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Research Paper

The Interdisciplinary Management of Tooth Agenesis; Clinical Update

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ABSTRACT
The term hypodontia is used when one to six teeth, excluding third molars, are missing, and oligodontia when more than six teeth are absent (excluding the third molars). The long-term management of hypodontia in the aesthetic zone is a particularly challenging situation. Although there are essentially two distinct approaches to manage this problem, that is space closure or opening for prosthetic replacements, implant or autotransplantation. Management of tooth agenesis can be realized by either closing or opening the spaces of congenitally missing teeth and by correction of dentoskeletal problems with orthodontic mechanics. Restorative dentistry procedures accompany orthodontic treatment when filling the spaces of missing teeth or when reshaping the teeth substituting missing teeth. As a conclusion, treatment of problems related with mild or severe tooth agenesis requires multidisciplinary treatment approaches. ***The purpose of this review article is to examine the etiology, clinical properties and treatment alternatives of tooth agenesis.***

Keywords: ***Aetiology of hypodontia ,Dental agenesis .Hypodontia ,Management of hypodontia ,Tooth agenesis***

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I. INTRODUCTION

Tooth agenesis, dental agenesis and congenitally missing tooth or hypodontia are terms used commonly when describing failure of tooth development. More specific terms hypodontia (one to five teeth absent, excluding third molars), oligodontia (six or more teeth absent, excluding third molars) and anodontia (complete absence of teeth) are in common use according to the severity of phenomenon.[1,2,3] Fig. 1

The prevalence of tooth agenesis in the primary dentition is relatively rare and no significant difference exists in prevalence by gender. The prevalence varies from 0.4 to 0.9% in the European population [1] but is reported to be higher, 2.4%, in Japan .[4] Typically one or two primary teeth are missing and the incisor region seems to be affected most often. In Europe the upper lateral incisors whereas in Asian population the lower incisors are the teeth most frequently missing in the primary dentition. Tooth agenesis of the primary tooth is a sign of the absence of the successor tooth.[1,3]

One or a few permanent teeth are missing in 3–10% of the humans (excluding third molars), and in more than 20% of the subjects, at least one third molar (wisdom teeth) fail to develop. The absence of one or two permanent teeth is most frequent, observed in 83% of the subjects with hypodontia. Most commonly, one or a few permanent upper lateral incisors and second premolars are missing; therefore, this mild phenotype is alternatively called incisor-premolar hypodontia. The prevalence of more severe tooth agenesis phenotypes becomes gradually more rare so that the prevalence of oligodontia (six or more permanent teeth missing) is approximately 0.1% [3]. Non-syndromic anodontia is extremely rare. If anodontia is diagnosed, it points to a syndromic form of tooth agenesis such as an ectodermal dysplasia syndrome [3].

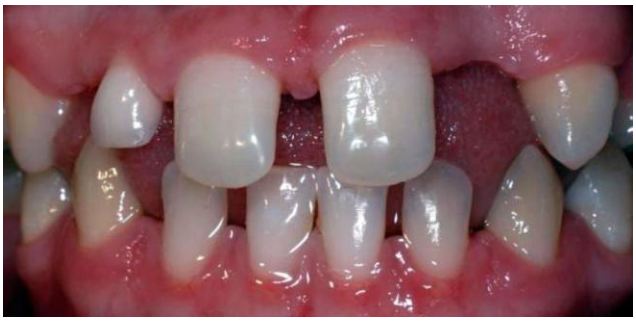

Fig.1; **Dental agenesis**

The frequency of tooth agenesis is similar in the maxilla and mandible as well as in the left and right sides of the jaws. For most teeth bilateral agenesis is noticed in about half of the cases. It is most likely that the last developing tooth within its dental group is congenitally missing: third molars, second premolars and lateral incisors.[5]

There are many different classifications for congenital tooth absence in the literature. Some researchers classify according to hereditary form, some according to the number of missing teeth and some classify depending on the severity. Usually the third permanent molars are not taken into account when assessing the presence and severity of tooth agenesis. Accordingly, the developmental absence of one or more teeth excluding the third molar teeth is defined as "hypodontia"[1]. Some other researchers suggested that the absence of one to six teeth should be called "hypodontia", and the absence of more than six teeth should be called "oligodontia"[6,7,8]. In order to reflect the genetic or morphological differences in terminology it was suggested to use subsections like isolated hypodontia or isolated oligodontia for non-syndromic cases and syndromic hypodontia or syndromic oligodontia for cases related to syndromes[7,8]. Some researchers graded the severity of congenital tooth absence to help diagnostic classification. Accordingly, the absence of 1-2 teeth is mild, that of 3-5 teeth is moderate and 6 or more teeth is noted as severe hypodontia.[1] Fig.2

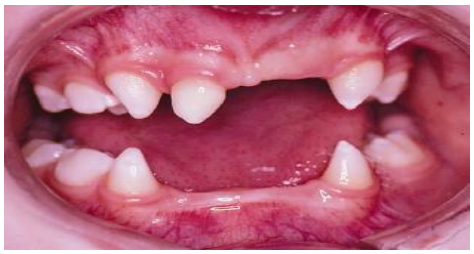

Fig.2; Dental agenesis

A part from the third molars, the most commonly missing teeth in permanent dentition of Caucasian populations are clearly mandibular second premolars (more than 40% of the missing teeth) followed equally by maxillary lateral incisors and maxillary second premolars and then the mandibular incisors [1,3].

The purpose of this review article is to examine the etiology, clinical properties and treatment alternatives of tooth agenesis

Aetiology of Tooth Agenesis

The long time span and complexity of human dental development means that abnormalities may arise from multiple genetic and environmental factors which may affect the teeth at different stages of development. The important role of genetics as a cause of tooth agenesis stems from the facts that tooth agenesis is usually observed without any obvious environmental cause and it is more common in monozygotic than in dizygotic twins and among relatives than in the general population. Many gene mutations have been discovered to cause isolated and syndromic tooth agenesis. However, both twin and family studies indicate that the relationship of the genotype and phenotype is not straightforward but shows variation presumably caused by genetic background, that is to say additional genetic factors, as well as epigenetic and external factors. Thus, family members affected by the same mutation typically show variation in the phenotype, and even monozygotic twins often do not have identical phenotypes [1,5].

- Environmental Causes of Tooth Agenesis

The most dramatic known external effect on tooth development is caused by treatment of cancer during early childhood. The effects include tooth agenesis, extreme microdontia and hypoplasia of tooth roots.

The effect is especially strong after radiological treatments but also chemotherapy can cause microdontia and agenesis [1,6]. Tooth germs may sometimes be destroyed by external trauma. It has been suggested that agenesis of mandibular third molars may be related to application of local anaesthetics during childhood dental care [1,5,7]. Tooth agenesis has been described in children whose mothers' have suffered rubella infection during pregnancy [8]. Both experimental animal and population studies have shown that certain pollutants, especially dioxins, are harmful for normal tooth development. As shown by animal studies, dioxins affect both tooth morphogenesis and cell differentiation, and predisposition to dioxins after an industrial accident in Seveso, Italy, was associated with increased prevalence of tooth agenesis [9]. Confirmed environmental causes of tooth agenesis are rare and do not have a significant contribution to tooth agenesis at a population level.

However, factors that affect the size of tooth germs may also play a role in determining the outcome of genetic predisposition.[1,5]

- Genetic Causes of Tooth Agenesis

During the embryonic development, morphogenesis and differentiation of teeth is the result of complex interactions at molecular level between the ectoderm and the mesenchyma [9]. Until now more than 200 genes in-volved in these processes have been identified [1,5,8,9]. A crucial role was attributed to those transcription factors that have a homeodomain. The homeodomain consists of 60 amino acids with a helix-turn-helix DNA binding motif and is encoded b y a homeobox sequence: short chains of 180 bp, located in the vicinity of the gene's 3'end. In addition to the homeodomain that facilitates the binding to DNA, the transcription factors also contain a transactivation domain that interacts with a RNA polymerase. The homeodomain transcription factors in turn are involved in the regulation of homeobox gene expression sites, thus having a role in the activation of gene expression in multicellular organisms during embryonic development [1,5,9].

The first genes containing homeobox sites were identified in the Hox cluster (cluster-related group of genes located on the same chromosome, each coding for a particular protein which are often regulated by the same cellular mechanisms). This cluster is highly conserved during evolution; sequences have remained relatively unchanged (75-90%) for hundreds of millions of years [1,5,9,10]. In embryogenesis, Hox genes cluster controls the development plan of the embryo during development. During tooth morphogenesis, expression of the homeobox genes is under the control of signaling cascades initiated by the interaction of certain proteins (either growth factors or other proteins secreted or available on the surface of neighboring cells) with receptors on the surface of target cells.[5,10] Important factors in tooth morphogenesis are: the family of fibroblast growth factors (FGF) and transforming growth factors (TGF, including BMP4 - bone morphogenetic protein 4), the family of Wnt (Wingless) and morphogenesis molecule Shh (Sonic hedgehog). The general scheme of dentition is determined even before the development of visible teeth. The proximal area of the molars to be developed is characterized by the expression of growth factors FGF8 and FGF9, while BMP4 is expressed in the distal region of the presumed incisors [11]. Transcription factors define spatially the domains of expression of the homeobox genes in the developing jaw. Basically every combination of homeobox genes expressed is a "code" that specifies the type of the tooth [5,9,10,11]. Tooth formation is a complex process, genetically controlled in two ways: on one side, by specifying the type, size and position of each tooth organ; on the other, by the processes of enamel and dentin formation. [1]Different genes involved in the formation of teeth belong to signaling pathways with functions in regulating morphogenesis of other organs. This explains the fact that mutations in these genes have pleiotropic effects in addition to causing non-syndromic dental abnormalities and dental anomalies associated with different genetic syndromes [12]

MSX1 is a homeobox gene located on chromosome 4 and encodes a DNA-binding protein.17 The main function of MSX1 protein is tointeract with TATA box-binding protein (TBP)18 and some transcription factors to increase the rate of the transcription process. [1] This protein regulates gene expression, which is essential for initiating tooth development. MSX1 protein is considered to be critical during early tooth development; it was found to hold sequence specific DNA-binding activity and supposed to regulate other genes involved in tooth development pathways.[1,17]

The Msx1 and Msx2 genes have arisen by two successive gene duplication events acquiring their expression properties. During mid gestation, Msx1 and Msx2 expressions occur at almost all sites of epithelialmesenchymal tissue interactions .[1] At E11.5, Msx1 is coexpressed with Msx2 in the dental mesenchyme .[1] However, the Msx1 is expressed quite broadly in the mesenchyme and the Msx2 expression is restricted to the mesenchyme around the tooth-forming regions. Msx1 is also strongly expressed in the developing molar and incisor tooth germs in a distal-to-proximal gradient in mesenchymeof the mandibular and maxillary processes.[1]

The Msx2 gene is expressed at early cap stage in the enamel knot, in the internal enamel epithelium and the dental papilla mesenchyme. With odontoblast differentiation, Msx2 becomes strongly expressed in the odontoblastic cells8. Mice deficient for Msx1 exhibit an arrest in molar tooth development at E13.5 bud stage,

while mice deficient for Msx2 exhibit defects in cuspal morphogenesis, root formation and enamel organ differentiation .[1,17,18,19,20]

PAX9 is a member of a gene family encoding transcription factors that play a key role during embryogenesis. Proteins encoded by PAX genes share a unique 128-amino acid long DNA-binding paired domain [8,9] . PAX9 gene products function primarily by binding the enhancer DNA sequences and by modifying transcriptional activity of downstream genes [9]. To date, 11 distinct disease-causing mutations in the PAX9 gene (59 patients in 15 families) have been identified in humans, most of which are located in the paired box domain of PAX9. In contrast to MSX1, both missense and frame-shift mutations in PAX9 have been associated with hypodontia.

Of the seven identified missense mutations, one is a premature termination mutation , and the remaining six are all residue substitution mutations. Of these substitution mutations, only five generate a substitution in the protein , with one believed to prevent PAX9 expression. Three frame-shift mutations have been identified, two of which are caused by the insertion of a single nucleotide and the other by the deletion of eight nucleotides with the insertion of 288 foreign nucleotides [21]. Some of the unique reported mutations, like frame-shift, insertion, missense, nonsense and deletions of entire PAX9 gene.[22] These mutations were identified in the DNA-binding paired domain of PAX9 gene, resulting in a disturbed regulatory process occurring for tooth formation.[15] Missense mutations in PAX9 gene at amino acid position Gly6Arg and Ser43Lys were detected in two Chinese patients with non-syndromic tooth agenesis. [23] Patients and their family members affected with oligodontia and other dental anomalies were carrying transition and nonsense mutation at C175T, resulting in an altered arginine 59 Stop codon, thus leading to premature chain termination (haploinsufficiency) in PAX9 gene. [23]

A patient with oligodontia showed missense mutation with the substitution of an arginine by a tryptophan in the paired domain of PAX9 gene and showed dramatically reduced DNA-binding activity[24].

Subsequently, other PAX9 mutations that led to non-syndromic oligodontia were found:

- transitions (C76T) and (C139T) that led to the replacement of arginine with tryptophan in N-terminus of the homeodomain [25].
- transversion (A340T) that created a stop codon at lysine 114 in the DNA binding domain [15];
- three different missense mutations leading to substitution of arginine with proline in the homeodomain (Arg26Pro), glutamic acid with lysine (Glu91Lys) and leucine-to-proline (Leu21Pro) affecting M1 [26];
- a cytosine insertion in exon 4 (insC793), frameshift mutation that led to the appearance of a premature STOP codon at amino acid position 315. [27]

Stockton et al. showed that a mutation in the PAX9 gene modified the open reading frame (frameshift mutation) causing premature termination of translation. [28]The affected individuals were normal, but lacked most permanent molars. The disease was transmitted in autosomal dominant fashion.[28] In all these cases, permanent parts of the molars were missing, which emphasizes the importance of this gene in development. The sequencing of PAX9 gene in samples from a Chinese family with many cases of

oligodontia showed a transition (A → G) in the initiator AUG codon, in exon 1. This is the first mutation found in an initiator codon that supposedly caused a severe inhibition of translation. [29] Numerous studies suggest the PAX9 mutant phenotype is dosage dependent: deletion of the PAX9 locus manifests as missing permanent teeth and the entire primary dentition;10 missense mutations result in oligodontia of only the permanent teeth; other mutations that would encode a truncated polypeptide present with missing permanent teeth, as well as some primary teeth.[5,7]These findings, however, fail to fully explain the mechanisms underlying disease-causing mutations that result in less severe and variable phenotypes where not all posterior teeth are affected.[30] AXIN2 gene (17q23-q24) encodes

the Axin2 protein that has an important role in regulating the stability of βcatenin, which is involved in the Wnt signalling pathway (wingless). When cells receive Wnt signals, β-catenin binds to stabilized transcription factors (TCF family), regulating the expression of Wnt target genes. It was found that changes in the functioning of the Wnt signaling pathway leads to cancer predisposition.[15.31] Oligodontia as the results of mutations in the AXIN2 gene was more severe than that described for mutations in MSX1 and PAX9 genes; there were more missing molars, premolars, upper lateral incisors and lower incisors, but upper central incisors were present.[31] EDA1 gene (Xq12-q13.1). Mutations in this gene cause X-linked hypohydrotic ectodermal dysplasia (HED), a rare disease characterized by hypoplasia or absence of sweat glands, dry skin, sparse hair and pronounced oligodontia. In 2010 Khabour et al. [32] identified a nonsense mutation in the EDA gene in a Jordanian family. The mutation resulted in the replacement of arginine with cysteine that has led to intolerance to heat, the absence of 17 teeth, speech problems and anhydrosis (reduced sweating) in affected individuals. In 2006 Tao et al.

[33] found a point mutation in the EDA gene in a Mongolian family in which affected males (females are carriers) did not present other features of the disease than hypodontia. Other cases of non-syndromic

hypodontia were described by Li et al. [34], in 2008 in two families in China with two nonsense mutations in the same gene is accompanied by the lack of central and lateral incisors, and canine teeth of the maxilla and mandible [35]. LTBP3 (latent transforming growth factor beta binding protein 3) is a gene that modulates the bioavailability of TGF-beta and is located on the long arm of chromosome 11. A study on a Pakistani family with a history of consanguineous marriage found that a mutation in the LTBP3 gene causes an autosomal recessive form of familial oligodontia [36].

Anomalies Associated with Tooth Agenesis

-Dental Anomalies

Tooth agenesis is commonly associated with different kinds of dental anomalies in other teeth .These anomalies can occur even in the dentition with mild hypodontia but are more frequent in cases of oligodontia. In addition, tooth agenesis contributes to the development of abnormal occlusion, malfunctions and aesthetic problems especially in subjects with severe oligodontia. The typical dental anomaly associated with tooth agenesis is a peg-shaped upper lateral incisor which is often noticed when the contralateral incisor is missing. It belongs to the spectrum of anomalies that are associated with tooth agenesis: reduction of tooth crown size (mesiodistal and bucco-lingual dimension of the crown), abnormal morphology (peg-shaped tooth, conical tooth, tapered- or shovel-shaped tooth, reduction of the cusp number and form) and shortened roots and taurodontism [36,37]. Fig.3

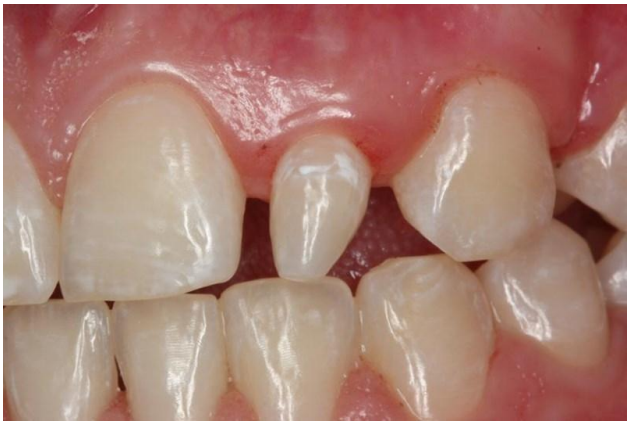

Fig.3; A peg-shaped upper lateral incisor

It has been shown that, as the severity of tooth agenesis increases, the delay of dental age also increases. A mean delay of up to 2 years compared to the chronological age has been reported. From a clinical perspective, it must be taken into consideration that a tendency to developmental delay is possible in teeth contralateral or adjacent to the missing tooth [38]. Ectopic teeth, especially ectopic canines (palatal or labial maxillary canines) but also other teeth such as first premolars and molars, as well as transpositions of teeth (canine-premolar, incisor-canine transpositions), show association with tooth agenesis [39]. An association exists between infraocclusion of primary molars and agenesis of premolars. In about 20% of the subjects with agenesis of second premolars, infraocclusion of primary second molars has been noted . In subjects with tooth agenesis, the prevalence of abnormal tooth positions such as rotations (especially premolars) as well as enamel defects (hypoplasia, hypocalcification) is higher than in the control groups [40,41,42].

-Tooth Agenesis and Cancer

It has been shown that tooth agenesis and cancer development share common molecular pathways. The connection between tooth agenesis and colorectal cancer predisposition as a consequence of AXIN2 mutations was found in a large Finnish family [43]. An increased prevalence of tooth agenesis has been reported among patients with epithelial ovarian cancer [44]. However, more studies on this subject are needed to understand genetic mutations and networks which together contribute both to tooth agenesis and to cancer.[1,45]

Odontogenesis is an intricate process of reciprocal interaction with the involvement of a larger number of genes and the opportunity of mutations in many of these genes can disrupt this process and be associated with hypodontia.[1,22,28] The genes that command teeth development also have important functions and molecular association with other organs and body systems. Therefore, a genetic alteration culminating in hypodontia can lead to abnormalities in other parts of the human body.[21] Some selected articles in this systematic review point to a potential association between dental agenesis and neoplasm.[46,47]

One of the most related genes to dental agenesis is AXIN2. The protein expressed by this gene has an important function in craniofacial morphogenesis.[1]Patients with SNP of the AXIN2 gene do not have permanent molars, premolars, lower incisors, and upper incisors.18 Interestingly, mutations in the AXIN2, MSX1, PAX9, and WNT10A genes may be associated with cancers.[46] This condition refers to a phenomenon called pleiotropy, characterized by a single genetic locus that truly affects multiple apparently unrelated phenotypic traits. It is often identified as a single mutation that affects two or more wild-type traits in human complex diseases that share the same genetic pathways.[1,37,47]

-Tooth Agenesis in Orofacial Clefting and Syndromes Cleft Lip/Palate

Anomalies in the number of teeth (tooth agenesis, supernumerary teeth), in the morphology of teeth (shape and size) and delayed development and eruption of teeth are common in patients with clefts. The prevalence of hypodontia increases with the severity of the cleft and has been reported to be 10– 68% in different cleft types, being 10% in cleft lip, 16% in submucous cleft, 33% in cleft palate and 49% in unilateral and 68% in bilateral cleft lip and palate. The teeth most commonly affected are in the cleft area (upper permanent lateral incisor), but tooth agenesis is more common than in general population also outside the cleft region [39,40,41].

Down Syndrome (Trisomy 21)

Down syndrome, the most common chromosomal abnormality in man, is caused by trisomy of all or a critical portion of chromosome 21. Together with typical dysmorphic craniofacial features, mental retardation and structural anomalies, tooth agenesis and other dental aberrations are very common. The prevalence of tooth agenesis is about 50% in the patients if the third molars are excluded and about 90% if they are considered. The upper lateral incisor is most commonly missing in Down syndrome, and peg-shaped upper lateral incisors are frequent. Other dental anomalies in the permanent dentition of patients with Down syndrome include taurodontism, ectopic eruption, impaction, delayed eruption, transposition of teeth and microdontia [30,43,45,46].

Axenfeld-Rieger (Rieger) Syndrome

Axenfeld-Rieger syndrome (ARS) is an autosomal dominant disorder with malformations of the anterior chamber of the eye, umbilical anomalies and tooth agenesis. The prevalence of ARS is approximately 1 in 200,000. ARS Type 1 is caused by mutation in a homeobox transcription factor gene PITX2; Type 2 maps to chromosome 13q14; and Type 3 is caused by mutation in the FOXC1 gene. The maxillary primary and permanent incisors and second premolars are most commonly missing and conical and misshapen teeth and microdontia have been reported. Maxillary hypoplasia is a typical craniofacial finding, which is caused, in part, by missing teeth in the region [46,47].

Ectodermal Dysplasias

Ectodermal dysplasias (EDs) include a large clinically and genetically heterogeneous group of rare conditions where at least two of the ectodermal derivatives such as hair, nails, glands and teeth are affected. There are about 200 EDs and ED syndromes with 11 subgroups [31]. Hypohidrotic (also named anhidrotic) ectodermal dysplasia (HED, EDA) is the most common ectodermal dysplasia. HED is genetically heterogeneous and caused by mutations in three different genes which all disrupt the same signalling pathway. Mutations in the X-chromosomal EDA gene coding for the tumour necrosis factor-like signal called ectodysplasin cause X-linked EDA, whereas autosomal dominant and recessive HED are caused by mutations in the TNF receptor EDAR and its intracellular regulator EDARADD.[45] Autosomal HED is clinically indistinguishable from X-linked form, but in autosomal HED both males and females can be similarly affected. Recently, mutations in WNT10A have been shown to cause hypohidrotic/ anhidrotic ectodermal dysplasia with distinctive clinical features including marked dental phenotype without facial dysmorphism.[46,47]

Odonto-onycho-dermal dysplasia is a recessive ectodermal dysplasia characterised by severe oligodontia in the permanent dentition with less affected primary dentition, conical teeth, lack of taste buds of the tongue, hypoplastic nails and thin, dry hair. Several different mutations in WNT10A have been identified in patients with OODD or the similar Schöpf-Schulz-Passarge syndrome where cysts of the eyelids are additional manifestations.[40,46,47]

Clinical Problems and Management of Patients with Tooth Agenesis

Tooth agenesis creates special functional and aesthetic problems, and several treatment phases starting in childhood and continuing to adulthood are necessary. An ideal management from diagnosis to treatment planning and treatment requires a multidisciplinary approach, and many specialities of

dentistry are needed. Nearly all patients, 90%, with hypodontia or oligodontia need orthodontic treatment. In some cases, medical and genetic consultation should be considered. A repetitive communication between the members of the team is also essential [33, 34].
Giving sufficient information about tooth agenesis to the patient and the family as well as support during the different phases of the treatment is important. It is recommended that siblings and children of the patient should be examined for tooth agenesis and associated anomalies at appropriate age, firstly in the early mixed dentition and then at approximately 9–10 years of age. [48]

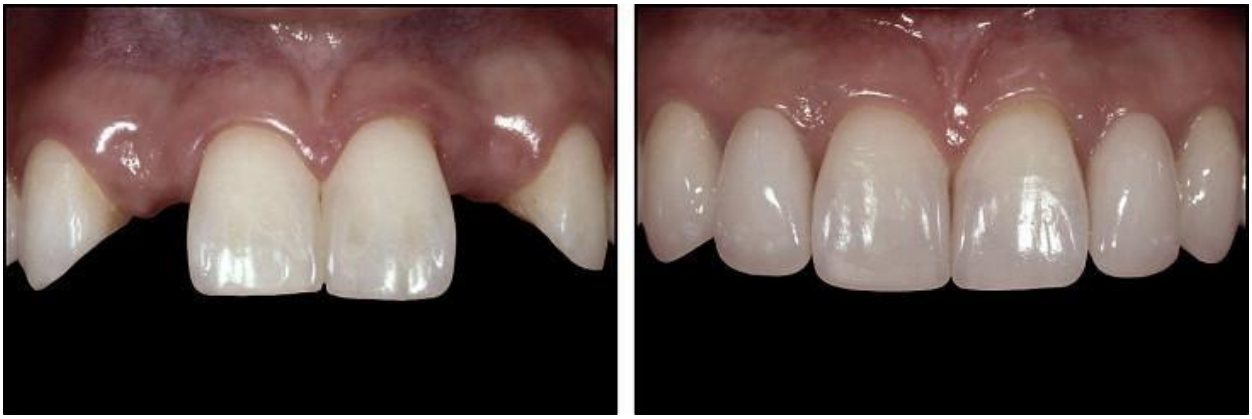

Fig.4: View of preoperative sites after the removal of orthodontic braces. The implants-supported restoration after five years.

During the growth period, it is important to follow and to evaluate the development of occlusion and the growth pattern of the jaws (sagittal, vertical, transversal growth). Patients with tooth agenesis often have typical dentofacial features, and the severity and location of missing teeth have a significant effect on them. Cephalometric analyses have shown bimaxillary retrognathism, reduced vertical facial dimensions, concave profile, decreased mandibular plan angle, incisors which are upright and overerupted in oligodontia patients [35,48].

In tooth agenesis cases, in order to optimise long-term success, forethought should be given into maintaining alveolar bone, for example, around a deciduous tooth where no permanent successor is present. Depending on the malocclusion, maintaining alveolar bone will improve the success of possible dental implants later and may facilitate possible orthodontic tooth movement into the space. The alveolar process grows with teeth and each tooth creates its own bone while erupting into the oral cavity. If there are no teeth developed in the jaws, there are no alveolar processes either. On the other hand, after losing a tooth, alveolar resorption continues for years which results in shortage of bone for later reconstruction.[1,40,45,46]

The diagnosis and treatment of tooth agenesis and the diagnosis and treatment of orthodontic malocclusion should not be planned in isolation but with an understanding of both entities. That said, it can be helpful to assess the patient from a malocclusion perspective first and then add the complexities of the tooth agenesis. In this way the missing teeth can be incorporated into the overall plan for the patient. For example, in a class I severe crowding case with a favourable skeletal pattern, premolar extractions may be planned. If the patient is missing premolar teeth, then this hypodontia can easily be integrated into the plan. Conversely, if the patient presents with a deep bite and closing- type growth pattern, then one would be more inclined to treat on a non-extraction basis, and it may be advisable to maintain the lower deciduous molars for as long as possible if lower premolars are missing.[2]

Primary and Early Mixed Dentition

Both functional and aesthetic problems can arise early in childhood. The preliminary evaluation of the facial growth pattern and type of occlusion is made, and interceptive orthodontics (elimination of crossbites, scissors bites) can be carried out to promote favourable orofacial functions and growth of the jaws.[2] Before a child starts school, it is advisable to evaluate orofacial functions (speaking, mastication, smiling) together with aesthetics (conical, malformed teeth, spacing). This is because children with tooth agenesis can be exposed to bullying at school. [2]Closure of diastema (midline maxillary diastema), composite build-ups of malformed primary and permanent teeth (incisors, canines) and removable dentures are possible in severe oligodontia or anodontia. In children with missing incisors, fixed constructions like banded molars with acrylic incisors fixed to lingual or palatal arches can be considered. However, all these early constructions will require regular follow-

up adjustments during the growth period. If the premolar is missing, an ankylosis and developing of infraocclusion of the predecessor tooth is possible.[2] This can result in tipping of the neighbouring teeth and overeruption of the opposing tooth. Ankylosis can be diagnosed by evaluating the alveolar bone levels between the primary molar and the adjacent teeth. A flat level of the alveolar bone indicates that the primary tooth is erupting evenly with the permanent ones. If the alveolar bone level becomes oblique and the bone level around the primary tooth is more apically, this confirms ankyloses [36]. In a Swedish study, 20% of the primary molars without successors were submerged 1 mm or more relative to the adjacent teeth at the age of 12 years and 55% of them between 0.5 and 4.5 mm at the age of 20 years. Whenever infraocclusion of primary molar is noted, a build-up of the occlusal surface can be made to improve occlusal contacts. However, if the infraocclusion worsens, extraction of the ankylosed tooth can be considered [2,33, 37]. In addition to ankylosis, root resorption of the primary molars must be assessed and monitored. Large individual variation is seen in an amount of root resorption. Lower primary molars without a successor have a good prognosis, and in more than 90% of the patients, these teeth survived up to late adulthood [2,38].Palatally or labially impacted permanent canines are common in patients with tooth agenesis. The maxillary permanent canines should be palpated labially at the age of 9–10 years, and if they are not, further radiological examination must be carried out to confirm their position. The positions of permanent canines have particular significance in cases of tooth agenesis, especially if the upper lateral incisor(s) are missing. The position and eruption pattern of permanent canines will influence the management of space of primary lateral incisors and canines.[48]

Mixed and Permanent Dentition

At approximately 8–10 years of age, making of a preliminary long-term treatment plan including orthodontic and future prosthodontic therapy is recommended.[2] Orthodontic treatment includes both management of general features of malocclusion and special problems linked to tooth agenesis.[2,50,53] During the growth period, orthodontic treatment with functional jaw orthopaedics to improve skeletal discrepancies and using of fixed appliances to arrange dental arches is often indicated.[42,50,51] A proper positioning of the incisors, canines and molars, treatment of deep bite and a decision on maintaining or closing spaces of missing teeth are advised.[54,54] When considering the treatment options, an evaluation of the facial components including hard and soft tissues and dental show in the face is essential. If the number of teeth is low, the arrangement of anchorage during orthodontic treatment can be challenging.[54,55] However, using of temporary skeletal anchorage devices has brought many new possibilities for the orthodontic therapy of tooth agenesis patients [2,33,44,48,55].

There are two options for treating patients with missing maxillary lateral incisors: to close the space or to open the space. In addition, a symmetrical appearance of the incisor region must be included as a treatment aim.[45] If the space is planned to be closed, permanent canines are allowed to erupt next to the central incisors, and extractions of primary laterals and canines can be considered before the permanent canines erupt. Posterior teeth are later protracted mesially to substitute the maxillary first premolars for canines. The second option is to open the space for prosthetic replacement of upper laterals.[2,46]

The desired occlusion at the end of treatment must be considered. If the patient has a Class I relationship in both the molars and canines, normal overbite and overjet, it is ideal for a prosthetic replacement of lateral incisors. [47]The ideal situation for closing the space is Class II occlusal intercuspation, or maxillary posterior teeth have to be brought mesially into a proper Class II relationship. Treatment is often required to make the canines look and function more like lateral incisors, and subsequently that the first premolars, now in the canine position, look and function more like canine teeth. [48]This may involve reshaping the teeth in three planes of space: vertically, mesiodistally and palato-labially. With regard to the first premolar, it may be advisable to grinding the palatal cusp, so that it does not interfere with the occlusion and also rotate the tooth mesio-palatally so that the tooth presents a wider crown and improved aesthetic result. In some cases, reshaping of the teeth may not produce an acceptable aesthetic result and the placement of prosthetic replacements can be considered.[48,49]

If the maxilla and the mandible have different number of teeth, it may be impossible to achieve a normal Class I molar and canine relationship without compensatory procedures such as an extraction of a lower permanent incisor or a reduction of the width of second primary molar. It must be noted that due to generalised microdont teeth, it is not always possible to close all spaces in the dental arches with orthodontics. Instead, composite build-ups or extra prosthetic teeth can be considered.[50,51]

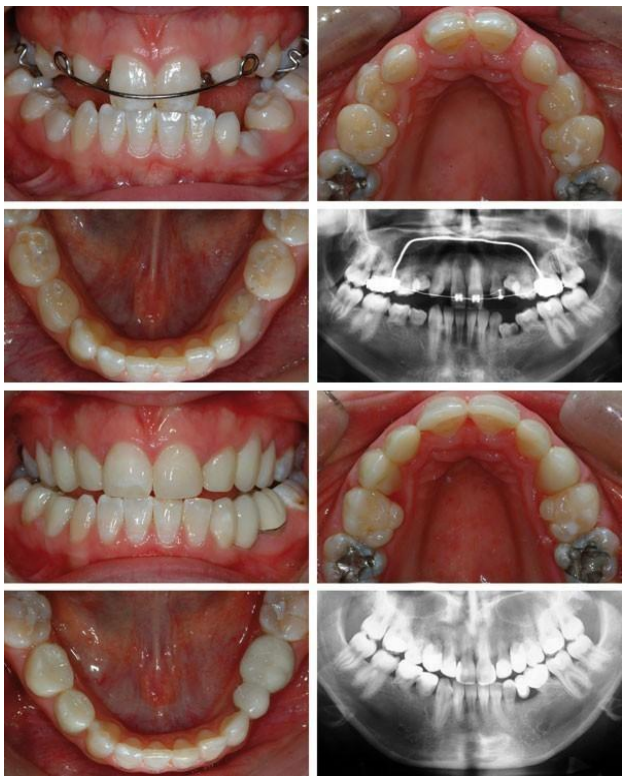

Fig.5; The management of severe hypodontia

Extractions of upper primary second molars without successors at appropriate time are beneficial because permanent molars tend to drift mesially closing the space. Mandibular molars do not drift as favourably and orthodontics may be challenging. Especially in skeletal deep bite, it is not recommended to extract lower primary molars because of an unfavourable worsening of the deep bite. Maintaining of the space, autotransplantation or later implants are the other alternatives.[48,52,53]

Before the orthodontic appliances are removed, it is essential to examine the patient for correct amount of space for tooth replacement and the placement of implants. In addition to dental study models, 3D radiography gives the most exact measurements for spaces. The roots of the teeth must be parallel and adequately separated for proper placement of an implant. For instance, the minimum space between the root and an implant should be approximately 1–1.4 mm, the minimum interradicular space for a maxillary lateral is 6 mm and the vertical space should be 7 mm. [54,55,56]

It should be remembered that the placement of dental implants should be delayed until growth of the jaws is complete. This is because dental implants, and the bone around them, do not 'grow' with the patient. If implants are placed too early, a vertical discrepancy between the prosthetic tooth and the neighbouring teeth can develop [57]. Even if implant treatment is not used in growing patients, children with ectodermal dysplasia syndromes and anodontia in the mandible have been treated with implants. However, treatment of ectodermal dysplasia patient is very demanding and should be centralised [2,48,58,59,60].

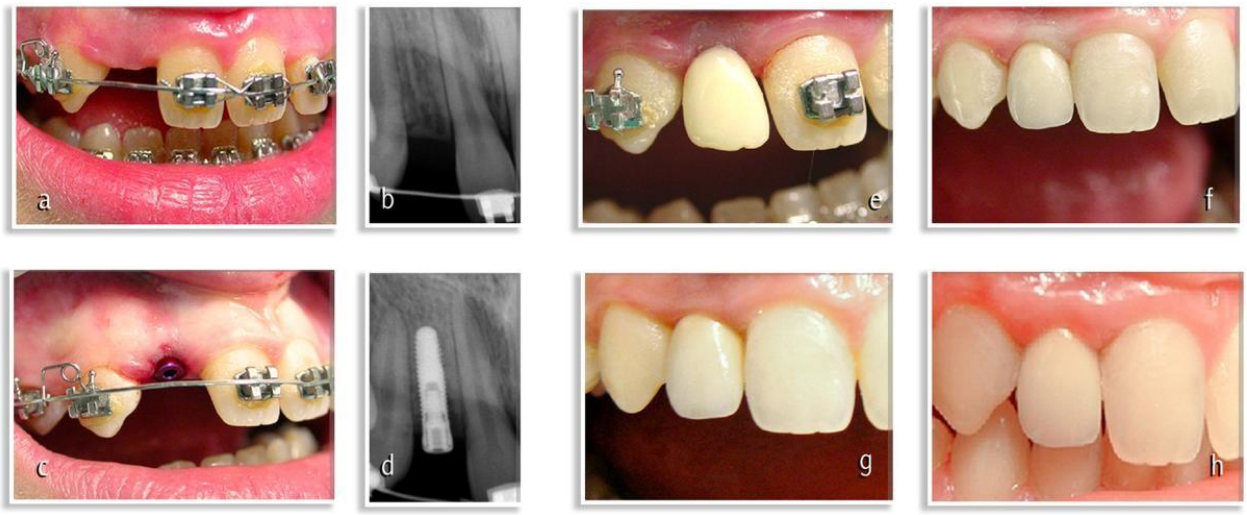

Fig.6; Prosthetic rehabilitation of maxillary lateral incisors agenesis using dental mini-implants

Patients should be provided with retainers which maintain the spaces created for replacing the missing teeth. Removable retainers with acrylic teeth replacing missing teeth can be used to improve dental appearance and oral function as well as act as a retainer. Resin-retained bridges are also possible as a permanent or temporary solution.[48,61,62]

Permanent Dentition

If the skeletal discrepancy is severe and camouflage treatment alone cannot provide the facial harmony, a combination of orthodontics and orthognathic surgery should be considered before prosthetic restoration. In addition, minor surgical procedures are often needed such as alveolar ridge and sinus floor augmentations and inferior dental nerve transpositions to ensure proper circumstances for the implants.[2,48,63] Fig. 4

Estimation of the craniofacial growth is essential in planning an appropriate time for placing implants in order to prevent later submergence of an implant tooth. Following of the general growth is not always sufficient because cessation of craniofacial growth exhibits a great individual variation.

Fig.5However, in most cases craniofacial growth can be considered to have ceased at approximately 18–19 years of age in males and 17–18 years of age in females. It must be kept in mind that patients can show continued craniofacial vertical growth late into adulthood and even into an old age which can create aesthetic and functional disturbances in the implant region. It is widely recommended, however, that implants into an incisor area are not placed earlier than over 20 years of age to ensure better function and aesthetics in the future.[48,61,62,63,64] Fig.6

Autotransplantation

Another treatment method is autotransplan- tation.[65]Referring prosthetic, transplantation is thought to be a better choice than the implant; osseointegrated implants placing to the growing alveolar bone is not correct. Successful autotransplantation of teeth, depending on the physiological stimulation of the periodontal ligament provides stability of alveolar bone volume. It is stated that children should be delayed until completion of adolescence implant treatment.[65,66,67]

Autotransplantation of premolars may be recommended in patients with multiple agenesis of maxillary incisors.[64,65] In growing children transplated teeth can induce alveolar ridge growth and development and also it may be a permanent solution for agenesis of teeth.[67,68]

In studies the long-term success of autotransplantation of premolars were reported to be between %70-%98. [69,70] In a study conducted by Dueled et al.78 two groups of patients having maxillary lateral agenesis were compared. One group had been treated with space opening prior to locating implants. The other group had been treated with conventional fixed bridges or other prosthetic appliances. Both esthetic and functional both in terms of patient satisfaction, the success rate of patients treated with the implant were higher. (%83-%92). In patients treated with fixed prosthesis was found between the rate of %41%47.[48,70]

II. CONCLUSION

Tooth agenesis is a complex problem for den- tists worldwide. In studies; tooth agenesis classification, prevalence, etiology, associated anomalies, clinical effects, treatment options are discussed. Also in recent years, based on current research and clinical observation, it has been suggested that genetic factors affect both tooth development and tumor formation commonly.

Early diagnosis of absent teeth is important and comprehensive treatment planning involving correction of skeletal discrepancies, elimination of deepbite, aligning and levelling of teeth and space arrangements is necessary for patients with hypodontia who require multidisciplinary treatment approaches. Future innovations in this field may bring up treatment of the genes causing tooth agenesis with gene therapies and development of tooth tissues from dental stem cells to the agenda.

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