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Oral Agenesis: A Review on Human Tooth Agenesis

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Abstract

Agenesis refers to the failure of an organ to develop during embryonic growth and development due to the absence of primordial tissue. Many forms of agenesis are referred to by individual names, depending on the organ affected such as eyes, dental or oral tissue agenesis and ear agenesis. Tooth agenesis is the most clearly documented developmental anomaly in humans and can be interesting and challenging to manage clinically. Agenesis of wisdom teeth is a normal condition, in literature missing teeth have been explained under various terms which include anodontia (complete loss of tooth), hypodontia (six or less than six permanent teeth excluding third molar are missing), oligodontia (more than six permanent teeth are missing), aplasia of teeth, agenesis of teeth and lack of teeth. The prevalence of hypodontia in primary dentition approximating to 0.1-0.9% and in permanent dentition is approximating to 2-10%. Genetics plays a crucial role in congenital dental anomaly. The present review was taken to strongly emphasize on reported causative mutation in MSX1, PAX9, AXIN2, and EDA genes and their effects on high prevalence rate of various types of tooth agenesis. The high rate of gene anomalies acts as a factor leading to various types of congenital teeth anomalies such as hypodontia, oligodontia and anodontia. Therefore molecular genetic analysis of different genes such as MSX1, PAX9, AXIN2, EDA and various similar genes will be useful in minimizing the risk of transmitted genetic anomalies.

Keywords: Tooth agenesis, genetic anomalies, developmental defects, transmission, Primordial tissue.

Introduction

Tooth agenesis is the most clearly recognized developmental anomaly in humans and can be challenging to manage clinically [1]. Tooth agenesis is a condition in which teeth are missing but limited to specific teeth which occurs commonly and is often considered as a normal variant. Agenesis of wisdom teeth is a normal condition that can differ widely by population, ranging from practically zero in Tasmanian Aborigines to nearly 100% in indigenous Mexicans [2,3]. Missing teeth have been explained under various terms in literature which includes Anodontia (Total agomphiasis) or hypodontia (six (or) less than six permanent teeth excluding third molar are missing) or oligodontia (more than six permanent teeth are missing), aplasia of teeth and lack of teeth and agenesis of teeth. The commonly used term ''congenitally'' missing teeth in a misnomer as a permanent teeth that are more

frequently missing are not present in the mouth at birth .Hypodontia and oligodontia are classified as isolated (or) non syndromic hypodontia or oligodontia and syndromic hypodontia/oligodontia or hypodontia / oligodontia associated with syndromes. Permanent dentition is more frequently affected than primary dentition. The most common congenitally missing teeth are maxillary lateral incisors followed by maxillary second premolar and mandibular central incisors [4,5]. The prevalence of hypodontia in primary dentition approximating to 0.1-0.9% and in permanent dentition is approximating to 2-10%.Congenitally missing teeth is a result of disturbances during early stage of development and expression of ectoderm .Genetics plays a crucial role in congenital dental anomaly [6,7].

Clinical Epidemiology and Prevalence of the Tooth Agenesis

Tooth agenesis is often associated with a group of conditions affecting the development or function of the teeth, hair, nails and sweat glands called ectodermal dysplasias [8]. A tooth is defined to be congenitally missing if it has not erupted in the oral cavity and is not visible in radiographs. The prevalence of tooth agenesis in the general population is estimated to be 0.25% which is limited to a few specific teeth which occurs commonly and is often considered a normal variant (REF) [9,10,11]. Third molar agenesis is the most common with an incidence of 20% followed by maxillary lateral incisor which is believed to be the second most commonly missing tooth while other investigators believe that mandibular second premolar agenesis has a higher incidence [12].

Hypodontia is highly prevalent and costly dental anomaly. It usually appears in female and in the permanent dentition it is not conclusive whether it trends to occur more in the maxilla or mandible and also in the anterior versus posterior segments. Non- syndromic hypodontia is the most common form of congenital tooth absence, which involves variable numbers of teeth [13]. Large differences in the prevalence of dental agenesis have been reported, varying from 1.4% in Japanese [14] to 11.3% in the Irish population [15]. The diagnosis of tooth agenesis is based on radiographic examination the report presented prevalence of agenesis excluding the third molar and the report did not mix the prevalence of agenesis of primary teeth. The prevalence of dental agenesis varied from outside of japan 2.8% in the Turkish to Irish population. In the most of the reports the prevalence of tooth agenesis in females was always higher than in males [16]. In Europeans, the mandibular second premolar was not frequently absent, followed by maxillary lateral incisor and second premolars [17, 18, 19]. In the Malaysian, Turkish and American populations the most frequently missing tooth was the maxillary lateral incisor; and in Chinese it was the mandibular central and lateral incisor [20, 21, 22] .The absence of maxillary central incisor, canine, first molar and second molar was rare. The prevalence of oligodontia, referring to the absence of more than six teeth, varied from 0% to 0.43% of the population. Unilateral occurrence of hypodontia is more common than bilateral occurrence [24- 29].

Age at Agenesis Diagnosis

An important concern of dental agenesis is the age at which diagnosis was achieved or realized. Visibility of tooth germs on radiographs depends on their mineralization stage. Major differences in mineralization stages and dental age occur among subjects of the same chronological age. Tooth buds with a late onset of mineralization (mandibular second premolars) could give misdiagnosis of agenesis on radiographs. On the average, the mineralization of the mandibular second premolar starts at the age of 3–3.5 years, but it may also begin many

years later [30]. A mandibular second premolar, diagnosed as agenetic at the age of seven showed to develop after the age of 10 years. The diagnosis of dental agenesis of a mandibular second premolar before the age of seven is probably not conclusive. The age range in the selected studies is 3–43 years. If any relation is found between age of the investigated populations and prevalence of dental agenesis, further exclusion criteria based on age has to be formulated [31].

Theories about Tooth Agenesis

Developmental defects of teeth have always were made an attempt to explain them with evolutionary and anatomic models such as Butler's field theory, odontogenic polarity or Sofaer's model of compensatory tooth size interactions. Butler's theory (1939) explained that why certain teeth fail to form more than others. Mammalian dentition can be divided into 3 morphologic fields corresponding to incisors, canine and premolar/molar. Based on this theory, the third molar and the first premolar would be predicted to be most variable in size and shape. Clinical epidemiology supports this view for the third molar, but not for the first premolar [32].

Sofaer et al have challenged the association between absent teeth and those reduced in size. In a study of Hawaiian children they noted that if the central incisor is large then the adjacent lateral incisor tends to be absent. If the lateral incisor is peg-shaped, the adjacent central incisor tends to be present, but relatively small. They speculated that agenesis occurs when there is insufficient primordial for tooth germ initiation, whereas peg-shaped laterals occur when there are sufficient primordia but a poor environment. Absent or reduction in size of the teeth on one side induces a compensatory increase in size of the teeth of the contralateral side [33].

Svinhufvud et al have explained the selectivity of tooth agenesis in terms of an anatomic rather than an evolutionary model. The researchers suggested that certain regions during tooth development (areas of embryonic fusion) are more susceptible to epigenetic influences and hence agenesis. The most frequently missing or variably sized tooth is seen in the maxilla and medial nasal processes. In the mandible, permanent tooth agenesis occurs most frequently in the area of the second premolar. This corresponds to the distal end of the primary dental lamina, and because of its susceptibility to agenesis, this area is called a 'fragile' site. Remarkably, however this site of mandibular agenesis appears specific for permanent dentition; the loss of second primary molars is rare. A third site where tooth agenesis occurs frequently is the area where the 2 lower central incisors develop. Here, the fusion of the 2 mandibular processes is required to form the midline of the future mandible. This midline region is likely to be another fragile site [34].

Kjaer has explained the location of tooth agenesis by neural development field in the jaws. The region within a single field where innervations occurs last is more likely to manifest tooth agenesis. Normal tooth developments are particularly sensitive to defects in craniofacial development. Disturbance of embryonic jaw mesenchyme are often revealed predominantly by their effects on the teeth. Early craniofacial defects, which could result in jaw abnormalities, are often masked by bone remodeling; therefore tooth agenesis may actually serve as a better indicator of developmental jaw defects [35, 36].

Etiology of Tooth Agenesis

Several factors like infection, trauma, metabolic disorders, and radiations, environmental and genetic factors are considered as possible etiological factors of tooth agenesis [37-41].

Genetic Factors

Several different genes have been found to be associated with hypo/oligodontia and anodontia including the EDA,

EDAR and EDARADD genes. The same genes are involved in so called isolated hypo/oligodontia (only missing teeth) or associated hypo/oligodontia with other symptoms in syndromes like ectodermal dysplasias. EDA, EDAR and EDARADD genes are indeed responsible both for isolated or syndromic hypo/oligodontia [43]. Many other genes are involved in hypo/oligodontia such as MSX1, PAX9, IRF6, GREM2, AXIN2, LRP6, SMOC2, LTBP3, PITX2, and WNT10B. WNT10A is now recognized as being the major gene involved in the etiology of hypodontia/oligodontia [44].

Depending on the gene involved, inheritance can follow different modes of inheritance. Most genetic diseases are determined by the status of the two copies of a gene, one received from the father and one from the mother. Recessive genetic disorders occur when an individual inherits a non-working gene from each parent. If an individual receives one working gene and one non-working gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. Dominant genetic disorders occur when only a single copy of a non-working gene is necessary to cause a particular disease. The non-working gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected individual. X-linked genetic disorders are conditions caused by a non-working gene on the X chromosome and manifest mostly in males. Females that have a non-working gene present on one of their X chromosomes are carriers for that disorder [45-48].

EDA

Ectodysplasin A (EDA) is a transmembrane protein of the TNF family which plays an important role in the development of ectodermal tissues such as skin in humans. It is recognized by the ectodysplasin A receptor. The encoded protein, which belongs to the tumor necrosis factor family, acts as a homotrimer and may be involved in cell-cell signaling during the development of ectodermal organs. Along with c-Met, it has been shown to be involved in the differentiation of anatomical placodes, precursors of scales, feathers and hair follicles in vertebrates. Defects in this gene are a cause of ectodermal dysplasia, anhidrotic, which is also known as X-linked hypohidrotic ectodermal dysplasia. Several transcript variants encoding many different isoforms have been found for this gene [49, 50].

MSX1

MSX1 is a homeobox gene located on chromosome4 and encodes a DNA-binding protein. The main function of MSX1 protein is to interact with TATA box-binding protein and some transcription process. The protein regulates gene expression for initiating tooth development. MSX1 protein is considered to be critical during early tooth development. Defects in MXS1 and PAX9 genes influence early tooth development, leading to the loss of maxillary first, second and third molars respectively. MSX1 gene mutation and their altered protein structure were also associated with multiple congenitally missing teeth such as severe form of autosomal dominant oligodontia [51-53].

PAX9

It was observed that PAX9 gene belonged to paired box families and encoded transcription factor that was necessary for positioning, morphogenesis of entire dentition and proper tooth development. EXON2 of PAX9 genes contain a sequence of specific DNA binding domain; the defects in paired domain of PAX9 gene lead to tooth agenesis. Studies show that deletion of PAX9 gene and mutation in initiation codon are closely associated with the most severe defects in whole post canine dentition [54, 55].

AXIN2

The identification of a four-generation fiunish family affected by autosomal dominant oligodontia has recently provided a rather unexpected further insight into the genetics of inherited tooth loss within this family 11 members were identified as lacking at least eight permanent teeth and rather surprisingly among that this individuals affected by oligodontia, a significant risk of developing colorectal neoplasia was also present. Linkage analysis of this pedigree identified a candidate region on chromosome 17, which contained approximately 80 genes, among which was a gene called AXIN2 (axis inhibition protein-2). Its position within this particular chromosomal region that was previously identified association with colorectal carcinoma put forward as a suggestive of functioning as a regulator of the wnt signaling pathway [56, 57].

Syndromic Effect

Down's syndrome patients have a higher prevalence of hypodontia. The reported prevalence rate was 63% and most frequently absent teeth were the lower lateral incisors in Japanese patients with Down's syndrome [58, 59]. Other researchers have reported that hypodontia was present in 38.6% and most often missing were the upper lateral incisors in Croatia. Patients with cleft lip and palate have a higher prevalence of tooth agenesis. The maxillary lateral incisor is most commonly affected in both primary and permanent dentition. Rieger syndrome is an autosomal-dominant disorder characterized by malformations of the anterior segment of eye, periumbilical skin abnormalities, maxillary hypoplasia and dental defects including microdontia and hypodontia .Both the primary and permanent dentition is affected [60-62].

Conclusion

The present study revealed strong emphasize on reported causative mutation in MSX1, PAX9, AXIN2 and EDA genes and their effects on high prevalence rate of various types of tooth agenesis. The high rate of gene anomalies act as a factor, leading to various types of congenital teeth anomalies, such as hypodontia, oligodontia, anodontia , etc. The clinical significance of number and location of dental agenesis and the relation with size and shape abnormalities of the other teeth is still not fully clear. Most publications on treatment of dental agenesis are case-presentations or reports. Therefore, molecular genetic analysis of different genes such as MSX1, PAX9, AXIN2, EDA and some other genes are useful in minimizing the risk of transmitted genetic anomalies. Hence further research with emphasis on long-term results and cost-benefit analysis is needed.

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