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Case Report

Ectrodactyly-ectodermal dysplasia clefting syndrome (EEC syndrome)

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ARTICLE INFO

Article history:

Received 5 June 2014

Accepted 5 August 2014

Available online 27 August 2014

Keywords:

EEC syndrome

Ectodermal dysplasia

Ectrodactyly

SHFM

ABSTRACT

Ectrodactyly-ectodermal dysplasia- clefting syndrome (also k/a. split hand- split foot malformation <SHFM>/split hand-split foot ectodermal dysplasia- cleft syndrome/ectodermal dysplasia cleft lip/cleft palate syndrome) a rare form of ectodermal dysplasia, is an autosomal dominant disorder inherited as a genetic trait and characterized by a triad of (i) ectrodactyly, (ii) ectodermal dysplasia and, (iii) & facial clefts.

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1. Introduction

Ectodermal dysplasia is not a single disorder but a group of syndromes deriving from ectodermal structures such as skin, hair, nail and teeth. “Thurman” in 1848 published a first case report of dysplasia but the term “ectodermal dysplasia” was coined by “Weech” in 1929 and suggested 3 features (1) tissues affected are ectodermal in origin, (2) the defects are developmental anomalies, (3) and the hereditary tendencies are strongly developed.¹ More than 170 different syndromes have

been identified. Despite some of the syndromes having different genetic causes, the symptoms are sometimes similar. The most common syndromes within this group are hypohidrotic and hidrotic ectodermal dysplasias. Several ectodermal dysplasia syndromes may manifest with mid-facial defects, mainly cleft lip and palate. Rudiger et al and Freire – Mai in 1970 reported a clinical condition called EEC syndrome. The two forms of EEC are found (a) cleft lip with or without cleft palate and (b) with cleft palate alone.² Both are inherited with variable expressivity i.e. partial penetrance in the former and complete penetrance in the latter.^{3,4} More than

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300 cases have been reported in the literature, affects both males and females but the prevalence and incidence is not known.⁵ Here is a case of EEC syndrome in a 5 year old male patient.

2. Case report

A 5 year old male patient reported to the department of Paedodontics and preventive dentistry in CPGIDSH, Lucknow, with a chief complaint of multiple decayed teeth. The family history was non-contributory and gave no history of consanguineous marriage between parents.

On general physical examination, the child was moderately built, had ectrodactyly of hands and feet showing lobster claw-like deformity, (also k/a split – hand and split – foot malformation SHFM) with difficulty in walking and holding with hands, presence of hypernasal voice and dry skin. [Figs. 1 and 2](#). The parents also reported about reduced sweating, intolerance to heat, intermittent fevers and reduced amount of tears while crying.

Extraoral examination showed thin and sparse hair on the scalp that was lighter in color, frontal bossing, depressed nasal bridge, sparse eyelashes on the lower eyelids, dry and warm facial skin, and a surgical scar on the upper lip that was operated. [Fig. 3](#).

Intraorally there were multiple grossly decayed and hypoplastic teeth, pointed crowns of canines, absence of maxillary primary lateral incisors and a repaired cleft palate. [Fig. 4](#).

2.1. P/D

Considering the clinical signs and symptoms a provisional diagnosis of Ectrodactyly-ectodermal dysplasia clefting syndrome or EEC syndrome was made.

3. Investigations performed

- (1) Radiographs
 - (a) Orthopantomogram (OPG) [Fig. 5\(a\)](#)
 - (b) A- P view of hands. [Fig. 5\(b\)](#)
 - (c) A- P views of feet. [Fig. 5\(c\)](#)
- (2) Sweat pore count [Table 1](#)
- (3) Schirmer test [Table 2](#)

3.1. D/D

1. Rapp – Hodgkin syndrome.
2. Hay–Wells syndrome (AEC syndrome)
3. Adult syndrome
4. Non- syndromic split- hand and split foot malformation (SHFM)

4. Discussion

EEC syndrome a genetic developmental disorder distinctly featuring ectrodactyly, ectodermal dysplasia and facial clefts

Fig. 1 – Patient with ectrodactyly of hands and feet.

may also be noticed with characteristics like recurrent urinary tract infections, vesicoureteral reflux, photobia, anomalies of kidney, hearing loss and speech defects.⁶ During reproduction each parent contributes 23 chromosomes: 22 autosomal and one sex chromosome. EEC is autosomal which means that there is an abnormal gene on one of the autosomal (non-sex) chromosomes from either parent. The gene is dominant, only one parent must contribute the abnormal gene for the child to inherit the disease and the contributing parent will usually have the disease, due to the expression of the dominant gene in the parent. Although, it is an autosomal dominant, some cases occur sporadically without previous history of the disorder (i.e. new-mutations.) The present case

Fig. 2 – Ectrodactyly of hands and feet showing lobster – claw like deformity.

could be a sporadic one as there was no previous history of the disorder in the family. Evaluating the etiology, chromosome 19, within the region of D19S894 and D19S416 has been postulated as the locus for the abnormalities observed in EEC syndrome. This is supported by reports regarding an association of cleft lip +/-palate on locus 19q suggesting that EEC could be an allelic variant.⁷ Nearly 90% cases are caused by mutations of TP63 gene. TP63 gene contains instructions for synthesizing a protein that is essential for the proper development of the limbs and structures derived from the ectoderm. Mutations of this gene lead to a reduction of functional levels of normally functioning P63 protein which interferes the proper development of these structures. In rare cases, individuals with EEC syndrome carry chromosomal disruptions on the long arm of chromosomes 7 (7q 1.2 – q.21-3) So, EEC caused by mutation in TP63 gene is k/a EEC syndrome type 3 (EEC3), whereas if caused by chromosomal abnormalities of chromosome 7 is k/a EEC syndrome type 1 (EEC 1). And a disorder designated as EEC syndrome type 2 no longer exists. Some cases of EEC may be due to Gonal Mosaicism or Germ-line Mosaicism, a condition in which some of the reproductive cells (germ cells) carry the mutations, while others contain a normal cell line (Mosaicism).⁸ Ectrodactyly involves the absence of one or more central digits of the hand or foot giving rise to claw-like appearance. Ectodermal dysplasia describes abnormalities of structures derived from the embryonic ectoderm and affects epidermis, mammary, pituitary

Fig. 3 – Frontal view of patient.

and sweat glands, enamel, nail, lens and ears. In addition to ectodermal, neuroectodermal and mesectodermal derivatives are often found. According to some authors, cleft lip ± cleft palate is used as a marker to distinguish EEC from other syndromes like ankyloblepharon. While others include cleft palate only (CPO) in conjunction with ectrodactyly and ectodermal dysplasia to be sufficient for the diagnosis of EEC. The clefting often causes hypernasal speech & language deficits which may be the result of impaired language acquisition due to hearing loss. Breathy voice may be noticed because the vocal folds may not be hydrated well due to reduced number of sweat glands and a complete seal between the folds is not accomplished leading to air escapement.^{9,10} EEC affected patients cannot perspire due to decreased/absence of sweat glands. Without normal sweat production the body cannot

Fig. 4 – Intraoral view.

Fig. 5 – (a) OPG, (b) A-P view of hands, (c) A-P view of feet.

regulate temperature properly leading to overheating and hyperthermia which could result in permanent brain damage or even death.⁸

Some of the disorders may be similar to EEC syndrome and a comparison may be useful for differential diagnosis. Rapp Hodgkin Syndrome is a form of ectodermal dysplasia involving skin, hair, nails, teeth and sweat glands with cleft lip/cleft palate. The common features are autosomal dominant, caused by mutation of TP63 gene, hypohidrosis, sparse

Table 1 – Sweat pore count.

	Number/cm ²
Golu	6
Normal value	12–14
Bold value is less than normal, indicating decreased sweating (hypohidrosis).	

Table 2 – Schirmer test.

Name of patient	Result	Values
Golu	9 mm	Normal – ≥ 15 mm wetting of the paper after 5 min Mild – 14–9 mm wetting of the paper after 5 min Moderate – 8–4 mm wetting of the paper after 5 min Severe – < 4 mm wetting of the paper after 5 min

Bold value is less than normal indicating decreased tear production.

hair and hypodontia. But absence of ectrodactyly differentiates it from EEC syndrome.¹¹ Hay–Wells syndrome (AEC syndrome/Ankyloblepharon ectodermal dysplasia – clefting syndrome) an autosomal dominant disorder caused by mutation of TP63 gene has varying forms of expression with features like congenital abnormalities of the skin, hair, teeth, nails and sweat glands. Growth of bands of fibrous tissue which fuse together between the upper and lower eyelids k/a Ankyloblepharon filiforme adnatum is the differentiating feature from EEC syndrome.¹² Adult syndrome (Acro – dermato – ungual – lacrimal tooth syndrome) an autosomal dominant disorder caused by mutation in TP63 gene is characterized by excessive freckling, abnormal teeth, tearduct obstruction, hypohidrosis, hand and foot abnormalities, hypoplastic nipples and xerosis. Lack of facial clefts and ankyloblepharon differentiates from EEC syndrome.¹³ Non-syndromic split-hand/split-foot malformations (SHFM) also k/a ectrodactyly is a congenital limb malformation characterized by a deep median cleft of the hand and foot due to the absence of central digits and may occur as an isolated entity. Its non-syndromic characteristic differentiates from EEC syndrome. Diagnosis of the present case was based on identification of characteristic signs and symptoms i.e. the presence of a triad of ectrodactyly, ectodermal dysplasia and cleft lip & cleft palate, a detailed patient history, a thorough clinical evaluation and some tests viz. radiographs, sweat pore count and Schirmer test. OPG revealed hypodontia due to the congenital absence of primary maxillary lateral incisors and tooth buds of permanent teeth except first permanent molars, right maxillary central incisor and right maxillary canine, grossly decayed teeth and pointed crowns of canines. A-P view of hands and feet showed a claw-like deformity due to ectrodactyly. There is median cleft in the hands and feet due to the absence of central rays giving rise to lobster. Sweat pore count was reduced to 6 number/cm² and indicative of hypohidrosis. Schirmer test determined the amount of tear production and showed less than normal values i.e. 9 mm wetting of the paper after 5 min and indicative of less tear production.

5. Other tests may be used to confirm diagnosis of EEC

1 Molecular genetic testing to detect mutation in the TP63 gene or chromosomal abnormalities.

- 2 Molecular examination of skin tissue.
- 3 A kidney ultrasound.
- 4 Ophthalmological examination.
- 5 X-rays of the limbs.
- 6 Routine fetal diagnostic tests:
 - (a) Prenatal fetal ultrasonography.
 - (b) Molecular genetic testing on cells obtained from amniotic fluid.
 - (c) Molecular genetic testing on chorionic villi also k/a chorionic villi sampling.

Management needs a systematic and comprehensive approach, is directed towards the specific signs and symptoms, require a team of specialists including pediatrician, pediatric surgeon, plastic surgeon, orthopedic surgeon, orthopedists, dentist, speech therapist and other health care professionals.

6. Conclusion

Early diagnosis would help parents to get accurate counseling. Genetic counseling may benefit the affected individuals and their families. Future genetic research should be emphasized to identify the loci contributing to EEC syndrome, to differentiate it from other syndromes and to help in diagnosis and treatment plan.

Conflicts of interest

All authors have none to declare.

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