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Review Article

Genetic Overview Of Syndromic And Non Syndromic Tooth Agenesis - A Narrative Review

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ABSTRACT

Teeth agenesis is the condition where a defective tooth germ fails to develop into a tooth. Mutations in any of the delicate and balanced signaling cascades during tooth formation and development may cause arrested odontogenesis and/or other dental defects. Understanding the delicate gene regulation and molecular interactions among the cell is crucial for understanding the origin of teeth, its development and various genetic abnormalities associated with it. The mechanism of odontogenesis is now better known and well understood as a result of increasing advancement in technology and research, yet the complexity of the mechanism of tooth formation reveals newer knowledge which is found to be associated with the development of teeth. The aim of this narrative review is to acquire a deeper understanding about the genetic aspects that are responsible for the various causes and conditions associated with tooth agenesis.

Keywords: teeth agenesis, genes, synchromic tooth agenesis, non – syndromic tooth agenesis.

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INTRODUCTION

Tooth agenesis refers to the developmental absence of one or more teeth. This condition occurs due to the failure of the tooth germ to develop during the early stages of tooth formation. Types of Tooth Agenesis based on number of absent teeth, Hypodontia being the Absence of 1-6 teeth, excluding third molars, Oligodontia which is the Absence of more than six teeth, excluding third molars.[1] Anodontia means Complete absence of all teeth, which is very rare. The most commonly congenitally missing teeth are the third molars (wisdom teeth), which is followed by the second premolars and the lateral incisors.[2]

The prevalence of anodontia is unknown. This condition affects males and females in equal numbers. The prevalence of hypodontia is 2 to 8% of the general population (excluding third molar) and oligodontia is 0.09%. to 0.3%.[3] There are various Causes of Tooth Agenesis which can be broadly classified as Genetic factors and Environmental factors. Tooth agenesis is often inherited and can be associated with mutations in genes and also be part of various syndromes. Various external factors during tooth development, such as radiation exposure, trauma, or infections, may interfere with normal tooth formation and can lead to agenesis of teeth.[4]

Tooth Agenesis can have various Clinical Implications like aesthetics, functional tissue, orthodontic and prosthetic problems. Missing anterior teeth, especially lateral incisors can lead to noticeable gaps in the smile hampering the aesthetics of the individual. More importantly missing teeth can affect mastication and speech, which may lead to shifting of adjacent teeth or bite misalignment. Depending on the number of missing teeth and their location, treatment may involve orthodontic solutions, dental implants, bridges, or dentures to restore functionality and aesthetics.[5]

Tooth agenesis can occur as an isolated condition associated with no other abnormality (non-syndromic) or as part of various syndromes causing agenesis (syndromic). It is important for a clinician to diagnose and make the patient aware of the syndrome as it can affect the future progeny and can affect the individuals lifestyle.[6]

NONSYNDROMIC TOOTH AGENESIS

Non syndromic tooth agenesis refers to the absence of permanent teeth without any other associated systemic abnormalities and is the only clinical finding. It is often caused by mutations in specific genes that are involved in dental development.

Genetic Factors may be inherited as an autosomal dominant, recessive, or X-linked mode.Mutation in the **MSX1 gene (muscle segment homeobox 1)**, located at 4p16.1, shows second premolar and third molar hypodontia.[7] Mutation in the **PAX9 (paired box 9) gene**, located at 14q13.3, can result in tooth agenesis of molars and premolars on mutation.[8] Mutation in the **AXIN2 (axis inhibitor 2) gene,** located at 17q24.1, results in hypodontia and severe oligodontia involving missing molars, premolars, upper lateral incisors, and lower incisors.[9] Mutation in the **WNT10A (Wingless-type 10A) gene,** located at 2q35, is associated with several syndromes (ectodermal dysplasia) and nonsyndromic hypodontia.[10] Mutation in the **EDA1 (Ectodysplasin 1) gene,** located at Xq12-q13, results in hypodontia and severe oligodontia involving congenital absence of maxillary and mandibular central incisors, lateral incisors, and canines, with the high possibility of persistence of maxillary and mandibular first permanent molars.[11] Mutation in the **LTBP3 (latent transforming growth factor beta binding protein-3)** gene located on chromosome 11 is thought to cause autosomal recessive form of oligodontia.[12]

Common Inherited Patterns and environmental changes are as follows. Missing third molars (wisdom teeth) are the most frequent form of isolated hypodontia. Missing maxillary lateral incisors or second premolars are also common.[13] medications such as the use of thalidomide while the mother is pregnant may result in hypodontia in her child. Rubella infection during pregnancy has also been proposed as a causative factor of hypodontia in the newborn [14]. Maternal smoking and/or the consumption of alcohol during pregnancy have been associated with hypodontia along with craniofacial anomalies such as cleft lip and palate [15]. Radiation and chemotherapy treatments with increased doses of chemotherapeutic agents such as vincristine, cyclophosphamide and doxorubicin over a long treatment period was associated with increased tooth agenesis [16]

SYNDROMIC TOOTH AGENESIS

Tooth agenesis can occur as part of a broader syndrome, where multiple organ systems are involved. Syndromic tooth agenesis is often accompanied by abnormalities in other parts of the body, such as the skin, hair, nails, or facial structures.[17] Even though these syndromes are not seen in day to day practice, Here are some of the commonly occurring genetic disorders which are associated with agenesis of tooth that are commonly seen across population.

Ectodermal Dysplasia

It is an X-linked recessive disorder with Prevalence of 1 in 10,000 to 1 in 100,000 individuals. It is characterized by dry skin, Sparse hair & nails, and hypohidrosis (inability to sweat normally). Dental characteristics include Hypodontia, teeth malformation (conical shaped teeth), delayed eruption, maxillary retrusion, collapse in anterior facial height, and cleft palete in rare occasions. It is caused by Mutation in **the EDA (Ectodysplasin A), EDAR (Ectodysplasin A receptor) and EDARADD (Ectodysplasin A Receptor Associated Adapter) gene which**causes defective ectodysplasin A protein production that hampers normal ectodermal-mesodermal interactions during 8th week of embryonic development. Diagnosis is based on clinical symptoms, family history, and sometimes genetic testing. Treatment is supportive and tailored to the specific symptoms: Dental care includes prosthetics, implants, or orthodontics to manage missing or malformed teeth.[18]

Axenfeld-Rieger Syndrome

It is a rare autosomal dominant disorder with an estimated prevalence of around 1 in 200,000 individuals. Characteristics features include anterior segment dysgenesis, cornea and iris malformation, glaucoma, redundant skin, umbilical hernias, cardiac complications, skeletal abnormalities. Dental characteristics include maxillary hypoplasia, hypertelorism, tooth agenesis, malformed (cone shaped) teeth, delayed eruption. Mutation in the **PITX2 (paired-like homeodomain transcription factor 2) and FOXC1 (Forkhead box C1) gene,** results in disrupted developments of teeth and other structures like eyes, heart and brain respectively. Diagnosis can be done by clinical examination, ophthalmologic examination and genetic testing. Treatment is a multidisciplinary approach include treating glaucoma with medications or surgery and routine checkup for eye, orthodontic, prosthetic and implant for teeth, and facial surgeries for maxillofacial deformities.[19]

Van der Woude Syndrome

It is a Rare autosomal dominant disorder with a prevalence of 1 in 35,000 to 1 in 100,000 individuals and contributes to 2% of all cleft lip and palate cases. It is Characterized by cleft lip/palate, lip pits (hallmark feature), speech delays, nasal sounding speech, velopharyngeal insufficiency. Dental features include Hypodontia, teeth crowding, missing permanent teeth in maxilla, lower incisor agenesis, delayed eruption, speech and mastication difficulties. Mutation in the **IRF6 (interferon regulatory factor 6) gene**, which is located on chromosome 1q32. **GRHL3 (Grainyhead-like 3) gene mutation** is also responsible for 30% of the cases. Diagnosis done by clinical examination, Family history, genetic testing. Treatment include surgical intervention to repair clefts and lip pit, speech therapy, orthodontic and prosthetic treatments, feeding support, and genetic counseling.[20]

Orofacial Digital Syndrome type 1

It is a rare X-linked dominant disorder with a prevalence of 1 in 150,000 to 1 in 250,000 individuals. Characteristics are facial anomalies like hypertelorism, underdeveloped mid face, flat nasal bridge, cleft lip and palate, oral structures, and digits, polysystic kidneys, intellectual disability. Dental characteristics are oral anomalies like, abnormal palate and tongue development, Hypodontia, oligodontia, supernumerary teeth, malformed teeth, delayed eruption, benign gingival fibromas. Hypodontia or oligodontia, with abnormal tooth shapes and delayed eruption is often seen. Other Features like Cleft tongue, lip pits, extra digits (polydactyly), and facial abnormalities are often associated with this syndrome.[21]

Laurence-Moon Bardet-Biedl Syndrome

It is a rare autosomal recessive genetic disorder with a mean prevalence of 1 in 100,000 individuals that varies demographically. It affects multiple organs in the body, including the brain, eyes, ears, stomach, kidneys, hands, and feet and can cause early death if untreated. Dental complications include microdontia, Hypodontia, taurodontism, short roots, deep palate, periodontal disease and potential supernumerary tooth. Mutations in various genes including BBS1, BBS10 can cause this syndrome. Other features include retinal dystrophy, postaxial polydactyly, obesity, hypogenitalism, Obesity, retinal degeneration, speech delay, developmental delay, behavioral abnormalities, learning disability, and intellectual disability.[22]

Witkop's syndrome

Commonly known as Tooth and Nail Syndrome (TNS), it is a genetic disorder that affects teeth and nails. With a prevalence of 1-2 in every 10,000 individuals, it is not as lethal as other syndromes. Mutation in the **MSX1 (muscle segment homeobox gene)** located on chromosome 4p16, is responsible for Witkop's tooth and nail syndrome. Tooth agenesis seen includes Missing or abnormally formed primary and permanent teeth including partial or total absence. Other features associated with this include thin brittle slow growing nails, incompetent lips, thin hair which get normal as age progresses.[23]

Hypohidrotic ectodermal dysplasia

HED is a rare genetic disorder that has an incidence of 1 in every 20,000 individuals. It is characterized by the faulty development of the ectodermal structure, resulting in most notably anhidrosis / hypohidrosis, hypotrichosis and hypodontia. Mutation in the **EDAR (ectodysplasin) gene,** mapped at Xq13.1, showed an X-linked HED, and is characterized by absence of sweat glands, dry skin, sparse hair, and pronounced oligodontia. Tooth Agenesis in this syndrome include Missing, pointed, globe-shaped or smaller-than-normal teeth, or teeth that are widely spaced, Abnormally positioned teeth and jaw.[24]

MANAGEMENT AND TREATMENT

The overall and common Management and Treatment for agenesis include Orthodontics treatment To close gaps or align teeth to improve function and appearance. Prosthetics like Dental implants, bridges, or dentures might be required to replace missing teeth and restore function. Restorative procedures like Composite bonding or veneers to address aesthetic concerns, particularly with missing anterior teeth can also help in management in restoring the natural functionality of teeth and oral cavity. Management with regular follow ups can help these individuals to restore normal aesthetics and functioning which directly improves the individuals health and confidence. [25]

CONCLUSION

It is important for the clinicians to be aware of agenesis of teeth as it can have various systemic involvement. Moreover, tooth agenesis bears a chance of being genetically inherited from the parents. Despite of the rare occurrence of these conditions in day to day practice becomes an important duty for clinician to identify, make the patient aware of the underlying abnormality, and treat them to make their lifestyle Healthier and better.

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CONFLICTS OF INTEREST

There are no conflicts of interest

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