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Review

An Overview of Syndromic Hypodontia

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Abstract

Hypodontia is collectively used to describe the developmental absence of primary or secondary teeth. A number of causes like alterations in the dental lamina development, lack of maturation of tooth germ at the appropriate time, space constraints, systemic and genetic factors may result in missing teeth. With the exception of the third molars, hypodontia is most frequently encountered in lower second bicuspids and upper lateral incisors. Hypodontia is most commonly categorized into two categories: syndromic and non-syndromic hypodontia. Syndromic hypodontia constitutes cases where agenesis of one or more teeth occurs as a result of underlying diagnosable syndromic conditions like ectodermal dysplasia. The more extreme phenotypes of hypodontia include oligodontia with the agenesis of canines, first molars, and second molars and anodontia, and are generally seen in syndromic hypodontia, accompanying and underlying developmental disease. over 200 cleft lip and palate syndromes present with differing extent of hypodontia as a component of their clinical phenotype. The number of missing teeth increases with the extent of cleft. Ectodermal dysplasia consists of a varied group of syndromic presentations resulting from mutations influencing a range of vital congenital pathways such as connection between the overlaying ectoderm and the underlying mesoderm during embryonic growth. Many of these cases present with dental dysplasia and agenesis. In general, dental agenesis may be caused by the arrest of tooth development in the initial bud or cap phase. Care guidelines for such individuals include tooth replacement therapy through fixed and removable prostheses with optional implant support in skeletally mature individuals.

Keywords: syndromic hypodontia, oligodontia, ectodermal dysplasia, tooth agenesis

Introduction

Hypodontia is collectively used to describe the developmental absence of primary or secondary teeth. It is also used to specifically describe the absence of one to six teeth with the exception of third molars. Oligodontia is a term used to describe the absence of over six teeth with the exception of third molars. Oligodontia prevalence is seen in 0.08% to 1.1% of the population (1, 2). The absolute failure of one or both dentitions to form in a person is known as total anodontia. The prevalence of hypodontia varies across different regions and populations. The highest prevalence is seen in African people (13.4%), followed by European people (7%), Asian and Australian populations (6.3%), North American people (5%) and Latin American countries (4.4%) (3). In addition to geographic factors, the variations in prevalence rates are partly attributed to differing radiographic techniques and clinical evaluation, age, sex, and demographic character of the populations (4). The prevalence rate in deciduous teeth is 0.5% to 0.9% (5). In over 80% of hypodontia cases, only a single tooth or two teeth are absent; in 10% cases, four or more teeth are missing, while in under 1% cases, six or more teeth are missing (6) (7). A number of causes like alterations in the dental lamina development, lack of maturation of tooth germ at the appropriate time, space constraints, systemic and genetic factors may result in missing teeth (8). Evolutionary changes are also believed to play a role in the variation in observation of hypodontia throughout history (9, 10). There is some evidence to support the gradual increase in the incidence of hypodontia in the recent centuries. However, certain researchers refute the claim. Bolks' theory of terminal reduction, based on the phylogenetics and evolutionary biology, proposes that diminution of the distal component of a unit of teeth happens more often than the mesial components (11). With the exception of the third molars, hypodontia is most frequently encountered in lower second bicuspids and upper lateral incisors. These are followed by upper second bicuspids, lower central incisors, lower lateral incisors, upper first bicuspids, lower first bicuspids, upper canines, lower second molars, upper second molars, lower canines, upper first molars, lower first molars and lastly upper central incisors (3). Studies have shown a female preponderance for hypodontia. This is in contrast to the gender predisposition for supernumerary teeth which shows a male preponderance (12, 13). Hypodontia is most commonly categorized into two categories: syndromic and non-syndromic hypodontia. Syndromic hypodontia constitutes cases where agenesis of one or more teeth occurs as a result of underlying diagnosable syndromic conditions like ectodermal dysplasia, Down syndrome (trisomy 21), Type VII Ehlers-Danlos syndrome, van der Woude syndrome, Book syndrome, and Type I Rieger syndrome. The more extreme phenotypes of hypodontia include oligodontia with the agenesis of canines, first molars, and second molars and anodontia, and are generally seen in syndromic hypodontia, accompanying and underlying developmental disease (8). Familial or non-syndromic hypodontia on the other hand is the more frequently occurring form of developmentally missing teeth, and primarily occurs due to agenesis (14). It is found in isolation without any other accompanying clinical manifestations and can impact a variable number of teeth (15). There is substantial evidence in literature for the association between hypodontia and neoplasms. Epithelial ovarian cancer in particular has been found demonstrate statistically significant association with hypodontia (16). This is an important clinical implication of hypodontia as it allows for detection and management of the condition in its initial phases. The condition has an adversely influence on the afflicted person as it results in poor facial aesthetics, speech and mastication difficulties, skeletal and dental malocclusion, and periodontal harm.

Methodology

This study is based on a comprehensive literature search conducted on September 15, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about syndromic hypodontia. There were no restrictions on date, language, participant age, or type of publication.

Discussion

There are over 120 syndromes in the Online Mendelian Inheritance in Man (OMIM) database which are linked to tooth anomalies (17). Another UK based database compiling dysmorphologic conditions has a list of 150 syndromes related to hypodontia (18). Multiple missing teeth are often related to the existence of particular syndromes or systemic aberrations. It is believed that over 200 cleft lip and palate syndromes present with differing extent of hypodontia as a component of their clinical phenotype (19). The number of missing teeth

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increases with the extent of cleft (20). Maxillary lateral incisor is the most commonly affected tooth in the region of the cleft in both dentitions (19). Other maxillary teeth are also sometimes absent, particularly in cases of permanent teeth.

Dentists must consider the potential presence of a syndrome if a person is developmentally missing teeth, and as the frequency of absent teeth increases, the probability of the abnormality being syndrome related also becomes higher (21). When the clinical presentation hints to the existence of an undetected syndrome, then a discussion with the patient or parent about referral to a physician or clinical geneticist for assessment should be carried out.

Ectodermal dysplasia

Ectodermal dysplasias (ED) consist of a varied group of syndromic presentations resulting from mutations influencing a range of vital congenital pathways such as connection between the overlaying ectoderm and the underlying mesoderm during embryonic growth (21). Traditionally, a medical description for the phenotype has been for persons in whom two or more ectodermally originating parts such as teeth, nails, hair, and sweat glands. The organs either do not develop (aplasia) or develop abnormally (dysplasia). In the case of teeth, a range of presentations can be seen including dysplastic teeth which are conical-shaped or microdontic, or complete agenesis. The most prevalent type of ED is X-linked hypohidrotic ED (21). This phenotype generally presents with a combination of manifestations such as hypodontia, oligodontia, and in rare cases, anodontia; conical teeth; abnormal hair growth or trichodysplasia; decreased sweating or dyshidrosis; irregular sebum production or asteatosis causing dry mucosa and crust formation; and change in keratin nail formation in some types which is known as onychodysplasia (21). The dental effects of the syndrome result in major physiological problems including functional deficit, hypoplastic alveolar ridges, dental arch and tooth size aberrations as well as deficient salivary secretions. Defective salivation, consequently, predisposes the teeth to caries formation. Care guidelines include tooth replacement therapy through fixed and removable prostheses with optional implant support in skeletally mature individuals (22).

Cleft lip and palate–Ectodermal dysplasia syndrome

These individuals present with scanty and dry hair and eyebrows, finger and toe syndactyly, cleft and/or palate, dysplastic nails, tooth shape and size abnormalities in addition to maxillary central incisors hypodontia (23).

Van der Woude syndrome

This is one of the most prevalent autosomal dominant disorders linked with cleft lip and palate occurrence in humans. It is present with hypodontia in nearly 70% of cases along with lower lip pits, and cleft lip and/or palate. Mutation in a gene coding for embryonic craniofacial tissues which include tooth buds is noted in the syndrome (24).

P63 syndromes

Mutations in the P63 gene present with oral clefts, hypodontia, split hands and feet (ectrodactyly), aberrations of lacrimal duct and urogenital tract, hypoacusis, chronic lung infections, ventricular defects, and developmental delay. The main phenotypes of P63 syndromes include ectrodactyly-ectodermal dysplasia (EEC) syndrome, ankyloblepharon ectodermal defects cleft lip and/or palate syndrome, and limb mammary syndrome (25).

Oral-facial-digital syndrome type I

Oral-facial-digital syndrome type I is a component of a heterogenous array of congenital conditions presenting with facial disproportionalities including asymmetry, hypertelorism and micrognathia, intraoral abnormalities including extra frenulae, alveolus thickening, and mandibular incisor hypodontia as well as aberrations in the development of digits. It has an X-linked dominant trait and affects the female gender while causing mortality in male counterparts (26).

Wiktop syndrome

This syndrome is presents with ectodermal dysplasia and has an autosomal dominant mode of transmission. Manifestations consist of nail dysplasia, extreme hypodontia, and conical-shaped teeth. Mutated MSX1 gene has been implicated in the occurrence of Wiktop syndrome (27).

Clinical genetic basis of tooth agenesis

Dental agenesis may be caused by the arrest of tooth development in the initial bud or cap phase (28). One of the first signals for the oral epithelial cells is the expressing of Pitx2 mRNA in the dental lamina (29). The condensing epithelium or the dental placode acts as a signall ing locus producing various growth factors and signalling molecules. Further, p21 and Notch genes coding for Notch1, Notch2 and Notch3 are up regulated

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in the placode. In the mesenchymal layer, the signals from the epithelium cause expression of Pax9, Ptc, Msx1, Msx2, Bmp4 and Lef1. Fgfr1c and Fgfr2b are expressed all over in the dental and oral epithelium. In the bud phase, the dental epithelial cells proceed to express many growth factors and signalling molecules. Shh and Bmp2 proteins are expressed at the tip of the bud, the future enamel knot. Notch1, -2 and -3 are expressed in the stellate reticulum of the enamel organ. Tooth mesenchyme expresses Pax9, Msx1 and Bmp4, participate in a reciprocating signalling loop. In the cap phase, the enamel knot (red) contains cells that have stopped proliferating and differentiate into a signalling locus secreting factors modulate the development of the enveloping tissue (epithelial and mesenchymal). Tooth mesenchyme, in response, secretes Bmp4 and Msx2. Fgf signalling loop consists of mesenchymal expression of Msx1, Runx2, Fgf3 and Fgf10, mediated by Fgfr1c, Fgfr2c, Fgfrb and Fgfr2b (29).

Skeletal pattern considerations in syndromic hypodontia

In mild cases of hypodontia, there are generally no notable effects on the skeletal structure. However, with the increase in severity of hypodontia and oligodontia, as seen in syndromes such as hypohidrotic ectodermal dysplasia, the syndrome lends a flattened or concave profile, widening of nasolabial angle, maxillary retrognathia, and facial vertical height reduction (30).

Clinical implications and management of syndromic hypodontia

Missing teeth have important clinical consequences because they can severely impact an individual's physical and psychological health. Missing anterior teeth affects the patients more adversely due to esthetic concerns. Further, management of the problem is challenging due to diagnostic difficulties, the severity of dental agenesis, and the overall impact on the rest of the dentition and occlusal relationship (22).

The main motivation for people wanting orthodontic therapy is esthetic enhancement. Some individuals, additionally, undergo depression therapy for dealing with impact on facial appearance and activity. There is no prevailing treatment regimen for managing hypodontic patients. It often requires an interdisciplinary approach, with the involvement of various specialties. The management may include isolated restorations to surgical procedures and multiple restorations (31). The plan is based on the location and extent of missing teeth, the number of spaces interdentally and the attitude of the patient. In milder cases, spaces are closed using orthodontic therapy alone, and in more severe cases, the void is filled through prosthodontic and orthodontic therapy. The specific procedures may include the provision of dentures, crowns, bridges, autotransplants, implants. Factors to consider prior to drafting of treatment plan include the age of the patient, skeletal and dental occlusal relationship, soft tissues, facial morphology, alveolar ridge height, the location of absent teeth, patient expectations, treatment timeline and cost of the procedure (32).

Conclusion

In humans, tooth development is regulated by a linear and reciprocative signalling mechanism between two neighbouring structures. Hence, genes responsible for epithelium-mesenchyme interplay in various phases of tooth development are important contributors to tooth agenesis. A number of tooth abnormalities, either in the form or number can probably be due to aberrant operation of these particular protein. Many genetic mutations have been identified in the etiopathogenesis of tooth agenesis, although studied mutations account for only a limited amount of agenesis incidences. More need to be learnt about the genetic defects responsible for the development of these complex syndromes. The management of hypodontia demands the skills of an interdisciplinary team and can be financially significant for the patient. Numerous dental interventions are available today for the patient to choose from, depending upon their age.

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Conflict of interest

There is no conflict of interest

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Data availability

Data that supports the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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