Frequent genetic disorders associated with missing teeth and revisiting classification of anodontia: a retrospective study

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Received 03 Febuary 2022
Revised 15 February 2022
Accepted 20 Febuary 2022
Published 08 June 2022

Middle East Journal of Medical Genetics
2022,2:95–100

Background
Absence of teeth in the oral cavity is one of the most common dental abnormalities. Anodontia is a term used to describe congenitally missing teeth. It can manifest either as an isolated finding or as a part of a syndrome.
Aim
In this single-center 7-year retrospective study, we report and describe the most frequent genetic disorders associated with missing teeth in patients who presented to the outpatient clinic of Oro-dental Genetics Department at the National Research Center, Cairo, Egypt.
Methods
The recorded patients were classified into true anodontia and pseudoanodontia, which was further classified into primary pseudoanadontia and secondary pseudoanodontia.
Results and conclusions
The collected data showed that ectodermal dysplasia, followed by Ellis-van Creveld syndrome, was the most frequent disorder in the true anodontia group. Cleidocranial dysplasia was the most frequent disorder in the primary pseudoanodontia group, whereas Papillon–Lefèvre syndrome followed by congenital insensitivity to pain with anhidrosis and hypophosphatasia, was the most frequent genetic disorder in the secondary pseudoanodontia group.

Keywords:
anodontia, genetic disorders, hypodontia, missing teeth, oligodontia

Middle East J Med Genet 2:95–100

2090-8571

Introduction

Tooth formation is considered a very complicated process, regulated by mutual and consecutive interactions between epithelial and mesenchymal cells. A strict genetic control masters the odontogenesis process in which more than 300 genes are involved and responsible for determining the final position, number, and morphology of different teeth (Thesleff, 2006). Many factors can disrupt this complex process starting from gene mutations to environmental factors (Brook, 2009). Congenital absence of teeth in the oral cavity is one of the frequent dental abnormalities. This condition can be either true, due to tooth agenesis, or false (pseudo), due to impaction, or failure of eruption (Chaitra, 2010). Moreover, relative to the number of missing teeth – excluding the third molars – the absence of teeth in the oral cavity can be classified into either partial or complete (Kulkarni *et al.*, 2011). Partial absence of teeth can be subsequently categorized into either hypodontia, in which less than six teeth are missing or oligodontia, which denotes the absence of more than six teeth, whereas the complete absence of teeth is called anodontia (Werther and Rothenberg, 1939; Salvi *et al.*, 2016). These abnormalities can occur either as an isolated condition, as a part of a syndrome, or as a nonsyndromic familial trait (Kulkarni *et al.*, 2011). This study focuses on specifying the most frequent genetic disorders associated with absence of teeth through a 7-year retrospective study of patients presented to the Oro-dental Genetics Clinic, National Research Centre, Cairo, Egypt.

Subjects and methods

This single-center 7-year retrospective study was carried out from June 2014 till June 2021. Following the guidelines of the Medical Ethics Committee of the National Research Centre, the study was carried out after obtaining informed consents from the patients or their guardians. Records of patients diagnosed with syndromes associated with absence of

teeth were retrieved from the medical records of the outpatient clinic of Oro-dental Genetic Department, National Research Centre, Cairo, Egypt. Data regarding patient features, symptoms, and oral, radiographic, and laboratory findings were extracted from the patients' files and reviewed. We excluded syndromes with less than four patients out of the frequent category.

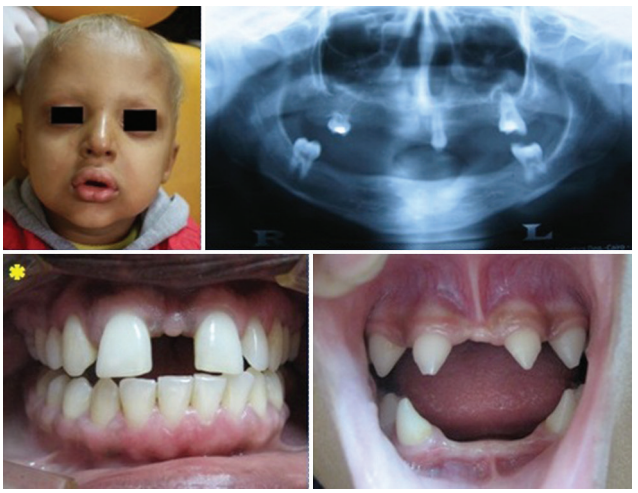
Results

A total of 53 patients were diagnosed with syndromic absence of teeth. The diagnosis of all patients was based mainly on both clinical and radiographic features, whereas laboratory investigations and molecular studies were done when needed. After studying the patients' records, it was evident that the most frequent genetic disorder associated with missing teeth is ectodermal dysplasia (13 patients, OMIM# 305100, 224900), followed by Ellis-van Creveld syndrome (seven patients, OMIM# 225500), and Papillon–Lefèvre syndrome (seven patients, OMIM# 2450000), then cleidocranial dysplasia (six patients, OMIM# 119600), congenital insensitivity to pain with anhidrosis (CIPA) (five patients, OMIM# 2568000), pycnodysostosis (four patients, OMIM# 265800), and hypophosphatasia (four patients, OMIM# 241520). Other syndromes were found to be associated with missing teeth; however, they were less frequent, like GAPO syndrome (two patients, OMIM# 230740), oro-facio-digital syndrome type I (two patients, OMIM# 311200), Hallerman–Streiff syndrome (one patient, OMIM#), focal dermal hypoplasia (one patient, OMIM#), and Rapp-Hodgkin syndrome (one patient, OMIM# 129400). Accordingly, 46 patients were included as frequent genetic disorders associated with missing teeth.

Ectodermal dysplasia (OMIM# 305100, 224900,129500, 614941, 129490)

A total of 13 patients with ectodermal dysplasia from eight families were included in this study. Nine of them showed X-linked mode of inheritance, whereas four showed autosomal recessive one. Classical features of ectodermal dysplasia were found, including oligodontia/hypodontia, malformed, peg-shaped, widely spaced teeth, lack of normal alveolar ridge development, loss of occlusal vertical dimension, prominent lips, sparse hair (hypotrichosis), hypohidrosis or anhidrosis, onychodysplasia, and dry skin. In the X-linked mode of inheritance, the mothers (carriers) showed partial manifestations of the disease ranging from peg shaped to total missing lateral incisors (Fig. 1).

Figure 1



Clinical and radiographic features of ectodermal dysplasia (carrier mother).

Ellis-van Creveld syndrome or chondroectodermal dysplasia (OMIM# 225500)

Seven Ellis-van Creveld patients from five families were included in this study. Autosomal recessive inheritance was observed in all patients. The main features were observed including skeletal dysplasia and postaxial polydactyly. The pathognomonic oral manifestations were recorded in most of the studied patients in the form of multiple labial frena, notched upper lip, hypodontia (permanent incisors agenesis), bilateral partial alveolar clefts at lower lateral incisor region, median fissure of the tongue, and bifid tip of the tongue. Other oral findings were also observed like abnormally shaped teeth, supernumerary teeth, and taurodontism (Fig. 2).

Papillon–Lefèvre syndrome (OMIM# 2450000)

Seven patients with Papillon–Lefèvre syndrome from six families were included in the study. Manifestations of the disease started in all patients at a young age, as early as 3.5 years old. Cutaneous lesions varied between red psoriatic scaly patches, cracking, and deep fissuring on the palms and soles. All patients showed normal dates of eruption of both deciduous and permanent dentition with normal form and structure. Simultaneously, or sometimes, following the cutaneous lesions, periodontal tissues displayed severe inflammation with deep pocketing and alveolar bone destruction causing loosening and subsequent loss of teeth. Panoramic radiographs of all patients revealed severe and generalized alveolar bone loss (Fig. 3).

Cleidocranial dysplasia (OMIM# 119600)

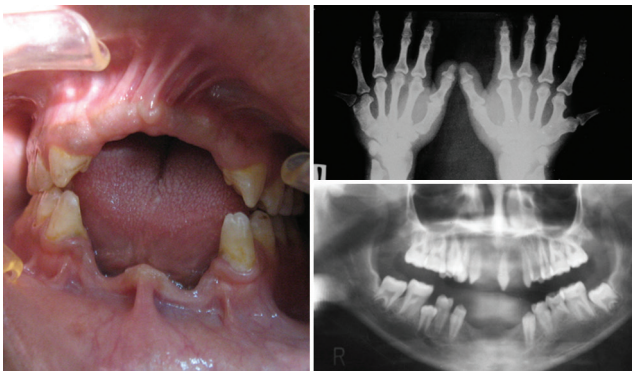
Six patients with cleidocranial dysplasia from four families were included in the study. All patients showed autosomal dominant inheritance. Clinically, the patients had a characteristic face, open fontanelle,

frontal bossing, and their clavicles showed a condition that ranged from hypoplasia to aplasia. The observed oro-dental manifestations were retained deciduous teeth, failure of permanent teeth to erupt (pseudoanodontia), mandibular prognathism, and subsequent malocclusion. The panoramic radiographs revealed the impaction of permanent successors and the presence of supernumerary teeth (Fig. 4).

Congenital insensitivity to pain with anhidrosis (OMIM# 2568000)

Five patients with CIPA from four families were included in this study. Consanguinity was reported in all affected families denoting autosomal recessive inheritance. The observed characteristic features of CIPA were self-mutilating behavior in form of severe finger biting, self-teeth extraction, lacerations, and ulcerations of the oral mucosa spacially tongue and lips. The absence of reaction to noxious or painful stimuli and recurrent episodic fevers were also observed in all patients (Fig. 5).

Figure 2



Clinical and radiographic features of Ellis-van Creveld syndrome.

Hypophosphatasia (OMIM# 241520)

Four patients with hypophosphatasia from four different families were included in this study. Autosomal recessive (three patients) and X-linked (one patient) were the modes of inheritance found in our presented patients. Laboratory investigations revealed low alkaline phosphatase levels. Three patients manifested skeletal deformities and were diagnosed as the childhood type of the disease. In all patients, teeth erupted successfully; however, teeth were lost early. The dental findings reported in the four patients were premature loss or loose teeth, as well as either periodontitis or gingivitis (Fig. 6).

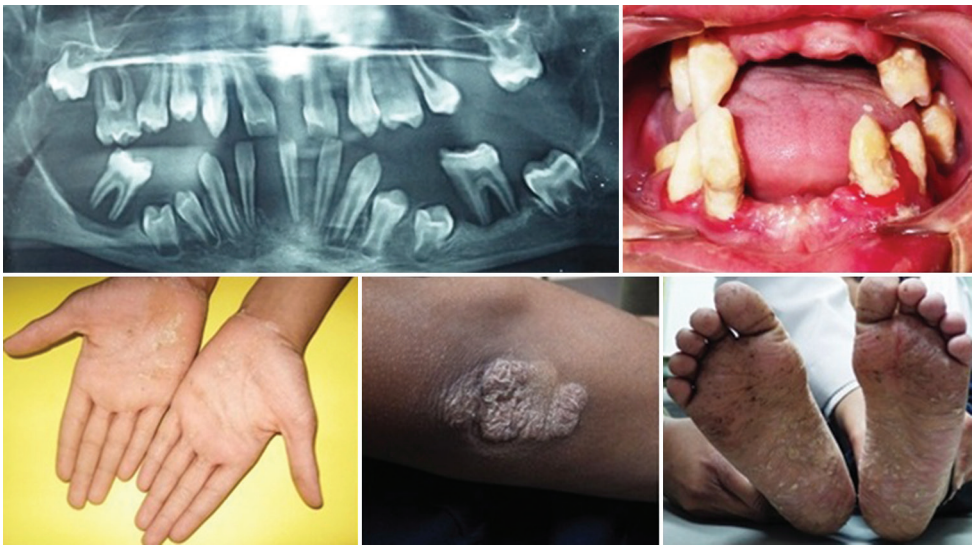
Pycnodysostosis (OMIM# 265800)

Four patients with pycnodysostosis from three families were reported. All patients showed consanguinity and recessive inheritance. Oro-dental examination revealed severe crowding in all patients which was due to the collapsed palate, maxillary hypoplasia, and obvious mandibular micrognathia. The crowding resulted in improper oral hygiene with subsequent caries and gingivitis. The panoramic radiographs showed absent mandibular angle and short rami, which are pathognomonic features of pycnodysostosis. Hypodontia was present in all four patients where the lower second premolars were the most affected teeth as they were missing in three out of the four patients (Fig. 7).

Classification

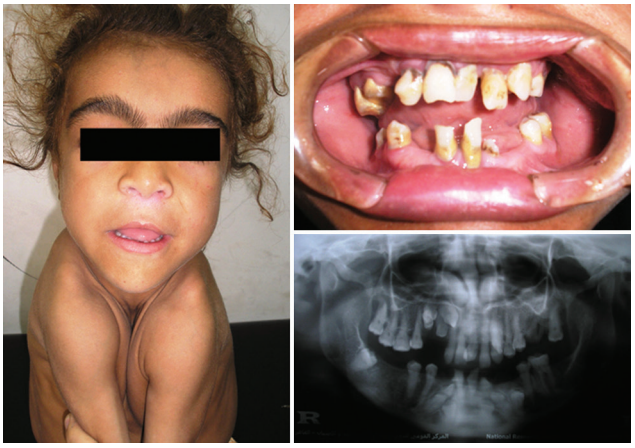
Based on further interpretation of the collected results, absence of teeth associated with genetic disorders was classified as shown in Fig. 8. According to the suggested classification, 24 patients were found

Figure 3



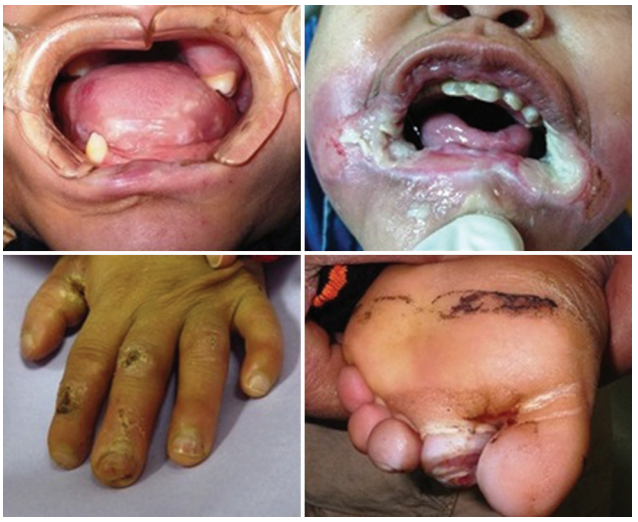
Clinical and radiographic features of Papillon–Lefevre syndrome.

Figure 4



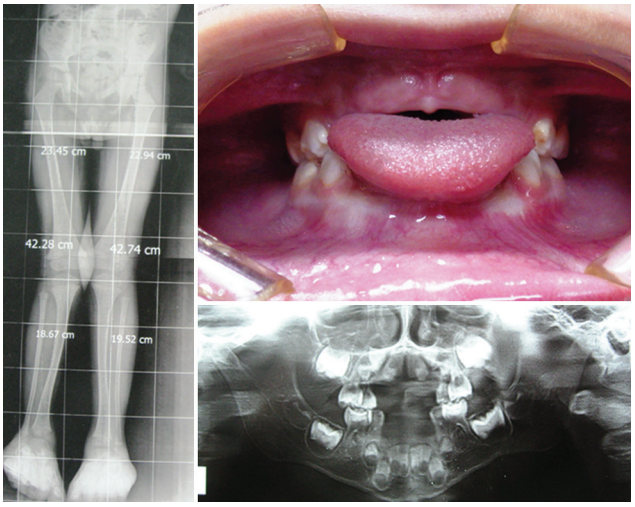
Clinical and radiographic features of cleidocranial.

Figure 5



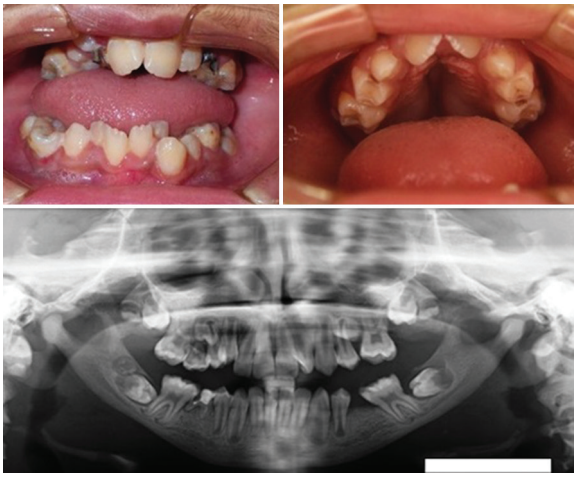
Clinical and radiographic features of congenital insensitivity to pain.

Figure 6



Clinical and radiographic features of hypophosphatasia.

Figure 7



Clinical and radiographic features of pycnodysostosis.

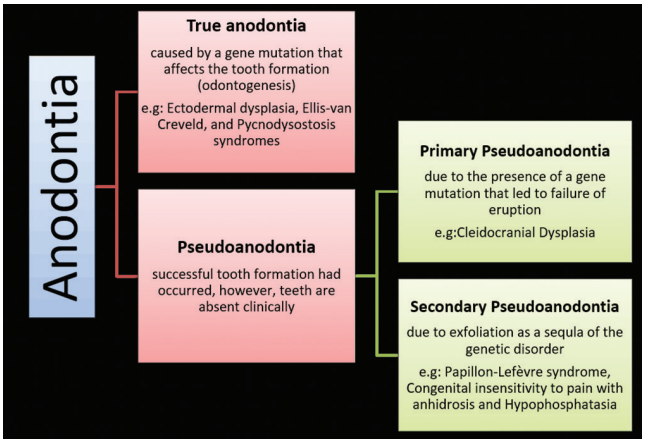
to have true anodontia, whereas 22 patients had pseudoanodontia: six with primary pseudoanodontia and 16 with secondary pseudoanodontia. The collected data showed that ectodermal dysplasia, followed by Ellis-van Creveld syndrome, was the most frequent disorders in the true anodontia group. Cleidocranial dysplasia was the most frequent disorder in the primary pseudoanodontia group, whereas Papillon–Lefèvre syndrome followed by CIPA and hypophosphatasia were the most frequent genetic disorders in the secondary pseudoanodontia group.

Discussion

Congenital absence of teeth either syndromic or nonsyndromic is considered one of the frequent dental abnormalities. More than 200 genetic disorders on the Online Mendelian Inheritance in Man (OMIM) have missing teeth as a phenotypic anomaly among their features (*https://www.omim.org/*). Owing to the high rate of consanguineous marriages in Egypt (35.5%), most of the diseases included in the study showed an autosomal recessive inheritance (Shawky *et al.*, 2011). On the contrary, most of the patients with ectodermal dysplasia showed X-linked inheritance, which is the most prevalent mode of inheritance of the disease (Fete *et al.*, 2014).

The term anodontia still has no constant definition. Anodontia is a Greek word that literally translates to 'no tooth': 'a' meaning 'no' and 'odous' meaning 'tooth' not teeth (Mosby's Dictionary of Medicine, 2013). Anodontia is commonly used to describe the complete agenesis of teeth (primary and permanent) in the oral cavity owing to developmental failure. However, it is also defined as an anomaly in which some or all of the teeth are congenitally missing (Polder *et al.*, 2004). On the contrary, the term partial anodontia is used

Figure 8



Suggested anodontia classification.

to describe agenesis of some of the teeth in the oral cavity (hypodontia: less than six teeth missing and oligodontia: more than six teeth missing) (Chhabra *et al.*, 2014; Rakhshan, 2015). Pseudoanodontia is a term that is commonly used to describe the clinical but not radiographic absence of teeth owing to failure of eruption (Haddock, 1939; Suri *et al.*, 2004). False anodontia is another term used to describe a condition where teeth have been exfoliated or extracted which would give the a false impression of anodontia (Rajendran, 2009). Similarly, when a tooth had been formed and erupted normally but was lost prematurely due to genetic or a systemic disorder, inexpert examiner could assume that it is congenitally missing, as it is absent clinically as well as radiographically (Mostafa *et al.*, 2017). Here, a classification is proposed for missing teeth based on the etiology of absence of teeth. Without doubt, unifying the terminology is significant when it comes to describing any congenital anomaly. Using different terms to describe a single condition or using a single term to describe different conditions is confusing (Allanson *et al.*, 2009).

Sometimes, the absence of teeth can be due to more than one cause such as in CIPA where the teeth are usually lost due to self-mutilation but some teeth are congenitally missing as well (Xue *et al.*, 2018). We have put the CIPA in this classification in the secondary pseudoanodontia group as absent teeth owing to self-teeth extraction are more common than tooth agenesis; however, it can be put in both the true anodontia and secondary anodontia groups.

Conclusion

In the Egyptian population, higher frequencies of true anodontia occur in cases of ectodermal dysplasia, Ellis-van Creveld, and pyknodysostosis. Primary pseudoanodontia has higher frequency in cases of cleidocranial dysostosis, whereas secondary pseudoanodontia has higher frequencies in cases of Papillon–Lefevre syndrome, CIPA, and hypophosphatasia. Awareness among dentists and clinicians regarding syndromes associated with missing teeth as well as the identification and classification of tooth anomalies helps in diagnosing genetic conditions and providing proper management. Therefore, we suggest that the term 'anodontia' should be used with proper specification of its type to describe the cause of absence of teeth.

Acknowledgements

The authors thank all of the members of Human Genetics and Genome Research Institute at The National Research Centre, especially the members of Clinical Genetics and Medical Molecular Genetics Departments, for their scientific assistance in this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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