(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 3 , Page No: 231-234
May-June 2023

IJMSCR

Ectrodactyly-Ectodermal Dysplasia Clefting Syndrome - A Rare Case

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Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

The trio of ectrodactyly-ectodermal dysplasia, facial clefting of the lip or palate or both, and some systemic signs make up the rare genetic condition known as ectrodactyly-ectodermal dysplasia clefting syndrome. Even though each of the three defects that make up the syndrome has been documented to occur independently, their convergence in a single person seems to be an incredibly unusual event, with an incidence of just 1.5/100 million people. It was first documented by Eckoldt and Martens in 1804 [2] and the term EEC syndrome was coined by Rudiger et al. in 1970 [1]. Ectrodactyly or split hand/split foot malformation (SHFM), by strict definition, is the congenital absence of central rays of limbs [3]. It was initially documented in 1770 among a tribe of Guiana Indians [3].

The most common disease caused by TP63 gene mutations is EEC syndrome, which serves as the model for all TP63 ectodermal dysplasia illnesses.(4,5).

Keywords:

Introduction

Ectrodactyly, ectodermal dysplasia, and clefting are the three defining characteristics of the EEC syndrome.

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome is an autosomal-dominant disorder with highly variable expression and reduced penetrance, resulting in a marked intrafamilial and interfamilial variability(6–8) . Clinical diagnosis and categorization are challenging because to the phenotypic spectrum and variable expressivity, and we are describing a sporadic case that called for strong clinical judgement.

A sizable variety of hereditary diseases collectively make up ectodermal dysplasia. It consists of initial flaws in the growth of two or more tissues originating from the embryonic ectoderm and manifests as hypoplastic teeth, dystrophic nails, dry skin, or sparse hair with sporadic lacrimal duct obstruction. Clefting may affect the lip and/or palate.

Hearing loss, lacrimal duct defect, genitourinary defect, delayed developmental milestones, malignant lymphoma, and occasional mental retardation are some other features associated with EEC syndrome [9].

Pathogenic mutations in the TP63 transcription factor have been identified as the molecular foundation of EEC syndrome, with 34 mutations documented so far (10). The majority of alterations involve heterozygous missense mutations in TP63's DNA-binding domain, a region crucial for direct interactions with DNA target sequences.

We report a sporadic case of this disorder in an 7-year-old male who had the classical split-hand/split-foot malformation of all 4 limbs and ectodermal

abnormalities with cleft palate and operated cleft lip and on the right side of the face.

Case report :

A 7-year-old male patient came to the paediatrics department with the main complaint of being unable to eat solid meals and having speech impediments since age 5. He also expressed concern over limb abnormalities.

Past medical history revealed that the patient had a cleft lip and palate on the right side of the face at the time of birth which was operated at the age of 6 months for cleft lip. He also gave history of decreased sweating. The older two of the patient's three siblings were unaffected; the patient was the youngest. No resembling family history was discovered. The patient was a nonconsanguineous marriage's offspring.

His fine, light-pigmented, sparse hair, dry, gritty skin, prominent occiput, low nasal bridge, broad nose, and large ears were all observed during the physical examination. Ectrodactyly was evident in both the both upper and lower limbs, with both the 2nd and 3rd toes missing.

The intraoral examination revealed oligodontia, with only teeth 9, 11, 16, 17, and 18 present. The hand and foot's radiographic scan identified a median cleft with varying degrees of aplasia/hypoplasia suggestive of ectrodactyly. The hand displayed syndadactyly of the first and second metacarpals together with aplasia of the second and hypoplasia of the third phalange. The foot radiograph further exhibited syndactyly of the first and second metatarsals as well as with aplasia of the second and hypoplasia of the third phalanges.

The child was suspected to be a case of ectrodactyly-ectodermal dysplasia-cleft (EEC) syndrome based on the history, clinical characteristics, and radiographic assessment. Investigations include complete blood counts that are indicative of an normal hematological picture. Imaging tests include X-rays of the hands, feet, chest, and abdomen. Furthermore, 2D echo imaging was normal. Additionally, otoacoustic emission observed was also normal. A whole genome sequencing was sent, and the authors proved a TP63 exon 5 heterozygosity defect.

Cleft palate surgery Palate is planned to enhance articulation and chewing of food. For a higher quality of life, the youngster is also receiving ongoing occupational therapy.

Discussion :

The phenotypic variability of the EEC syndrome and the existence of sporadic as well as familial cases have raised the question of genetic heterogeneity in this condition

Mutations in transcription factor p63 are associated with developmental disorders that manifest defects in stratified epithelia including the epidermis. The underlying cellular and molecular mechanism is however not yet understood. Differentiation defects of EEC iPSCs caused by p63 mutations occurred during the specification switch from the simple epithelium to the basal-stratified epithelial fate.

The transcription factor p63 is a key regulator in development of stratified epithelia in many organs (11–13). Deletion of p63 in mice results in striking developmental defects or even complete absence of stratified epithelia in organs such as the epidermis (12–15). In humans, heterozygous mutations in TP63 encoding the p63 protein give rise to several autosomal dominant developmental disorders (16). These disorders manifest defects in tissues and organs where stratified epithelia are present, and their phenotypes resemble those in p63 knockout mice (12,1 3), although in milder forms. One of these disorders is ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC) syndrome that is associated with mutations located in the p63 DNAbinding domain (17)

EEC patients exhibit all of the characteristic phenotypes of p63 mutation-associated diseases, namely, defects in the epidermis and epidermal-related appendages, limb malformation, and orofacial clefting.

It has been established that p63 plays a pivotal role in epidermal keratinocytes (KCs) and orchestrates essential cellular programs, including stem cell maintenance and proliferation, differentiation, and adhesion (18–20). . The cloning and identification of p63 as the causative gene for the EEC syndrome has allowed an objective molecular diagnosis and provides a basis to explore the pathogenesis of the ocular phenotype of EEC syndrome which was taken as a diagnostic test by us detected p63 mutation in whole exome genome.

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There are two clinical forms in which EEC syndrome may exist: one with cleft lip with or without cleft palate and the other with cleft palate alone [21]. In this case, the patient was born with both cleft lip and cleft palate. This disorder has been attributed to mutations in a gene encoding p63 [22]

The ectodermal dysplasia comprises dry or eczematous skin, sparse hair on the scalp, eyebrows and eyelashes, nail dystrophy and hypodontia with 'peg-shaped' teeth (Fig. 1). Absence, or more commonly a reduced number of sweat, sebaceous and salivary glands may occur in some affected individuals. Additional clinical manifestations include syndactyly (fusion of digits), mammary gland ⁄nipple hypoplasia, conductive or sensorineural hearing loss, and urogenital or lacrimal duct abnormalities(23-25). All TP63-associated disorders have clinical features that overlap with EEC syndrome, although several distinct scharacteristics may help distinguish them. Ankyloblepharon filiforme (partial eyelid fusion) and skin erosions are typical features seen in AEC syndrome,(26) whereas mammary gland ⁄nipple hypoplasia, an absence of clefting and increased skin freckling are common features of ADULT syndrome.(27) Rapp–Hodgkin syndrome is typically similar to AEC syndrome, although there is usually an absence of ankyloblepharon and a characteristic facies with mid-facial hypoplasia and microstomia.(28,29) Individuals with LMS have similar limb defects to those seen in EEC syndrome, including absence or severe hypoplasia of digits and fusion ⁄separation defects such as syndactyly. However, the additional clinical features of LMS comprise mammary gland ⁄nipple hypoplasia, cleft palate only and limited or no skin or hair abnormalities.(30)

Conclusion :

Simple features like syndactlyly and physical examination should raise eyebrows and suspect ectodermal syndromes.

Early diagnosis and management of clinical manifestations associated with EEC syndrome requires a multipronged approach by a team consisting of physicians from several clinical modalities to provide comprehensive medical care. A sympathetic, rationale, and multidisciplinary approach is necessary to improve the physical, psychological, and social integration of such patient.

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