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Tooth Agenesis

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Research Paper: Tooth Agenesis

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Abstract

In this literature review, I will discuss tooth agenesis, which is a congenital absence of one tooth or more, and the terminology associated. I will then discuss and compare the studies regarding the etiology and the prevalences of tooth agenesis throughout the world population. The second half of the paper will cover tooth agenesis from a clinical standpoint. I will describe the capital different complications and phenotypes that tooth agenesis creates. In the last section, I will explain how tooth agenesis is medically treated, and the multidisciplinary management needed to improve the patient's quality of life.

Introduction

Dental agenesis is defined as the absence or formation of one or more teeth. The non-existence of the germ makes this absence categorical and definitive: the affected teeth will never appear in affected patients. It is the most common developmental anomaly of permanent dentition. It can appear as part of a syndrome, or non-syndromic, which is the most common form. It is usually isolated, although other anomalies may sometimes be associated (anomalies of position, structure, shape, or eruption) (Letra, 2021). The permanent dentition is much more affected than the primary dentition, where agenesis is rarely reported. It can be unilateral or bilateral. The number and type of teeth affected vary, although the premolar-incisal group predominates, apart from the wisdom teeth (Al-Ani, 2017). Wisdom teeth are often excluded from general studies because they are more difficult to diagnose and more prevalent than other

teeth. These particularities make the results incomparable and categorize these teeth differently: separate studies are therefore often dedicated to them (Carter, 2015).

Very large differences in the prevalence of agenesis can be reported according to the studies (from 2.6% to 40%) (Albu, 2021& Ercal, 2020). The reference meta-analyses show significant variability in the prevalence of agenesis between populations, which itself differs significantly between men and women (Khalaf, 2014). Indeed, in the majority of studies reviewed, women were more frequently affected than men. In terms of geographical distribution, the average prevalence in Europe is 5.5%, excluding wisdom teeth. The highest prevalence was found in the Chinese population (28.7%), and the lowest in women from Saudi Arabia (2.2%) (Khalaf, 2014).

Today, it remains difficult to determine a precise etiology for this number anomaly. The majority of studies suggest that it is the result of several complex interactions between genetic, epigenetic, and environmental factors during the dental development process. Of all these predisposing factors, many authors agree on the importance of genetic expression, which is predominant in the development of agenesis (Letra, 2021 & Yu, 2019).

Dental agenesis poses specific problems and questions. The aesthetic, functional, and psychological impact of agenesis can be important for the patients affected (Al-Ani, 2017). Their management requires a long series of multidisciplinary treatments (orthodontic, implant, prosthetic, surgical) to achieve aesthetic and functional rehabilitation, which is particularly complex in subjects with oligodontia (Al-Ani, 2017). These solutions remain compromises and

require a certain motivation and availability of the patient for many years, often starting at an early age. Their cost may also create social disparities in access to care. In addition, early diagnosis will prevent a possible reduction in therapeutic possibilities caused by late treatment.

Tooth agenesis leads to several complications with various severities. It impacts the functional, structural, and aesthetic of the mouth. Different treatments are used to fully manage all these problems. In these patients, teeth are in unfavorable positions. Implants are used in most cases to fulfill the interdental gap. The other complications such as overbite, uprighting, and space management must be treated with orthodontic treatment (Boeira Junior, 2012).

Definition and Classification

The formation of a tooth is a complex process involving interaction between epithelial and mesenchymal tissues. A lack of developmental initiation of the dental lamina can result in the absence of a tooth (Letra, 2021). Dental agenesis is defined as the absence of at least more than one tooth. This condition is classified as a developmental number defect. This alteration of the dental formula can be expressed differently at several levels. It can occur in permanent dentition as well as in temporary dentition. During the writing this literature review. When tooth agenesis is mentioned throughout this literature review, it will concern by default the permanent dentition, unless otherwise specified. It can be said to be "unilateral", or "bilateral" when it also affects the contralateral tooth. In quantitative terms, one or more teeth can be affected in the same subject. Agenesis can therefore adopt a specific term according to its severity (except for wisdom teeth). If one tooth is missing it is called a congenitally missing tooth. The absence of 2

to 6 teeth is called hypodontia. The absence of at least 6 teeth is called oligodontia The total absence of teeth is called anodontia (Letra, 2021). This anomaly can be found as a symptom of the systemic syndrome. However, the so-called "non-syndromic" agenesis, found in the general population, is much more widespread (Letra, 2021).

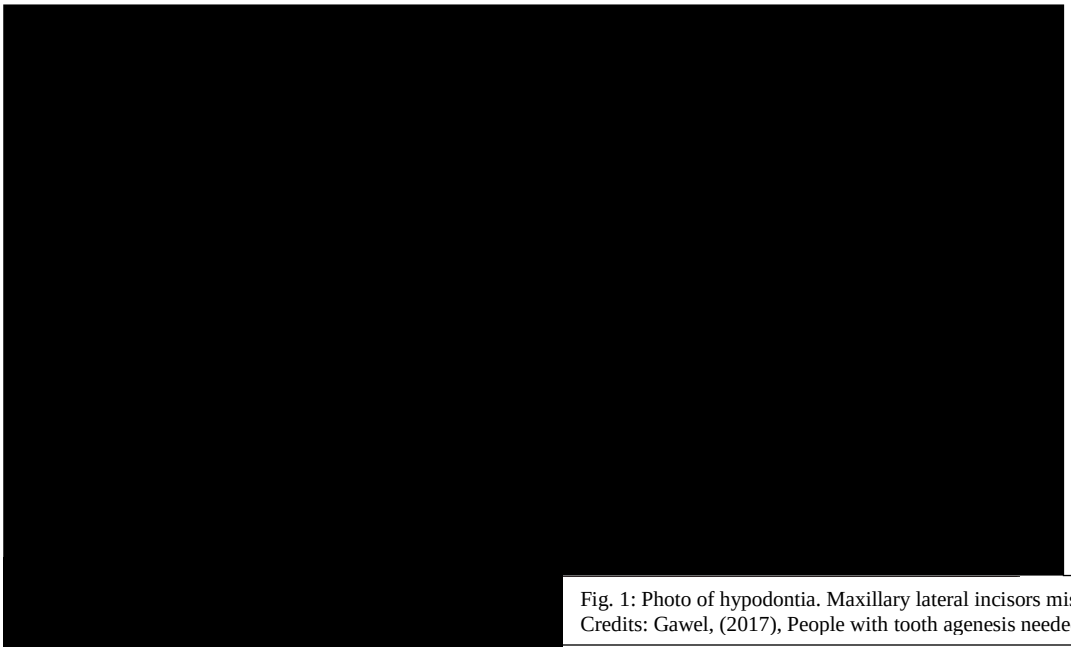

Fig. 1: Photo of hypodontia. Maxillary lateral incisors missing. Credits: Gawel, (2017), People with tooth agenesis needed for study

Prevalence

The systematic review by Al-Ani states that the prevalence of agenesis varies between 1.6% and 6.9%, depending on the population studied (Al-Ani, 2017). Others even state up to 40% of statistical biases, are still very present in this field (Albu, 2021). The majority of the literature contains retrospective epidemiological studies. Many studies couldn’t be used because of certain biases, in particular age-related diagnostic biases. They could be avoided if more prospective studies were envisaged. In comparison, the reported prevalences of the opposite

number anomaly, i.e., supernumerary teeth, are lower: between 0.5% and 3.8% depending on the population studied (Sony, 2018).

In their meta-analysis, Khalaf and his team estimated the prevalence of agenesis in the general population to be 6.4%. Their review of the literature aims to update the data from the leading meta-analyses in the field (Khalaf, 2014). They observe that the prevalence of agenesis has increased globally since the previous studies: in Asia (4.7 - 6.3%), Europe (5.5 - 7%), and North America (3.9 - 5%) (Khalaf, 2014). This increase may be due to the inclusion of more studies in this systematic review, or to the non-exclusion of orthodontic patients, a condition that is generally systematized as a selection bias. However, in this study, no significant difference was found between the schoolchildren, dental patients, or orthodontic patient populations. It is therefore important to continue to conduct standardized studies and meta-analyses on this topic to determine if this pattern is indicative of different biases or if it can be considered a recurring fact (Khalaf, 2014.

A significant difference is observed between continents and countries. In Khalaf's research, they found that Africa had the highest prevalence with 13.4%. Europe, Asia, and Australia had a prevalence of tooth agenesis between 6.3 to 7% (Khalaf, 2014. The lowest prevalence was found in America. North America had a prevalence of 5% while South America had a prevalence of 4.4%(Khalaf, 2014). Shimizu and his team gathered data from different countries. They found that the highest prevalence was in Ireland and Japan. In Japan, the prevalence depending on the study used is between 1.4 and 9.9%. In these studies, women tend

to be more likely to suffer from tooth agenesis. In Ireland, the prevalence is 11.3%. The lowest prevalence is in the USA with a prevalence between 2.8 and 3.6% (Shimizu, 2009).

The data for tooth agenesisi demonstrates a prevalence in females as opposed to males and are consistent with Khalaf's findings. The vast majority of studies show a higher risk of agenesis in female subjects, with the difference consistently found to be significant (Al-Ani, 2017& Letra, 2021). While some studies determine this difference to be too small to be truly significant. In comparison, cases of supernumerary teeth are more frequent in male subjects (Sony, 2018).

The incidence of agenesis in the temporary dentition is considerably lower, with reported prevalences ranging from 0.5% to 2.5% depending on the population. The most frequently missing teeth are the maxillary lateral and mandibular central incisors. In 60% of cases, only one tooth is missing, usually, a lateral incisor and only 8% have more than two teeth missing (Al-Ani 2017 & Rakhshan, 2015). There is no clear correlation between primary tooth agenesis and permanent tooth agenesis. The causes for primary and permanent tooth agenesis appear to be different. Although the genetic pathways responsible for the formation of a temporary tooth and the associated permanent tooth are thought to be fundamentally similar, several studies suggest that they function more like two independent modules (Yu, 2019).

Most epidemiological studies agree that the maxilla and mandible are affected by agenesis to a similar extent. The symmetry of agenesis is determined within the same arch by the simultaneous absence of a tooth and its contralateral. There is little difference between the

prevalence of symmetrical and asymmetrical agenesis. Nevertheless, a small difference is noted according to the type of tooth: maxillary lateral incisors are more often part of bilateral agenesis, whereas the other teeth seem to tend preferentially towards a unilateral pattern (Polder, 2004).

More than 80% of dental agenesis involves one or two teeth and is considered mild. Simple agenesis where only one tooth is missing remains the most common. Severe forms range from oligodontia (more than 6 teeth missing) to anodontia (total absence of teeth). Respectively, the prevalence of these forms is reported to be less than 3% and less than 1%. Cases of severe agenesis are usually associated with a systemic condition (Polder, 2004).

Wisdom tooth agenesis or third molar agenesis has its classification due to the persistent discrepancies in research. The literature in this area is rich but can be highly contradictory. One of the reasons is that it's not as impactful as not having an incisor or a canine from an aesthetic, functional, and structural standpoint. Due to these contradictions, there is no clear prevalence identified.

Etiology

For non-syndromic tooth agenesis, the cause is often genetic. There are 15 genes responsible for non-syndrome tooth agenesis, and 7 of them are responsible for about 92% of the cases. The 7 genes are AXIN2, EDA, LRP6,MSX1,PAX9,WNT10A, and WNT10B. These genes are all involved, to a certain degree, in the Wnt signaling pathway. The Wnt signaling pathway, is "an ancient and evolutionarily conserved pathway that regulates crucial aspects of

cell fate determination, cell migration, cell polarity, neural patterning, and organogenesis during embryonic development" (Komiya, 2008).

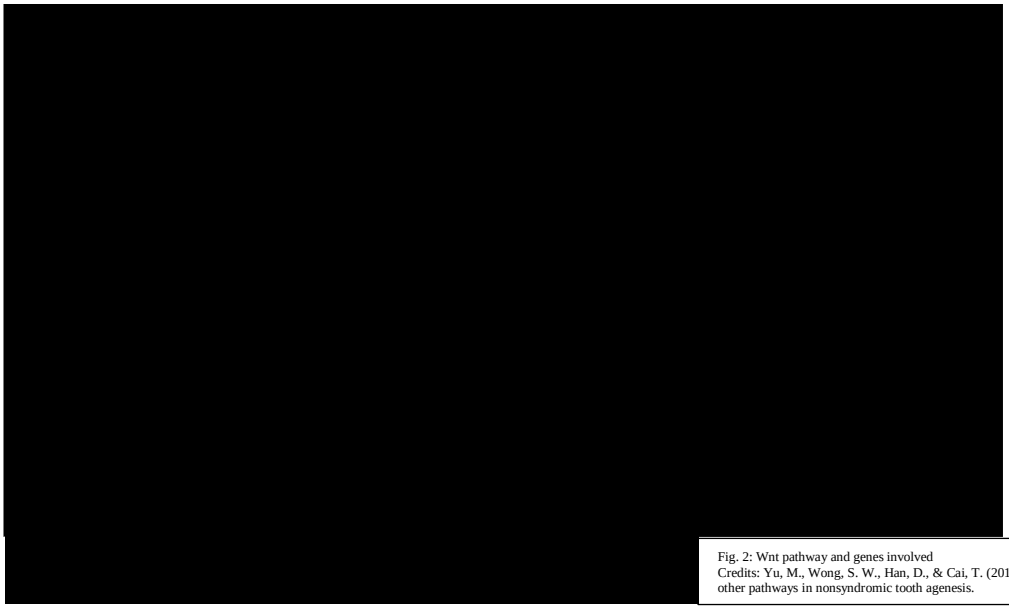

Fig. 2: Wnt pathway and genes involved
Credits: Yu, M., Wong, S. W., Han, D., & Cai, T. (2019). Genetic analysis: Wnt and other pathways in nonsyndromic tooth agenesis.

The Wnt structure goes across the cell membrane. The proteins produced by Wnt10A/10B are part of this structure and stay in the extracellular space. LRP6 produces an integral protein for this structure. This protein is a transmembrane-spanning-receptor. AXIN2 produces a peripheral protein that stays inside the cell. MSX1 and PAX9 are Wnt-associated proteins. The Wnt activation has a pre-required step which is the interaction of beta-catenin with CBP. The mutation of the AXIN2 gene enhances beta-catenin degradation which reduces the Wnt activity. The mutation of Wnt10A/10B is encoding for Wnt ligands. Since the ligands are faulty, the structure of the Wnt is not confirmed. The Wnt activity is drastically reduced and may be inhibited in some cases. LRP6 encodes for a key part of the co-receptor complex (CBP) of the Wnt pathway. The cells fail to activate the Beta-catenin (Yu, 2019). In tooth agenesis, the Wnt pathway can be defective for different reasons as we discussed above. As a result, the epithelium and the mesenchyme do not specialize so there are no teeth created. The lack of specialized tissue stops tooth development (Yu, 2019).

Dr. Tamura and Dr. Nemoto provided a review regarding the specific role of the Wnt in the tooth. Wnt signaling plays a central role in different processes during embryonic development and adult homeostasis. During tooth development, Wnt signaling pathway components are expressed. They are involved in the specialization of tissues such as dental epithelium and mesenchyme (Tamura, 2016). Mutations in these components are involved in tooth agenesis. In some cases, a single mutation can result in a deficient Wnt signaling pathway. This pathway is studied for other diseases such as cancer and can play a crucial role in treating a broad range of diseases. This research encourages more research on the Wnt signaling pathway (Tamura, 2016). Regarding the well-understood genetics behind tooth agenesis, it would be interesting to test genetic editing treatments such as gene therapy. I will discuss more about these techniques in the treatment part of this literature review.

Several studies have been conducted on the issue of agenesis in families and twins to determine if there is an inherited genetic influence (Jeong, 2015). There is disagreement about the number of genes involved and the type of inheritance. Some studies propose the idea that agenesis is caused by a single faulty gene and follows an autosomal dominant inheritance pattern. However, it has been clinically shown that this trait has a variable expression (Polder, 2004 & Shimizu, 2009). This suggests a polygenic mode of inheritance, with an interaction of several genes and environmental factors that interfere with the phenotypic expression of the genes involved in dental agenesis.

Brook's study on the inheritance of numerical dental anomalies concludes that agenesis occurs significantly more often in closely related parents of a subject with dental agenesis. The following observations could be drawn from this study (Brook, 1984). The prevalence of agenesis in closely related people is significantly higher than in the general population. However, the risk varies from family to family: some study groups showed a significant difference in outcomes. The frequency of affected family members increases with the degree of severity of the agenesis in the initial subject: the more severe the agenesis, the higher the risk of finding this condition in family members (Brook, 1984). This risk is also increased when more than one family member is affected (Brook, 1984).

Shimizu explains in his research that non-syndromes tooth agenesis could follow a variety of different inheritance patterns (Shimizu, 2009). The most commonly observed would be autosomal dominant, autosomal recessive, and, X-linked traits. These patterns have been tested by gene targeting in mice and proved their impacts on tooth agenesis. In these experiments, they were editing the gene orthologue of the mice. Some of these genes were tested using gene knockout techniques such as PAX9. In this case, the mice had their tooth development stopped at an early stage (Shimizu, 2009).

Diagnosis

The diagnosis of tooth agenesis is relatively straightforward. Most patients are already aware of their missing teeth but tooth agenesis can be rapidly identified during a dental examination too. The sign of tooth agenesis is the presence of unusual spacing between teeth.

The dentist can count and identify the missing teeth to prepare a treatment. After this step, the dentist will utilize a radiographic examination to verify his observations and what is underneath the gum tissues. If a tooth is missing and there is no tooth about to erupt at this location, the patient suffers from tooth agenesis (Letra, 2021).

Tooth Agenesis Impacts

The absence of one or many teeth will always lead to complications to a certain extent. In this second part, I will introduce the major problems caused by tooth agenesis from a functional, structural, and aesthetic standpoint.

Functional Impacts

In the case of multiple ageneses, the dentist may be in the front line of early detection of systemic pathology. He must know how to orient his patient for optimal medical management. Multiple ageneses cause functional disorders affecting mastication, phonation, swallowing, and breathing (Veneziano, 2019).

Mastication is the first stage of the nutritional function. It is the function that appears most affected in the presence of multiple ageneses (Veneziano, 2019). Each missing tooth leads to a decrease in the masticatory coefficient according to its value. Since mastication plays an important role in digestion, its dysfunction leads to gastric tract disorders, as the stomach has to do more work. A decrease in the masticatory coefficient can lead to a dietary imbalance, as solid

food is difficult to swallow for the child (Veneziano, 2019). This imbalance can lead to long-term growth problems.

The pronunciation of certain phonemes is dependent on the presence of teeth and their physiological positioning, to give the tongue the necessary support during language acquisition (Veneziano, 2019). In children, the learning of certain phonemes requires contact between the tongue and the incisors. Agenesis of the incisors can therefore lead to a lisp. Other phonemes require contact between the lower lip and the upper incisors, such as the letter “f” and “v” (Veneziano, 2019). The agenesis of these incisors complicates this learning process and the patients may still have the lisp after treatment. In this case, the dentist may refer the patient to a speech therapist or physiotherapist who will set up rehabilitation exercises to help restore and maintain physiological functions.

Up to 3 years of age the primary infantile swallowing presents a physiological lingual interposition. When all the temporary teeth are in place, the interposition should disappear allowing occlusal contact. The persistence of dysfunctional swallowing appears to be associated with multiple ageneses (Veneziano, 2019).

Structural Impacts

Patients with multiple ageneses often show specificities in their growth. The absence of effective functions that we discussed in the previous part, such as mastication, swallowing, and phonation, does not allow an optimal stimulation of the bony structures of the middle face. In

these patients, there is a reduction in the transverse dimension, and a reduction in the inter-canine and inter-molar distances in both arches (Heriksson, 2019).

Bu's study shows that tooth agenesis can have a structural impact on the other structures' growth. The mean lengths of the maxilla and mandible were reduced by 4.40 and 2.80 mm respectively, compared to normal bones (Bu, 2014). The inter-canine distance were also reduced by 2.82 mm in the maxilla and 2.70 mm in the mandible. The inter-molar distance of the maxillary and mandibular arches were reduced by 3.40 and 1.80 mm respectively (Bu, 2014). Overall, the maxilla and mandible bones cannot develop properly if teeth are missing and if there is a loss of function.

The main consequence of multiple ageneses in the vertical direction is the decrease in facial height of the lower level due to the reduced amount of alveolar bones which normally contain the tooth socket. In addition, mandibular anterior rotation growth increases incisal overbite (Heriksson, 2019). This results in increasing functional and aesthetic disorders that will need structural and plastic surgeries.

Aesthetic Impacts:

Tooth agenesis is easily diagnosed because it’s visible. It greatly impacts the aesthetics of the dentition and the patients’ smiles which leads to other complications. The aesthetic and psychological parameters are fundamental, increasingly topical in our societies, and strongly linked to each other. The variations of the skeletal bases of these patients with multiple ageneses

have direct repercussions on facial aesthetics. The facial aesthetic affects patients' self-esteem, behavior, communication, and quality of life. The dentist will be charged to also fix this aesthetic problem which will improve the psychological quality of the patient. Other health professions will be suggested to the patient for him to improve his self-esteem and speech rehabilitation could be also recommended.

Aggravating Factors

Some factors have been identified in making tooth agenesis worse or/and more likely. They can act separately or together in influencing the development of the tooth.

The mechanical factors are mainly the result of facial trauma, which can be of various types. The major facial traumas are bone fracture, surgical procedures, extraction of the temporary tooth, or even a sudden change in muscle pressure (De Coster, 2009). These facial traumas are affecting the bite and the aesthetic of the mouth. They lead to worsening of the problems that were discussed earlier.

Certain chemical substances have been identified as risk factors. The use of chemotherapy is also considered an important factor in the development of agenesis (Shugaa-Addin, 2016). Radiation exposure also plays a role in this defect, especially during irradiation by radiotherapy directed at the affected dental site (Shugaa-Addin, 2016). Radiotherapy leads also to other structural problems such as bones weakening. The bones are less likely to support dental

implants (Shugaa-Addin, 2016). These treatments are still necessary to treat cancers and are prioritized over many risk factors.

Dental agenesis may be associated with hormonal disorders, allergies, exposure to certain dioxins, and endocrine disruptors. Deficit disorders, such as low birth weight, malnutrition, and nutrient deficiency, should also be considered (Polder, 2004 & Khalaf, 2014). Malnutrition and nutrient deficiencies were highlighted as risk factors in Khalaf's study because the regions without great food availability were more likely to suffer from tooth agenesis. Regions with better food availability were less likely to have tooth agenesis.

Tooth agenesis can be symptomatic in rare genetic syndromes and diseases. In syndromes, the ectodermal tissues, in general, are damaged and tooth agenesis is one of the primary features (Shimizu, 2009). It is found in 49 known syndromes. It is particularly expressed in patients with ectodermal dysplasia, Down syndrome or trisomy 21 (63%), and Crouzon syndrome, cleft palate. It also appears in more specific cases such as Van Der Woude, Pierre-Robin, Ellis van Creveld, or Prader Willi syndromes (Shimizu, 2009).

Treatment

Different treatments are available depending on the functional and aesthetic severity of the tooth agenesis. Treatment of tooth agenesis is different depending on the patient's age. If the patient still has his deciduous dentition or even a mixed dentition, in most cases no treatment will be done, since the patients are young and are still growing. The bones are not fully developed so

there is no reason to do a dental implant. Also, there is a possibility that these patients will still have all of their permanent teeth. The diagnosis and the radiography are very important to prepare the best treatment plan for these patients. In the case of tooth agenesis, which will also impact their permanent teeth, the dentist could decide on using a softer technique first such as orthodontic treatments. In some cases, fixed space maintainers or special fixed appliances can be placed to maintain the gap between teeth and facilitate the permanent tooth eruption. These treatments are orthodontic and are uncomfortable. The patients will need to keep these appliances until permanent tooth eruption.

The treatment for tooth agenesis requires multidisciplinary treatment. The most common will be tooth implants (Boeira Junior, 2012). Implants are made of titanium, a very resistant metal. Titanium is also used because, after healing, the dental implant will fuse with the bone. During the surgery, the dental implants will be placed into the mandible or the maxilla depending on the location of the missing tooth/teeth. The implants are used as a root. The second part of the surgery is to screw the crown into the artificial root. Dental implants are a great solution with long-lasting effects except for patients who had radiotherapy (Shugaa-Addin, 2016). Patients treated by radiotherapy have their bones affected. The bones are growing slower and healing slower. This is causing the implants to be less likely to last long.

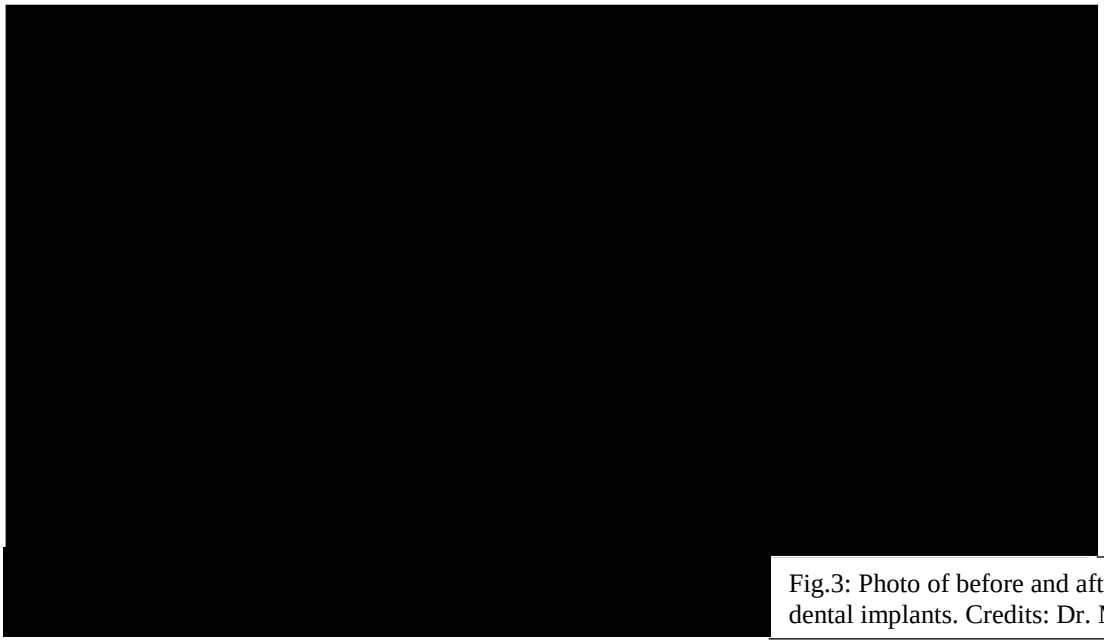

Fig.3: Photo of before and after dental implants. Credits: Dr. Martin

In cases with few adjacent teeth missing, a dental bridge is used (Boeira Junior, 2012). The same dental implant surgery can be used to create artificial roots. Two implants will be placed into the bone with most distance in between. These implants will be used to create a bridge instead of a single crown. The bridge is constituted of the missing teeth crowns attached. This can be a better alternative to a single dental implant in the case of multiple adjacent missing teeth. There is an alternative where the bridge can also be supported by prepared natural teeth. In this case, the teeth are prepared in the same way as for a crown. This alternative is interesting for older patients, patients with fragile jawbones, and patients that had radiotherapy.

Lastly, we have orthodontic treatments. I already introduced the treatments for primary teeth, but there are still orthodontic treatments for permanent teeth. Braces can be placed to reposition the teeth in the arch. This treatment can fix most bite problems and aesthetic problems by straightening and moving the teeth back on the arches. There are also alternatives to braces such as aligners. The aligners are less noticeable, more convenient, and can fix many orthodontic

problems. Other orthodontic and surgical treatment should be taken into account regarding underdeveloped maxilla or mandible bones.

Molecular genetic and Bioengineering

New medical technology is being developed and could play a key role in the clinical management of tooth agenesis. Molecular genetics and bioengineering provide already crucial tools in dentistry and especially tooth agenesis. For example, the BMP2 synthetic protein BMP2 was produced in the laboratory and helps the growth of alveolar bone (Boeira Junior, 2012). By creating and strengthening the alveolar bone the dental implant is more likely to be successful (Boeira Junior, 2012). In some cases of tooth agenesis, mutations in some genes lead to the abnormal alveolar bone. The alveolar bone is not properly developed, which makes the dental implant surgery more difficult because the implant is acting as an artificial root and must be placed into a healthy alveolar bone.

In molecular genetics, researchers found better insights into how the DNA codes for craniofacial development. Boeira Junior suggests that " a biological replica of a missing tooth is the natural evolution of a therapeutic approach that is entirely compatible with the human organism" (Boeira Junior, 2012). By saying this, Boeira Junior wants research to focus on regenerative dentistry. Regeneration of tissues is already possible. In the case of tooth agenesis, the health providers will need a certain amount of stem cells that could differentiate into dental pulp, dental follicle, and other dental tissues, and a bioengineered tooth could be produced (Boeira Junior, 2014). There are still many obstacles before producing a bioengineered tooth

such as the exact number of stem cells, and how morphology and tooth size is managed (Boeira Junior, 2014).

Regarding all the findings in developmental genetics and all the documentation on mutations causing tooth agenesis, it would be interesting to try gene editing technology on animals first. Gene therapy has already been used on animals and is a promising avenue to treat a wide range of diseases, such as cancer, and diabetes. It could be used to fix tooth agenesis, although there is no information in the literature that this technology has been used in animal models.

Conclusion

Dental agenesis is caused by complex interactions between genetic, epigenetic, and environmental factors during dental development. A wide variety of genes are involved in odontogenesis, and the mutation of a single gene may negatively affect the development of the alveolar-dental complex and even induce its failure, resulting in agenesis. Although in recent years, many genes involved in dental agenesis have been discovered, not all of them are yet known. The management of these patients must be early. Dental agenesis leads to functional and aesthetic disorders with psychological consequences and an impact on the general well-being and quality of life of these patients. Due to the great phenotypic heterogeneity of oligodontia, it is not possible to establish systematized therapeutic rules. However, therapeutic decisions require multidisciplinary collaboration involving pediatric dentistry, genetics, psychology, conservative dentistry, orthodontics, prosthetics, implantology, and surgery. Reference and competence

centers for the ontological manifestations of rare diseases have been set up to assist in this multidisciplinary management. The management of these patients is evolving to ensure better treatments. Other treatments will probably be considered in the future such as the conservation of dental stem cells for autologous use or even gene therapy.

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