-
lay compared to the contralateral side, the involution of the corticated border with bone infill and the absence of cusp tip calcification\textsuperscript{13}.

2. TREATMENT OPTIONS:
Upon the diagnosis of agenesis two main treatment options may be considered, namely, the extraction of the primary second mandibular molar (PM\textsubscript{5}) or its maintenance in the arch.

In most cases of extraction in patients with normal occlusion, our goal is to mesialize the first permanent molar in conjunction with orthodontic treatment, possible extractions of the other 3 premolars, as well as autotransplantation. With the introduction in the recent years of Temporary Anchorage Devices (TADs) and therefore the reduction of anchorage requirements, the unilateral space closure without other extractions has become increasingly popular.

In the case of tooth maintenance, our goal is to maintain the tooth with the alveolar bone for future implant and prosthetic reconstruction. No less than 13 factors must be considered to decide whether to extract or maintain the second primary molar.

3. CRITICAL FACTORS:
1. Dental and skeletal age of the patient: At the time of diagnosis, the skeletal and the dental age of the patient are important both for definite diagnosis of the agenesis and/or the presence of the ipsilateral third molar. Furthermore, vertical growth often continues past the pubertal growth spurt. Treatment initiations to close the space before or close to the peak of the pubertal growth spurt stimulate mesial dental drifting of the molars\textsuperscript{14,15}.

2. The presence of the respective third molar: Agenesis of L\textsubscript{5}s is associated with absence of other permanent teeth, especially the third molars of the same quadrant\textsuperscript{7,8,13}, which may be found in 48% of the cases. Usually, initial calcification of the third molars is observed at 9 years of age\textsuperscript{16} and third molars are considered to be missing only after 14 years of age\textsuperscript{19}.

3. Additional aplasiae\textsuperscript{18} may influence the treatment decision.

4. Gender: Males and females have different maturation rates. Fudalej et al. (2007)\textsuperscript{14} showed that on average girls’ facial growth continues until about 17 years of age, whereas the average boys’ facial growth is complete at about 21 years of age\textsuperscript{17,18}.

5. The distance of the second PM from the occlusal plane (possible presence of ankylosis): In ankylosis, vertical growth of the adjacent alveolar processes continues while the PM and its surrounding bone remain stable, a fact which leads to the submergence of the tooth relevant to the adjacent teeth, especially during adolescence. In adults, if submergence has not yet occurred, there is little or no chance of occurring during the rest of the life of the primary tooth, due to the fact that little growth of the alveolar ridges occurs\textsuperscript{18}. However, PM crowns are shorter than permanent molar crowns, therefore slight submergence might not be diagnosed as ankylosis\textsuperscript{20,21}. Certain methods for the detection of ankylosis, such as the tapping the tooth to detect a difference in sound are considered inaccurate. The most reliable indicator of PM ankylosis is to evaluate the interproximal alveolar bone levels on a bitewing radiograph. Flat bone levels between the PM and the adjacent permanent teeth indicate that the primary tooth erupted evenly with the adjacent tooth while angled or oblique bone levels between the PM and the adjacent permanent first molar indicate that the primary tooth is ankylosed and the permanent tooth continued to erupt\textsuperscript{17,22}.

6. The condition of the second primary molar, the degree of its root resorption, the presence of tooth decay, fillings and pulp pathology, the size difference between primary and permanent teeth, the condition of the bone after extraction of the primary tooth: Once the decision is made to extract the PM because of caries, resorbed roots or ankylosis, care should be taken to maintain the cortical plates intact during the extraction, especially in cases of ankylosis.

7. The stage of development of adjacent teeth: Peck et al. in 1996 had associated the agenesis of third molars and L\textsubscript{5}s with the occurrence of peg-shaped laterals and of palatally displaced canines\textsuperscript{23}. Two years later, Baccetti had also included the presence of submerged primary molars and enamel hypoplasia in the above findings\textsuperscript{24}. Contemporary data correlate agenesis of one or two L\textsubscript{5}s with delayed tooth maturation. More specifically, in cases with unilateral CML\textsubscript{5}, it can be expected that the canine and the first molar are delayed in development in men and women compared to dentitions without agenesis (canines, second premolars and first molars belong to the same developmental field)\textsuperscript{12}. Furthermore, there seems to be an association between the agenesis of premolars and the reduction of the size of the remaining teeth, suggesting that in these cases extraction treatment may be often unnecessary\textsuperscript{25}.

8. Lip prominence in relation to pronasale, pogonion and protrusion of the jaws: The extraction of the mandibular second primary molar is contraindicated in subjects with deep bite or hyperdivergent vertical skeletal pattern, mandibular retrusion or generalized spacing of the teeth. In addition, closing spaces may be detrimental to the facial profile of these patients\textsuperscript{23}.

9. Lack of space for the permanent dentition and proclination of incisors may suggest extraction treatment.

10. The axial inclination of the teeth\textsuperscript{16}.

11. The degree of interlocking intercuspation\textsuperscript{14}.

12. The type of sagittal occlusion\textsuperscript{16}.

13. Parents and patients agreement in the treatment selection.

In contemporary democratic societies the clinician makes the treatment proposals and the patient with his/her parents make the decision taking in consideration their finances.
4. CASE REPORTS:

PATIENT 1:
An 8-year old white Caucasian boy with Angle Class III dentofacial malocclusion, has congenitally missing (CM) #45 and #38 (FDI numbers). Clinical (fig. 1a,b,c,e,f,g) and radiographic (fig. 1d) examination revealed the following: a) Incomplete formation of #44 b) #47 has not erupted at all c) #48’s sperm was present d) #85 was present.
At that stage, a 3-month inclined plane treatment for the anterior crossbite correction was performed. The above findings in combination with the patient’s age and facial profile led to the decision of extracting # 85. Glassionomer cement was positioned on the mesial of # 55 (fig. 2a,b) and occlusal grinding of the distal cusps followed. Movement of both # 44 and # 46 (fig. 2c) was then noticed until age 12.1. This space reduction occurred without any orthodontic action and was followed by sectional orthodontics at age 14.8 (fig. 3) for 11 months and by full-banded orthodontic treatment for 18 months, finishing with a Class III molar and Class I cuspid relationship (fig. 4a,b,c,d,e,f,g). Total treatment time with appliances was 32 months.

PATIENT 2:
A 12 year 3 month old white Caucasian boy presented an Angle class II div. 1 dentoskeletal malocclusion and a CML5 (# 45). Clinical and radiographic (fig. 5a,b,c) examination revealed the following: a) eruption of the teeth proximal to # 85 b) slight crowding c) increased overbite d) lack of # 85’s root resorption and mild infra-occlusion of its clinical crown.
The above findings in combination with the patient’s age and facial profile led us to decide the maintenance of #85 in addition to interproximal reduction of the mesiodistal width to the width of the #35 to improve interocclusal relationship.
To estimate the correct amount of reduction, without causing any pulpal damage, the mesiodistal width of the PM was
measured at the level of the cementoenamel junction on a bitewing radiograph. The estimate was marked on the occlusal surface of the PM and subsequently the bur (fig. 16a,b) was positioned to cut toward the gingiva following the marked line on both mesial and distal surfaces. The average mesiodistal width of the PM was 9.5 mm and 2mm were removed from both surfaces. This procedure had left the crown 7.5 mm wide, which corresponds to the width of the contralateral L5 (7.5 mm) (fig. 6c). Despite the root proximity of the adjacent permanent molar the enamel removal was asymptomatic and this is further discussed in the discussion section chapter 5. In order to prevent decay from interproximal surfaces where dentin is exposed, a layer of light cured restorative composite resin was applied to the proximal lateral and the occlusal surfaces of the typically short primary molar, so that it can function with the teeth in the opposing dental arch preventing supraeruption\textsuperscript{17,26} (fig. 7). The total treatment length was 22 months and the class II correction was achieved thoroughly.

PATIENT 3:
A 12 year 9 months old white Caucasian boy, presented an Angle class II div. 1 dentoskeletal malocclusion with CM teeth # 25, # 35 and impacted # 43. Clinical (fig. 8a,c,e) and radiographic (fig. 8b,d) examination revealed the following: a) incomplete formation of # 34 b) # 37 had not yet erupted c) # 38's sperm was present. d) significant restoration of #75. The above findings in combination with the patient’s facial profile (fig. 8c) led us to decide the extraction of # 65, 75 and 83 (fig. 9), along with a Delaire face mask, as anchorage to facilitate the anterior movement of the posterior teeth anteriorly (fig. 10a,b). Alternatively TADs could have been used. The impacted # 43 was guided in transposition with the # 42. Mesial movement of # 26 and # 36 with improved occlusion and facial profile was noticed (fig. 11a,b,c,d). The total treatment length was 34 months.

PATIENT 4:
A 9 year 1 month white Caucasian girl presented an Angle class II div. 1 dentoalveolar malocclusion with CM #45. Clinical (fig. 12a,c,d) and radiographic (fig. 12b) examination revealed the following: a) incomplete formation of # 44, b) # 47 has not yet erupted, c) # 48's sperm was present, d) # 85 was intact. The above findings in combination with the patient’s facial profile led us to decide the hemisection of # 85 (fig. 13a,b) and removal of its distal part to facilitate # 46's mesial movement. The pulp was extirpitated from the pulp chamber and calcium hydroxide was placed to seal it off from contamination. There was no need to provide endodontic extirpitation to the mesial half. Once the mesial movement of the first permanent molar had slowed, due to its approximation to the mesial half of the hemisected tooth (fig. 14a,b), the mesial half of the # 85 was removed and space closure was completed by applying orthodontic forces\textsuperscript{27} (fig. 15a,b,c,d,e). At this point, an anchorage protection appliance was used (Class II elastics) to hold the lower anterior teeth forward. Such appliances may alternatively be an activator, a Jasper Jumper, a Herbst, a Forsus, a protraction face mask, or a Hickham chincup\textsuperscript{2,27}. The total treatment length was 33 months.
UNILATERALLY CONGENITALLY MISSING SECOND MANDIBULAR PREMOLAR
TREATMENT OPTIONS

5.a. Maintain the primary second mandibular molar.
(Reproximation of its mesiodistal part in order to limit its size to the dimension of the second premolar of the other side)

5.a.1. The primary mandibular molar remains until late adulthood

5.a.2. The primary mandibular molar remains until early adulthood

5.a.3. The primary mandibular molar is lost early

5.a.4. The primary mandibular molar becomes ankylosed depending on the age

5.a.4.a. Decoronation

5.a.4.b. Reestablish crown height to avoid BOTH supraeruption of the antagonist tooth and inclination of the adjacent teeth.

5.a.3.i. Autotransplantation

Adjacent teeth are left to drift and occupy its space until orthodontic treatment opens the space maintaining the alveolar bone.

5.b. Extract the primary second mandibular molar

5.b.i. Controlled slicing of the primary mandibular molar

5.b.ii. Bisecting the PM

5.b.iii. Push and Pull technique

5.b.iv. T.A.Ds

5.b.v. Reverse Headgear

5.b.vi Corticotomy

5.b.vii Standard orthodontic treatment if bicuspid of contralateral side is recommended for extraction

Implant placement

Prosthetic reconstruction

Close space
5. DISCUSSION:

5.a. Maintain the PM5:
According to Ten Cate, as the subjects grow older, the upcoming increase in masticory muscle force applied to the immature periodontal ligament could lead to occlusal trauma, initiation of resorption of the primary roots and surrounding bone and ankylosis. Therefore, probable causes for extraction of primary molars without permanent successors are pulpal pathology, large restorations, carious lesions close to the pulp, normal or pathological root resorption, ankylosis, differences in tooth sizes between primary and permanent teeth as well as clearly crowded cases. Judging from the above, it is difficult to say that the aforementioned changes rather support an extended life for the primary tooth than condemn it to its loss12,19.

In contrast to the above, if the patient has an ideal or acceptable occlusion, the preservation of primary second molars is a reasonable plan, since many can be retained at least until the patient reaches the early twenties17. Bjerklin et al. (2008)26 reported survival rates of PM without permanent successors greater than 90 per cent. In their study in the 99 subjects with retained PMs (mean age 24 years and 7 months) only 7 primary molars were lost because of root resorption, caries or infraocclusion. Bjerklin and Bennett (2000)26 noted a 60 percent resorption of the mesial and 46 percent resorption of the distal roots of retained PM5 molar between 11 and 20 years of age. Ith-Hansen and Kjaer (2000)27 had found that from 16 years of age 64.5 percent of patients with retained PM5 showed no signs of severe root resorption or significant infraocclusion. The rate of root resorption of primary teeth diminishes with age28.

There are many reports of primary posterior teeth surviving until the patient attains 40–60 years of age10,20,29, although none of these teeth had been slenderized. However, there is lack of a long-term study of teeth retained from childhood to late adulthood to establish the actual PM survival, especially when these teeth are slenderized. Maintaining the PM5 equals maintaining the alveolar bone both vertically and buccolingually.

On the other hand, maintenance can create an anteroposterior arch-length discrepancy. PM5 can be 2 to 3 mm wider than their permanent premolar successors, and a Class II or “end-on” molar relationship will typically be found with a maintained PM5. Therefore, it is favorable to reduce the width of the primary second molar to the size of the L5 of the other side and make it function like the absent premolar by establishing an ideal Class I molar relationship. If the decision to reshape the tooth is made, radiographs need to be examined to detect the divergent roots that limit the extent of reduction. This procedure can be initiated from age 8 to 9 and can be performed until age 14 to 1520. The onset or acceleration of the progress of root resorption of the primary tooth is likely to be an adverse side effect as the adjacent teeth converge on the often divergent, bell-shaped roots of the PM5 during space closure. Depending on the malocclusion, it is quite possible that PM5 need to be moved orthodontically. Unfortunately, common sense suggests that severe root resorption may occur when primary molars are moved. In this direction, existing data are insufficient so further research is required in order to clarify the risks of severe root resorption during primary tooth movement16. The conclusion, the decision lies on the orthodontist either to compromise with an “end-on” molar relationship by leaving the PM5 intact or to risk potential root resorption by slenderizing it17,19.

According to the prognosis of the PM5 the following options are proposed:

5.a.1. The PM5 remains until late adulthood.
It is widely accepted that a retained intact PM5 with a decent crown, roots and supporting alveolar process bone can offer an adult patient many years of service. It has been found that once these teeth survive into adulthood, they can function. Even for PM5s that are eventually lost, the average “lifetime” rivals the lifespan of some prosthetic appliances19.

5.a.2. The PM5 remains until early adulthood.
Once the patient reaches adulthood, osseointegrated implants are currently becoming the most biologically conservative and the mostly indicated option for replacing congenitally missing single teeth, provided that the patient can afford the expense. Alternatively, prosthetic reconstruction or in some cases autotransplantation of a maxillary third molar may be the treatment of choice. (See 5.a.3)

-Implants and bone preservation
If implant therapy is the treatment of choice, the implant should be placed soon after extraction close in time to extraction or exfoliation of the primary tooth, to achieve maximal preservation of alveolar bone. Extracting the primary teeth is sometimes difficult, requiring a flap and bone removal that could narrow the buccolingual alveolar ridge. Even an uncomplicated extraction will reduce the alveolar bone volume. This reduction has been estimated to be 18–25% of the bone mass and might jeopardize future implant therapy21,22. Ostler and Kokich (1994)23 estimated the long-term changes in the width of the alveolar ridge after the extraction of lower primary second molars and revealed a 25% reduction during the first 4 years, another 5% after 7 years, for a total reduction of 30% over 7 years. Nevertheless, the ridges could still receive a dental implant without a bone graft, even though the facial side was more resorbed than the lingual. Therefore the implant position should be more lingual, which suggests that the restorative dentist is about to alter the loading of the buccal and lingual cusps of the crown on the implant in order to prevent fracture of the abutment or the implant crown17.

Although implants seem to be the first choice, an obvious drawback is that they cannot be inserted until growth has been completed and they cannot be moved orthodontically since they behave as ankylosed teeth. The appropriate age for implant insertion is determined by the cessation of verti-
cal facial growth. Cephalometric superimpositions practical-ly show the cessation of vertical growth as they determine when the ramus stopped growing. Maintaining the primary tooth could be a semi-permanent solution, until the patient is old enough for the implant. It is the opinion of many au-thors that implants should be placed not immediately but close to exfoliation or extraction of persisting primary teeth in order to preserve alveolar bone. If an implant is placed in this site, a bone graft might be necessary to provide adequate ridge width and height. Vertical bone grafting is usually an added expense for the patient and has variable results of success.

When implants are placed in young individuals in their late teens or early 20s, the time perspective is different, often 60–70 years with the life expectancy of today. Very little is known about the risks for complications and adverse effects in this elongated long-term perspective. Wear and degrada-tion of the dental materials of the superstructure will neces-sitate revisions for functional and, most probably, aestheti-cal reasons. Therefore, a viable strategy is to place implants as late in life as possible and to use the different biological treatment modalities first.

5.a.3. The PM5 is lost early.

In case a PM5 without a permanent successor needs to be extracted early (caries, root resorption, infraocclusion), the choices are either to proceed to autotransplantation or to close the space. Another widely accepted treatment modality (known as orthodontic implant-site development) is to modify the eruption of the permanent first molar and first premolar, in a manner that they erupt adjacent one to the other, without maintaining the edentulous space. Despite the fact that such a plan requires longer orthodontic treat-ment to reposition the teeth apart to create the implant space, bone deposited equal to the width of the premolar and the molar is producing a more vigorous alveolar ridge, excellent for an implant placement.

The first premolar can be pushed into the position of L5, creating space for a single-tooth implant in the first pre-molar location, usually resulting in a much better ridge in which to place the implant. The alternative to implant replacement of the missing L5 is the prosthetic reconstruc-tion. This treatment modality, though financially attractive to the patient, requires tooth preparation, which advertently requires the sacrifice of the enamel of the adjacent teeth to the missing L5. Additionally, prosthetic replacements have a greater tendency to accumulate plaque and develop ginv-gititis. Keeping the tooth clean is more difficult in the molar region and can jeopardize not only the periodontal health but also the prosthetic result and the functional status. Eckert and Wollan (1998) had reported a 10-year implant survival rate of 95% while Nääpangeläns and al. (2002) showed an 84% success of conventional fixed restorations for the same period.

In general, biological methods i.e. growth-adapted mea-sures, orthodontic treatment and autotransplantation are preferable to prosthetic replacement.

5.a.3.1. Autotransplantation

In an uncrowded arch in which the PM5 is at risk of progres-sive root resorption or pronounced infraocclusion and the mesial movement of the first permanent molar is considered difficult or undesirable, autotransplantation may be the treat-ment of choice. Transplantation preserves alveolar bone volume and replaces a missing tooth without involvement of adjacent teeth, as, e.g. in tooth-supported prosthetic treat-ment. The tooth that can be used for such transplantation is a maxillary third molar, which has approximately the same crown size as a mandibular second primary molar. The suc-cess rates for autotransplantation range from 79 to 94 per cent for up to 26 years.

Autotransplantation of a maxillary third molar, typically around age 18-19 years, is a viable option. Autotransplanta-tion of maxillary premolars combined with orthodontic treat-ment should be the first treatment alternative in cases of missing L5s, when a suitable donor tooth is available, as it reduces the severity of some orthodontic cases without compromising the dental status or interfering with conven-tional procedures in case of failure.

At this stage donor teeth that have not completed their root formation continue their root development. The manipulation of extractions apply great forces on teeth and the re-sistance of periodontal ligament fibers affects not only the healing process but the prognosis of transplants as well. The trauma produced during re-implantation can cause un-desirable periodontal reactions and pulp damage, which have the potential to heal through various pulpodental pro cesses. Success rates are higher in teeth with wide open root apices compared to teeth with complete root forma-tion, as their pulp easily “recovers” vitality. Andreasen et al. (1990) claimed that “immature” teeth have a periodontal healing that reaches the 90%, while teeth with closed apices only 60%. The most serious complications of transplanta-tions are ankylosis (usually “replacement ankylosis”), per-sistent external root resorption (surface resorption and in-flammatory resorption) and micro trauma to the periodontal membrane during removal of the donor tooth. Despite the fact that autotransplantation in children may have a successful outcome decades later, this treatment modality suffers from 3 main disadvantages: First, it is subject to time constraints and can only be performed when the root has reached but not exceeded a specific developmen-tal stage, which means that radiographic monitoring is re-quired. Secondly, a suitable donor tooth such as a premolar or a third molar must be available, which is not always the case. Thirdly and finally, it involves surgical intervention.

5.a.4. The PM5 molar becomes ankylosed.

In case of an ankylosed and submerged PM5 depending on the age may result in a narrow alveolar ridge with a vertical defect. Two possibilities exist in these cases: (a) In early ankylosis, decoronation or extraction. It seems possible that decoronation of the ankylosed tooth may pre-serve the alveolar bone. Decoronation is a simple and safe surgical procedure for preservation of alveolar bone prior
to implant placement\textsuperscript{29}. Decoronation can also be indicated after active growth of the jaws during which eruption of the teeth is minimal. Tooth eruption continues even after active growth of the jaws (usually 1/10 of a millimeter per year)\textsuperscript{40,41}. It has been clinically shown that decoronation preserves the alveolar width and rebuilds lost vertical bone of the alveolar ridge in growing individuals. The biological explanation is that the decoronated root serves as a matrix for new bone development during resorption of the root and that the lost vertical alveolar bone is rebuilt during eruption of adjacent teeth\textsuperscript{42}. Fines et al.\textsuperscript{1} showed that the mean increase of infraocclusion in retained primary molars was 1.0 mm from the ages of 11 to 20. Bjerklin and Bennett (2000)\textsuperscript{26} showed that 41 subjects with 59 primary second molars in situ had 0.5 to 4.5 mm infraocclusion (ankylosis) at the age of 19 years. In other cases when ankylosis occurs early, immediate extraction of the ankylosed tooth is recommended to preserve normal alveolar bone growth and avoid a narrow alveolar ridge with a vertical defect.

(b) If the ankylosis occurs in early adulthood, then the submergence is slow. This creates the necessity of reestablishing crown height, in some cases to avoid supraeruption of the antagonistic tooth and reduce the possibility of mesial inclination of the adjacent permanent first molar, which could compromise the finished orthodontic and prosthetic result\textsuperscript{15,20,22}.

5.b. Extract the PM5

It has been suggested that early treatment may allow spontaneous space closure by guiding tooth eruption\textsuperscript{43}. Svedmyr (1983)\textsuperscript{44} suggested extracting the PM5 molar prior to eruption of the first molar in order to stimulate mesial eruption of the first molars. However, a definite diagnosis of aplasia of the L5 in patients under 9 years of age can rarely be made\textsuperscript{15,44}. Other proposals have included extraction of a premolar in the opposing arch with, or without, active orthodontic treatment\textsuperscript{46} or extraction of three premolars in the fully dentate quadrants\textsuperscript{46}.

In subjects with agenesis of the L5, extraction of the PM5 before the eruption of the permanent first molar is believed to create favorable conditions for spontaneous space closure and to cause minimum tipping of the molars\textsuperscript{39}. However, the diagnosis of agenesis at this age is not reliable. If the decision to extract the PM5 is made early, for instance at 11 years of age, before the eruption of the second permanent molar, spontaneous improvement is often expected. Joondph and McNeill (1971)\textsuperscript{46} suggested that in subjects with hypodontia, the PM5 molar should be extracted early, before 11 years of age, to allow spontaneous space closure. In a 4 year follow-up after the extraction of the PM in subjects with agenesis of the L5, Mamopoulos et al. (1996)\textsuperscript{36} showed that 80 percent of the resultant space was closed, leaving a mean residual space of 2 mm. Lindqvist (1980)\textsuperscript{45} reported similar findings. In 84 percent of selected cases, the space was closed by mesial drift and tipping of the first molar and distal drift and tipping of the first premolar. Extraction of the PM after completed root development of the second molar and first premolar often leads to more tipping of these teeth. Lindqvist (1980) also reported a significant mandibular dental midline shift towards the extraction site. Follow-up studies demonstrate that early extraction is likely to produce inclination in 46% of patients with mesial rotation of the permanent first molars and distal drift of the first premolar and the canine in 80% of these closures\textsuperscript{47}. Furthermore, extraction of the PM after completed root development of the adjacent teeth often leads to more tipping of these teeth.

Closure of the space is beneficial in cases of a protrusive facial profile or crowding in the opposite dental arch\textsuperscript{30,43}. The major advantage of orthodontic space closure is the permanence of the finished result.

5.b.i. Controlled slicing of the PM5

5.b.ii. Hemisection of PM5

Controlled slicing is a good option for treating patients with CML5 for several reasons. It preserves the buccolingual ridge and produces bodily controlled mesial movement of the permanent first molar with no or minor rotation and inclination. In addition, it abolishes the need for prosthetic replacement, which could compromise the final occlusion or create bony defects.

The success rate of controlled slicing is high. A 90% success may be achieved when the technique is applied at an early age (8 to 9 years); the success rate tends to decrease as age increased. Controlled slicing is advantageous at an early age as it controls the inclination of the permanent first molar. It allows the permanent tooth to move through the buccolingual bone plate, which is maintained by the residual crown-root portion of the PM5 molar, thus avoiding undesirable mesial rotation. Sequential slicing followed by hemisection and extraction of PM5 molars in cases of CML5s is reported to be more successful than extractions avoiding the flattening of the facial fullness. An obvious disadvantage of controlled slicing technique is that the patient must visit the pediatric dentist or surgeon’s office twice, for the hemisection and the extraction of the primary tooth. The initial slicing of the distal crown portion of the PM can be done in the orthodontic office and requires only topical anesthetic. Care must be taken to protect the permanent molar\textsuperscript{48}. In a hemisection study of Northway (2004)\textsuperscript{45}, the hemisection groups demonstrated diminished distal movement of the upper incisors, as well as of the upper and lower lip, whereas the lower molar protraction and molar relation were significantly improved\textsuperscript{2}. Hemisection facilitates the preservation of upper premolars, a fact which further enhances the facial fullness.

5.b.iii. Push and Pull technique

One other way to close the space is the push-pull technique, which refers to localized space closure (push and pull mechanics- PPM). The application of conventional space closing mechanics, such as powerchain, closing coils and closing loops should be avoided in order to mini-
mize intrusive forces on the anterior teeth while maximizing mesial movement of the lower molars (Zimmer et al.). Utilizing PPM traction to the anterior teeth may also be avoided, as well as dental restorations and surgical procedures. This treatment modality is indicated for the majority of patients affected with aplasia[36].

5.b.iv. T.A.Ds and 5.b.v. Reverse Headgear
In patients with no dental crowding and a normal facial profile, closure of the edentulous space from a CMLS could alter undesirably way the facial profile by flattening it. In this case additional anchorage is needed, intraoral or extraoral, in order to prevent these unwanted changes. Intraoral methods of additional anchorage are mini orthodontic implants or other temporary anchorage devices (TADs). However, the application of TADs has been reported to fail frequently in younger patients[47]. Extraoral appliances able to accomplish this type of movement are a protraction facemask and a chin cup and elastics[39]. By utilizing these methods, the molars can be protracted without side-effects on the anterior teeth of the arch.

5.b.vi. Corticotomy
Corticotomy has long been used in orthodontic treatment to accelerate dental movement and improve its efficacy. In 2001, Wilcko et al.[48] suggested that, based on computed tomographic studies, the rapid tooth movement associated with corticotomy-facilitated orthodontics was more likely the result of a demineralization/ remineralization process consistent with the initial phase of regional acceleratory phenomenon, namely an increase in cortical bone porosity and a dramatic increase of trabecular bone surface turnover due to increased osteoclastic activity. In corticotomy-facilitated orthodontics, the optimal tooth movement seemingly occurs when only a thin layer of bone overlies the root prominence in the direction of the intended tooth movement, in close approximation to the osseous insult. This thin layer of bone will demineralize and the remaining soft tissue matrix and islands of osteoid will be transported with the root surfaces, where the bone matrix will remineralize at the completion of the orthodontic therapy. In adolescents, the demineralization/ remineralization of the alveolar housing is seemingly complete, without a net tissue loss. In the adult population, however, the remineralization is less complete, albeit to a clinically insignificant degree, due to the decreased vitality of adult tissues in comparison with adolescent tissues. The tooth movement in this treatment is merely the result of a physiologic process and not the repositioning of segments of bone. Conversely, the movement of the teeth in the traditional orthodontics treatment is accomplished through tipping and uprighting and thus the pretreatment angulations of the teeth weigh heavily on the amount of tooth movement.

Compared with traditional orthodontic treatment, this treatment has the obvious advantage of dramatically shorter treatment times, which represents an attractive alternative for many patients. This convenience, additionally, is claimed to possess the ability to move teeth farther and yet provide a greater alveolar volume for increased post-treatment stability with decreased side effects[49].

CONCLUSIONS:
- Recommendations on treatment in young individuals with tooth agenesis are based mainly on clinical experience. Establishing registries for monitoring of clinical outcomes in this group of individuals is strongly advocated.
- The L5s have a tendency to form late and may be thought to be missing only to be discovered to be forming at a subsequent visit. CMLS5s can be diagnosed with a very high degree of certainty, in the early mixed dentition at about 9 years of age. Good quality premolars seldom form after the child is 9 years of age. To reduce the chance of misdiagnosis, correctly taken radiographs should be scrutinized for early indications of a tooth germ before mineralization[1].
- Early detection of CML5s is important to enable appropriate interceptive orthodontic treatment. After the age of 9 options become more limited. Spontaneous space closure might no longer be an option1.
- No less than 13 factors must be considered to decide whether to extract or maintain the PM. These include the dental and skeletal age of the patient, the presence of the respective third molar, an additional aplasia, gender, a possible ankylosis, the condition and morphology of the primary molar, the stage of development of adjacent teeth, a lip prominence, the skeletal pattern, space conditions and finally the agreement of parents and patients in the treatment selection.
- In adults with missing L5 and retained PM5 in good condition, its long-term prognosis seems promising 5. There are cases of PM that are eventually lost, but whose average duration of functionality competes the lifespan of some prosthetic appliances. There are many reports of primary posterior teeth surviving until the patient is 40 to 60 years of age 5. In adults, the shortening of retained PM5 roots and changes in their submergence usually go unnoticed[19]. The introduction of TADs enables absolute anchorage making the choice of space closure more accessible even in adults[47].
- PM5 maintenance serves as an excellent tool to preserve bone for future implant replacement. In the case of early lost PM, the adjacent teeth are left to drift and to occupy the space until orthodontic treatment opens the space, while maintaining the alveolar bone for future implant placement, autotransplantation or space closure.
- In adolescents, space closure is definitely a more appealing solution because the final result is more permanent, as there is no need of maintaining space and awaiting the completion of growth for a permanent restoration.
• Hemisection provides an excellent first step in the process of space closure. It diminishes the backward movement of the anterior teeth, as well as the flattening effect that space closure might generate on the facial profile.

• In cases of primary mandibular molar ankylosis the treatment choice is influenced by the continuing growth. At early phases, decoronation or extraction are proposed. In adulthood, crown height is reestablished to avoid supraeruption of the antagonist teeth and inclination of the adjacent teeth.

In conclusion, the timely cooperation of dentists and orthodontists allows the occlusal assessment, as well as the detection of other orthodontic problems, such as the absence of third molars and possibly pre-existing disparities in lower midline. Bearing in mind the final result in regard to the occlusion and profile, the thorough assessment that we have described should point to the most appropriate solution for the individual patient case.

Bibliography:


Ετήσια έκδοση Εταιρείας Ορθοδοντικής & Γναθοπροσωπικής Μελέτης & Έρευνας

Ελληνικό Περιοδικό Ορθοδοντικής

«Οδοντικές Αγενεσίες»

- Ακτινογραφικές απεικονίσεις για τοποθέτηση εμφυτευμάτων
- Επιδημιολογικά στοιχεία των οδοντικών αγενεσιών στην Ελλάδα
- Γενετικό υπόβαθρο της οδοντικής αγενεσίας
- Αντιμετώπιση αγενεσίας πλαγίων τομέων άνω γνάθου: Ορθοδοντική σύγκλειση διαστημάτων
- Αντιμετώπιση αγενεσίας πλαγίων τομέων άνω γνάθου: Επανορθωτικές και προσθετικές επιλογές
- Προσθετική παρέμβαση με εμφυτεύματα
- Ετεροπλευρή συγγενής έλλειψη δευτέρων προγομφίων της κάτω γνάθου: Θεραπευτικές επιλογές

ISSN: 2241-388X

Greek Journal of Orthodontics
Greek Association for Orthodontic Study & Research

www.eogme.gr