



CURRENT APPROACHES FOR TOOTH AGENESIS: A REVIEW

DIŞ EKSİKLİĞİNDE GÜNCEL YAKLAŞIMLAR: DERLEME

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Makale Kodu/Article code: 3126
Makale Gönderilme tarihi: 10.11.2016
Kabul Tarihi: 29.12.2016

ABSTRACT

Hypodontia is defined as the congenital deficiency of one or more teeth and is one of the most common dental anomalies in humans. Multifactorial etiology can include environmental factors as well, since a combination of environmental and genetic factors might contribute to the occurrence of dental agenesis. Patient with missing teeth; reduced masticatory ability, inarticulate pronunciation may encounter esthetics and periodontal problems. Tooth agenesis definition, etiology, genes that cause tooth agenesis and treatment of tooth agenesis is mentioned in this review. Nowadays, many genes which play role in tooth development reported to be a potential candidate gene in tooth agenesis. Functional changes seen in genes which play role in tooth agenesis are mentioned that there may be a relationship with the development of cancer and tooth agenesis may be a significant marker for cancer.

Key Words: Hypodontia, prevalence, neoplasms

ÖZ

Hipodonti, bir veya daha fazla dişin konjenital eksikliği olarak tanımlanır ve insanlarda en sık görülen dental anomalilerden biridir. Genetik faktörlerin yanısıra çevresel faktörler veya bunların kombinasyonu diş eksikliklerinin görülmesine sebep olabilmektedir. Eksik dişlere sahip hastalar; azalmış çiğneme yeteneği, telaffuzun anlaşılabilmesi, estetik ve periodontal problemlerle karşılaşabilmektedir. Bu derlemede konjenital diş eksikliği tanımı, etiyolojisi, diş eksikliğine sebep olan genler ve tedavisinden bahsedilmektedir. Günümüzde, diş gelişiminde rol alan birçok genin, diş eksikliğinde de potansiyel aday genler oldukları bildirilmektedir. Diş eksikliğinde rol alan genlerde görülen fonksiyonel değişikliklerin kanser gelişimiyle bir ilişkisi olabileceğinden ve diş eksikliğinin kanser için belirleyici bir marker olabileceğinden bahsedilmektedir.

Anahtar Sözcükler: Hipodonti, prevalans, tümörler

INTRODUCTION

Tooth agenesis is defined developmental deficiencies of one or more deciduous or permanent teeth except third molars.¹

Tooth agenesis is the term most frequently used when describing the phenomenon of congenitally missing teeth in general. Many other terms appear in the literature to describe less number of teeth (oligodontia, anodontia, aplasia of teeth, congenitally

missing teeth, absence of teeth, agenesis of teeth and lack of teeth). The term hypodontia is used in a narrow sense when the number of missing teeth is one or a few except third molars oligodontia is defined as missing a large number of teeth six or more than six teeth except third molars. Anodontia is an extreme case, denoting complete absence of teeth.²

Prevalence

While the most frequently missing tooth is third molar, except third molars the prevalence of tooth agenesis varies according to population.²

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In many studies on the prevalence of tooth agenesis, differences were observed between populations, continents and countries. Ethnic differences in the prevalence of tooth agenesis is outstanding.³ The prevalence of permanent tooth agenesis were found to be between studies in Asia continent %1.4-%9.4,⁴ in European studies %4.5-%11.3,^{5,6} in the United States studies %3.5-%3.8,^{3,4} studies in the Middle East %0.3-%6.2.^{6,7}

In Europe, the United States, Asia and Middle East studies, the most frequently missing teeth were found maxillary lateral incisors and mandibular second premolars.^{4,7-9}

The most common dental anomalies in Turkish population is said to be hypodontia.¹⁰ In Turkey, studies showed that the frequency of hypodontia were found between %1.77-%21.6,^{11,12} the prevalence of oligodontia were found to be between %0.13-%0.3.^{10,13} The most commonly missing teeth were found to be maxillary lateral incisors and followed by mandibular second premolars.¹⁰ The prevalence of missing maxillary lateral incisors were found between %1.74-%46.5^{10,13} and the prevalence of missing mandibular second premolars were found between %0.57-%38.8.^{11,14} The prevalence of bilateral missing maxillary lateral incisors were found between %72-%84.^{10,15} The prevalence of tooth agenesis in females were more common than males and the prevalence in females were found to be between %0.50-%8.9, in males have shown to be between %0.17-%6.4.¹⁴⁻¹⁶

Etiology

Although there are many studies on tooth development, the etiology of tooth agenesis is not fully understood.¹⁷⁻¹⁹

Recent studies shows that tooth agenesis affected by a multifactorial etiology like gen functions, environmental factors and tooth development timing. Tooth agenesis might be familial or sporadic, associated with the syndrome or non-syndromic.²⁰

Environmental Factors

Such as tooth agenesis is mostly due to genetic factors, environmental factors are also effective. Infection, trauma, traumatic extraction of primary teeth is stated that the major environmental factors.²¹

In many studies; allergy, using digoxin, chemotherapy, disease observed in pregnancy, environmental factors such as birth weight might have an affect on the prevalence of hypodontia.²²⁻²⁶

Genetic Factors

Tooth agenesis is a heterogeneous condition as genetic and phenotypic. So far, more than 200 genes were identified in tooth development.²⁷ Transcription (constituting DNA nucleotide sequence of a process of copying the mRNA sequence by RNA polymerase enzyme) factors, growth factors, growth factor receptors, cytokines, encoding extracellular matrix molecules have been shown to be expressed in tooth development of many gene family.²⁸

Genetic plays a crucial role in tooth agenesis, as confirmed in studies on twins.⁶ All previous studies in monozygotic and dizygotic twins conducted hundreds of genes that regulate the shape and size of the teeth is genetically determined.²⁹⁻³¹ In a Sweden family study, tooth agenesis has been reported to be inherited. In this study, the majority of cases seen familial hypodontia autosomal dominant deficiency has been shown.⁴

Recently it has been identified many mutations associated with tooth agenesis. First genes identified in tooth agenesis were reported to be PAX-9 (paired box 9) and MSX-1 (muscle segment homeobox 1).^{32,33}

Many different mutations in genes such as MSX-1 and PAX-9 might cause tooth agenesis. It was reported that MSX-1 and PAX-9 play a significant role in mediating direct epithelial-mesenchymal interactions during in the early stages of tooth development especially bud and cap stages.³⁴

Mice with the gene that causes the tooth agenesis show similar phenotypes like MSX-1, PAX-9 in humans. In addition, mice models shows that genes such as Lef gene might cause tooth agenesis.³⁵

Except PAX-9 and MSX-1 genes, Lammi et al.²⁷ have found that AXIN-2 (axis inhibition protein 2) and WNT10A (Wingless-Type family, member 10A) genes is also responsible for tooth development and these genes mutations cause to be tooth agenesis in 2004. This modified gene nucleotide changes in the protein structure or protein interaction may result in incorrect structural proteins are mentioned. These cells and organs that need the function of the proteins causes one or more missing teeth not to be working properly.³⁶ Furthermore, AXIN-2 mutations are associated with familial oligodontia and susceptibility to colorectal cancer.²⁷

PAX-9 and MSX-1 methylation was found to be associated with cancer, but the relationship between



this situation could not be fully described with tooth agenesis.³⁷ Posttranscriptional activity differences in these genes are reported to be caused dentoalveolar defects.³⁸ In studies a potential regulatory point functional relationship between MSX-1 and PAX-9 during tooth development has been identified. Such interactions can affect the development phase of the dental organ directly on DNA or by causing on their posttranscriptional activity changes and it is thought to MSX-1 and PAX-9's combined reduction of gene dosage may increase oligodontia prevalence.^{39,40}

Prager et al.⁴¹ reported that PAX-9, AXIN-2 and MSX-1 genes are associated with non-syndromic tooth agenesis; EDA (Ectodysplasin A), EDAR (Ectodysplasin A receptor), EDARADD (EDAR associated death domain), IRF-6 (Interferon regulatory factor 6), MSX-1, NEMO (NF-Kappa-B Essential Modulator), P63 (Tumor protein P63), PITX-2 (Paired like homeodomain 2) and SHH (Sonic hedgehog) genes are associated with syndromic tooth agenesis.

Tooth Agenesis and Cancer Relationship

Studies in recent 10 years is mentioned there might be a marker for cancer predictor of tooth agenesis.⁴²⁻⁴⁶ (Table 1)

Table 1. Hypodontia patients with different tumors

THE TYPE OF CANCER	GENE RESPONSIBLE
Breast Cancer	AXIN2
Colorectal Cancer	AXIN2
Hodgkin Lenfoma	TP63
Over Cancer	BRCA1
Pancreas Cancer	AXIN2

The first family of tooth agenesis with cancer was seen as a family with autosomal dominant oligodontia. The majority of the affected family member was found to be missing more than eight teeth; permanent molars, premolars, mandibular incisors, maxillary lateral incisors and colorectal neoplasia was seen in eight people in this family. If normal dentition has been observed that family members have to be seen any neoplasia.²⁷

In another study it has been reported to be a more complex pedigrees. In family history; oligodontia, rare eyebrows, thin hair, colon polyps, early colon cancer and breast cancer were identified. At least six teeth of these patients were reported to be missing.⁴⁵ In patients with familial adenomatous polyps were observed tooth agenesis. A 39 year old

patient with 100 units of polyps was found to be some teeth are missing.⁴³ In an epidemiological study, half of women with ovarian cancer were observed missing teeth; so it can be considered that the women with tooth agenesis for the estimates reduce the risk of ovarian cancer.⁴⁶

Although studies suggest an association between tumorigenesis and tooth agenesis, there are still some weak spots, cases may not reflect the population as a whole. In addition to environmental factors, individual differences in the development of the disease has a great impact. Studies have shown a small sample size.⁴⁶

Dental Anomalies Associated with Tooth Agenesis

There are many dental anomalies associated with tooth agenesis. These are; late tooth formation and eruption, microdontia, conical crown shape, prolonged retention of primary teeth (persistence), impacted teeth (especially maxillary canines), ectopic eruption, malposition of the teeth, infraposition of primary molars, short-rooted teeth, molar taurodontism, rotations on premolars or/and maxillary lateral incisors, enamel hypoplasia and hypocalcification.⁴⁷

Syndromic Tooth Agenesis

Tooth agenesis can be a primary feature of many syndromes affecting several other ectodermal organs at the same time. A constantly updated catalog of human genes, OMIM (Online Mendelian Inheritance in Man), that examined the characteristics of human genes and genetic disorders in terms of gene-phenotype relationship. In this catalog, more than 60 syndromes listed related tooth agenesis.⁴⁸

Agenesis of maxillary central incisors, canines, second molars and molars are rarely seen. Tooth agenesis of these teeth is often associated with significant syndromes.^{4,49-57} (Table 2)

Table 2. Other syndromes associated with tooth agenesis and related genes

NAME OF SYNDROME	GENE RESPONSIBLE
Witkop Syndrome	MSX1 ^{49,50}
Rieger Syndrome	PITX2 ⁵¹
Van der Woude Syndrome	IRF6 ⁵²
Wolf-Hirschhorn Syndrome	4p deletions ⁵³
Inkontinentia Pigmenti	NEMO ⁵⁴
EEC3 Syndrome	p63 ⁵⁵
AEC Syndrome	p63 ⁵⁵
Seckel Syndrome	ATR ⁵⁶
Oral-Facial-Digital Syndrome	CXORF5 ⁵⁷



Treatment of Tooth Agenesis

There are clinical implications of tooth agenesis affecting the physical and emotional state of the person. Treatment is expensive and comprehensive and requires a multidisciplinary work.¹⁸ A treatment including oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, specialists in restorative dentistry, dental nurses, speech therapists, psychologists should be considered.^{6,18,58-60}

Considering the risk factors about tooth agenesis and early detection of missing teeth number, the number and size of the teeth in both two dental arch is important to manage the treatment plan.^{6,17,61} Determining the type of malocclusion and facial profile, final treatment plan plays a big role.⁶ Other therapeutic challenge is the treatment in growing young patients.^{18,62} Treatment should begin during adolescence is indicated.^{18,61,62}

Treatment Methods in Agenesis of Primary Teeth

Agenesis of primary teeth rarely seen. During this period, for the treatment of hypodontia or anodontia, removable prosthesis can be used to provide in terms of function and achieve an esthetic appearance. Using removable prosthesis would have avoided difficulty with speech and eating problems, and ensure that children are psychologically happy.⁶³

Lexner and Almer,⁶⁴ in a study conducted in ectodermal dysplasia patients, they have reported success in terms of using removable prosthesis for patients, parents and dentists. They have said that young patients have better adaptation to the prosthesis.

Treatment Methods in Permanent Tooth Agenesis

Treatment of permanent tooth agenesis is indicated as a treatment should be evaluated multidisciplinary.⁶⁵⁻⁶⁹

If tooth agenesis is on anterior region, esthetics problems may occur. There is no formal procedure defined for the treatment of these patients. The treatment should be planned according to the severity of tooth agenesis, occlusion, soft tissue and skeletal pattern, facial profile, the number of remaining teeth-shape-color, location of the missing tooth, alveolar bone quantity, oral hygiene, patient care, expectations of the patient's from treatment,

communication between patient-dentist and the cost of the treatment.⁷⁰ Closing space or according to the requirements of the protection of the space; orthodontic treatment, restorative treatment (crowns, bridges), autotransplantation, different treatment options such implants can be done.^{70,71}

If maxillary lateral incisor is missing in mixed dentition, with early extraction of primary incisors and canines; maxillary canines rather than be allowed to erupt instead of maxillary lateral incisors. Its purpose is to protect the alveolar bone for the implant to be placed in the future.^{6,65,66}

Guidance eruption can also be use in treatment of tooth agenesis. The purpose of the guidance eruption is, to provide the teeth take place in dental arch in a natural way without using any appliances. Agenesis of maxillary lateral incisors, closing space with guidance eruption aims maxillary canines eruption instead of maxillary lateral incisors and class 2 occlusion. For this purpose, maxillary first and second primary molars should to be abrade from both mesial and distal. Abrasion operations is made six months ago from maxillary first premolars eruption. Success depends on the order of the teeth eruption and direction. In agenesis of maxillary and mandibular premolars, if the space of the maxillary and mandibular molars' closure with guidance eruption; abrading maxillary and mandibular molars from distal, primary second molars both mesial and distal, early extraction of maxillary and mandibular primary first and second molars, guidance eruption can be done.^{72,73}

Another treatment method is autotransplantation.⁷⁴ 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.⁶ It is stated that children should be delayed until completion of adolescence implant treatment.^{6,75}

Autotransplantation of premolars may be recommended in patients with multiple agenesis of maxillary incisors. In growing children transplated teeth can induce alveolar ridge growth and development and also it may be a permanent solution for agenesis of teeth.⁷⁶



In studies the long-term success of autotransplantation of premolars were reported to be between %70-%98.^{76,77}

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.

Robertsson and Mohlin,⁷⁵ have closed space in a group of patients with orthodontic treatment in agenesis of maxillary lateral incisors and they have shaped canine like lateral incisor. Other groups of patients they have placed fixed bridges by opening space. Between the two groups of patients, satisfaction of the patients that treated with closing space were higher than those of patients who had bridges. Plaque accumulation and gingivitis in these two groups in terms of a comparison is made and the patients who have closed space was seen with more satisfying results.

In the literature, the survival rate of the implants is observed studies on implant treatment in patients with the hypodontia vary from %35.7 up to %98.7.^{78,79} About that, the most important risk factor is implant localization. The loss of implants in maxilla have seen more than mandibula because of the bone density. The patients with oligodontia, anodontia and ectodermal dysplasia in a comparison to healthy patients was found more implant loss due to lower bone mass.⁷⁹ Guckes et al.⁸⁰ reported that patients with ectodermal dysplasia is not a contraindication for implant treatment.

Some studies have used the oral health related quality of life test to assess patient satisfaction after implant treatment and the results found that particularly high in patients with oligodontia.⁸¹

CONCLUSION

Tooth agenesis is a complex problem for dentists 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. Tooth agenesis has shown to be a potential marker for the development of future cancer in studies. It is stated that prospective studies are needed to fully elucidate the mechanism. The first point about tooth agenesis in the future, dentists care not only the state of the maxillofacial region, they will care about the whole body health generally.

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