Case Report

A Sporadic Case of Ectrodactyly, Ectodermal Dysplasia, Clefting Syndrome in a 5 Years Old Male Child

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Abstract

Background: EEC syndrome comprises ectrodactyly, ectodermal dysplasia and facial clefting.
Case characteristics: A 5 years old male child presenteds with ankle and toe pain. He had absence of 2nd toes in feet, had cleft lip, cleft palate, conductive hearing loss and nasolacrimal duct blockage.
Intervention: Skin biopsy suggested ectodermal dysplasia thus completing the triad of EEC syndrome. Shoe modification with toe filler was prescribed.
Outcome: Ankle pain was relieved. Parents became more confident after diagnosis and prognosis were explained.
Message: A proper diagnosis helps in searching for other hidden problems as well as in confident management of the disease.

Key words: **Ectodermal dysplasia, ectrodactyly, ectodermal dysplasia, clefting syndrome, split hand–split foot malformation, transcription factor tp63.**

Introduction:

Ectodermal dysplasia (ED) is a group of heritable disorders where involvement could be seen in more than one ectodermal derivatives including the hair, teeth, nails, skin and exocrine glands. More than 170 distinctive syndromes exist with all possible modes of inheritance pattern. The most common syndromes among them are hypohidrotic ED and hidrotic ED. Several ED syndromes may coexist with midfacial defects, mainly cleft lip and palate[1]. Ectrodactyly is another feature which may be seen in association with ED.

Ectrodactyly or split hand–split foot malformation (SHFM) involves the absence of one or more central digits of the hand or foot and may even have syndactyly of the remaining digits[2]. Though the unique mix of Ectrodactyly, ectodermal dysplasia and cleft lip or palate was first described by Cockayne in 1936 but the acronym EEC syndrome was first used by Rudiger *et al* in 1970[3]. Most cases of EEC syndrome demonstrate mutations of the tp63 gene and are either new (spontaneous) mutations or are inherited as autosomal dominant disorders.

It is interesting to note at this point that there are at least four other syndromes caused by mutations of the tp63 gene including ankyloblepheron-ED-cleft (AEC)/Hay-Wells syndrome, Rapp-Hodgkin syndrome (RHS), limb-mammary syndrome (LMS), and acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome. In addition, tp63 mutations have also been associated with several non-syndromic split hand/foot malformations and non-syndromic cleft lip/palate[4].

The transcription factor tp63 have such a close association with EEC syndrome because of its regulatory action on ectodermal, orofacial and limb development. This fact was established in 1999 by the generation of tp63 knockout mice who clearly lacked all squamous epithelia and their derivatives including hair, whiskers, teeth, as well as the mammary, lacrimal, and salivary glands. Also those hapless mice's had severe limb truncations characterised by complete absence of the phalanges plus carpals and variable defects of ulnae plus radiae[5].

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Case Report:

A 5-year-old male child, born from healthy non-consanguineous parents, was referred to our department for bilateral persistent ankle pain suspected to be a case of dislocation of talotibial and talocalcaneal joint (Fig1) after a trivial left ankle sprain. But during patient observation, his cleft lip and feet deformity aroused our attention.

According to the parents, he did not have any medical problem and was not on any medication. No other family member had similar features. He was delivered by caesarean section and had a birth weight of 3 kg. At birth the child was observed to have multiple congenital anomalies namely bilateral complete cleft lip, cleft palate (Fig2) and absence of 2nd toes in both feet along with fusion of 3rd and 4th toes (Fig3). Repair of bilateral cleft lip was done at the age of 3 months and palatoplasty operation done at 10 months. Next phase of lip and palatal repair, i.e., refashioning of central lip defect and augmentation of pre-maxilla is pending. Till then the patient is using maxillary bite plate. His personal history showed that he takes mixed diet and had received up to date immunisation.

As the child grew few other deformities became apparent. Parents noticed squinting and watering of both eyes associated with itching. The child was diagnosed with alternate divergent squint (due to refractive error) and congenital dacrocystitis (due to bilateral nasolacrimal duct blockage). Eyes became straight with bilateral refractive correction of +1.5 Dsph while digital massaging and antibiotic eye drops were prescribed for the time being to combat the dacrocystitis component with future plan of bilateral dacrocystorhinostomy (DCR) operation for NLD blockage.

Another problem noticed by the parents were dental malocclusion and multiple caries involving mainly the upper row (Fig4). Treatment including temporary cemented maxillary bite plate and other phased procedures are going on from a private dental college. Hearing defect was also present but took somewhat more time to recognise in the child. Audiological evaluation (clinical examination plus audiogram and tympanogram) revealed adenoid hypertrophy and mild conductive hearing loss of 35-40 dB due to bilateral otitis media with effusion but intact tympanic membrane. Since the sensory neural reserve was found to be normal on BERA examination, management of the conductive loss is being tried with mucolytic and nasal decongestant.

As has been apparent on first presentation a diagnosis of ectrodactyly-ectodermal dysplasia-clefting syndrome was made based on the presence of split toes, dental malocclusion, cleft lip and cleft palate. Further clinical examination revealed a total nail dystrophy, characterised by a slow growth, yellowing and eroded distal part, white transverse ridges and thinning (Fig5). His skin appeared dry and ichthyosiform (Fig6); further, he complained of decreased sweating and heat intolerance, suggestive of hypohidrosis. Also the skin and hair appeared hypopigmented with sparse eyebrows (Fig7). Skin biopsy from forearm shows epidermis with hyperkeratosis and mild acanthosis. The sebaceous glands were absent in the dermis while the hair follicles and eccrine glands are found to be rudimentary. Overall the histopathology features were compatible with ectodermal dysplasia.

Physical examination of both feet showed ectrodactyly and syndactyly. X-ray of feet revealed the absence of some dactylic segments and the fusion of others (Fig8). An abdominal and genitourinary ultrasonography ruled out the possibility of other organ involvement. Chromosomal analysis revealed normal male chromosomal pattern of 46 XY but the specific test for tp63 mutation could not be arranged. Thyroid profile and serum cortisol level were within normal limits but oestradiol level (< 10 pg/ml) is slightly below normal (11-44 pg/ml). Also peripheral blood film and routine haematological examination could not detect any gross abnormality. The patient had a normal IQ and intellectual development albeit somewhat hyperkinetic. No other family members were known to be affected by this disease. Based on all of the above findings, a diagnosis of sporadic ectrodactyly-ectodermal dysplasia-clefting syndrome was confirmed in our case.

Management:

Orthopaedic and rehabilitation evaluation ruled out any significant dislocation of talotibial and talocalcaneal joint and modified shoe was provided to the patient. The shoe modifications include soft heel, firm heel counter and soft ‘filler’ in between 1st and 3rd toes bilaterally. Also a course of NSAID (ibuprofen) and contrast bath was given in the initial acute phase of ankle pain and when the pain subsided he was encouraged to do bilateral ankle dorsiflexor, plantar flexor, evertor and invertor progressive resistive strengthening exercises. The patient remained asymptomatic during the entire follow-up period of 6 months.

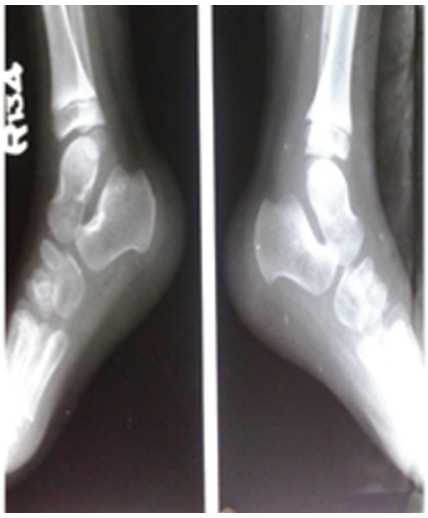

Fig 1- X-ray Showing Bilateral Dislocation of Talo-tibial and Talo-calcaneal Joint

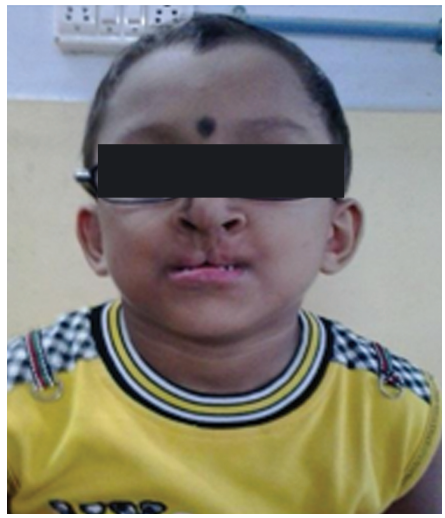

Fig 2- Five -Year Old Male Child with Cleft Lip and Sparse Hair

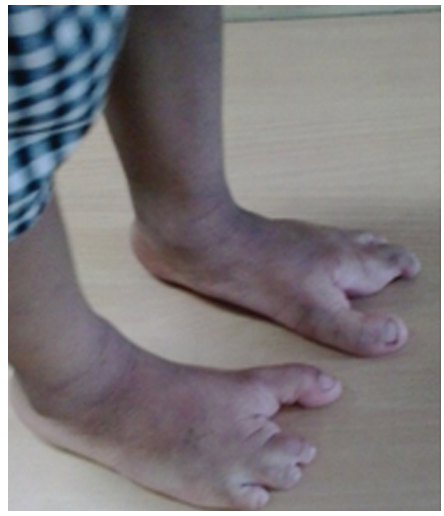

Fig 3- Absence of 2nd Toes in Both Feet with Deep 'v' cleft and Fusion of 3rd and 4th Toes

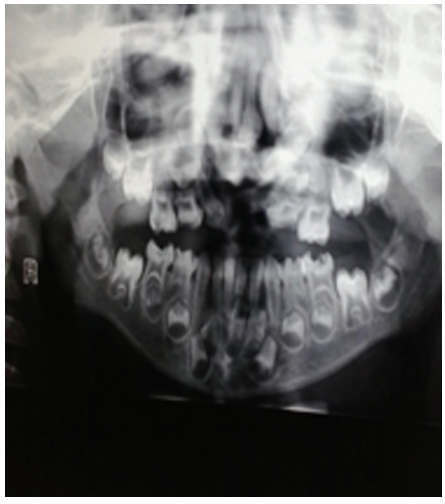

Fig 4- Orthopantomogram Showing Multiple Caries and Malformed Dental Eruptions Mostly on the Upper Row

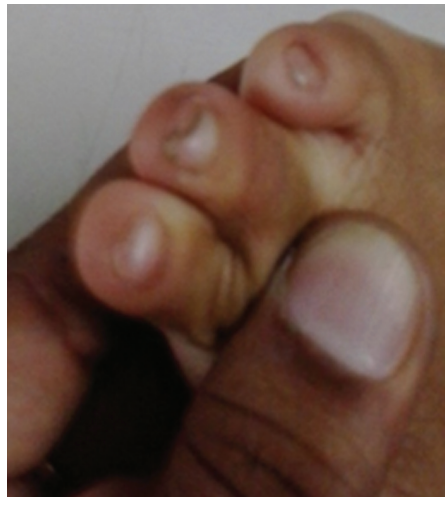

Fig 5- Nail Dystrophy, Characterised By Eroded Distal Part, White Transverse Ridges and Thinning

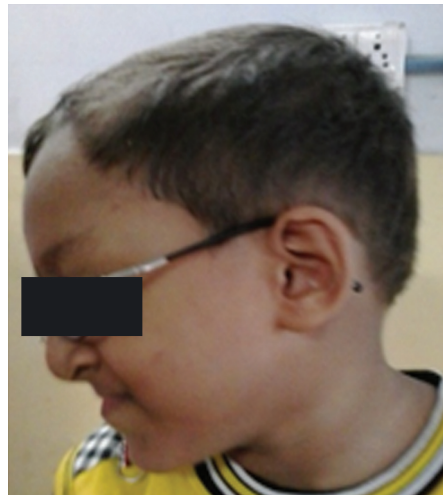

Fig 6- Dry and Ichthyosiform Skin along with Hypopigmentation of Hair

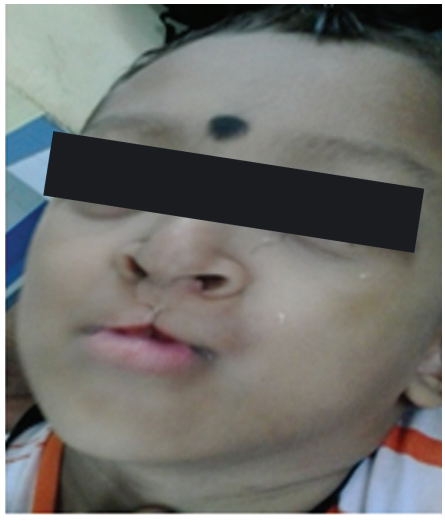

Fig 7- Hypopigmented and Sparse Eyebrows

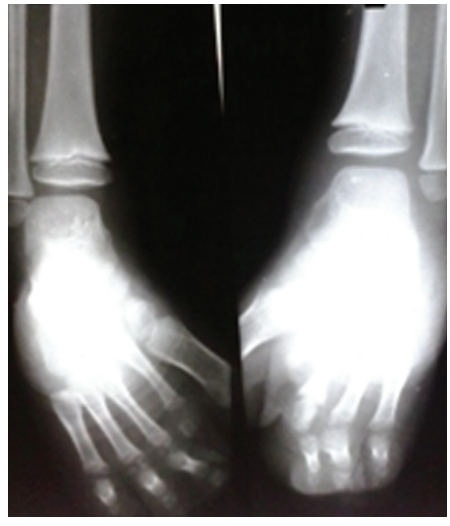

Fig 8- X ray Revealing Absence of Some Dactylic Segments and the Fusion of Others

Since the management of EEC syndrome is multidisciplinary, the parents were guided to prioritise dental, eye and especially ENT treatment. Keeping his heat intolerance and hypohidrosis in view, he was suggested to stay in cold and moist environment only and avoid excessive and strenuous physical activities. Extensive investigations ruled out any other serious concerns like endocrinal abnormality or genitourinary problems at present. The parents are now more confident in managing their child's disease as they have the diagnosis and prognosis explained to them.

Discussion:

Thurnam published the first report of a patient with ED in 1848, but the term "ectodermal dysplasia" was officially coined by Weech in 1929 [6,7].The condition occurs in approximately 1 in every 100,000 live births[8]. The first classification system for EDs was devised by Pinheiro and Freire-Maia in 1982[9]. Pure ectodermal dysplasia is characterised by only ectodermal signs; but if it combines ectodermal signs and malformations, the terminology changes to ectodermal dysplasia malformation syndrome or an ED syndrome [10]. The present case belongs to ED syndrome category.

Likewise the individual frequency of ectrodactyly is reported to be 1.5 per 100,000 live births and that for cleft palate with or without cleft lip is 1 per 100,000 live births [11].The term ectrodactyly denotes congenital absence of all or part of one or more fingers or toes while syndactyly signifies fused or webbed fingers or toes[12]. In comparison a permanent deflection of one or more fingers is referred to as clinodactyly[13].

The occurrence of all three disorders in one, i.e., ectrodactyly, ED, and cleft lip/ palate is reported to be approximately 1.5 per 100 million[3]. More than 300 cases have been described in the literature[14]. EEC syndrome is a rare congenital syndrome with autosomal dominant inheritance and incomplete penetrance, characterised by a highly variable clinical expression[15,16]. Sporadic forms like in our case are very rare and generally the most severe[12].

EEC syndrome consists of ectrodactyly (E), ectodermal dysplasia (E) and cleft lip (C) with or without cleft palate[17]. The ectodermal component of ED can involve skin (hyperkeratosis, hypopigmentation and atrophy) hair (hypotrichosis and hypopigmentation), teeth (hypodontia, microdontia and enamel dysplasia), nails (dystrophic in most case) and exocrine glands (reduction or absence of sweat, sebaceous and salivary gland)[18]. In addition to the 3 cardinal features of the EEC syndrome, other manifestations are often reported like nasolacrimal duct anomalies, photophobia, corneal ulceration, urogenital malformations, mammary gland or nipple anomalies, choanal atresia, comedo or white sponge nevus, ear anomalies, conductive hearing loss, hypopituitarism and growth hormone deficiency[19].

The tp63 gene contains codes for synthesizing a protein that is necessary 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 p63 protein, which hampers the proper development of these structures. Investigators have determined that the tp63 gene is located on the long arm (q) of chromosome 3 (3q27)[20]. EEC syndrome caused by mutations of the tp63 gene located in chromosome 3 is sometimes referred to EEC syndrome type 3 (EEC3). But rarely when it is caused by chromosomal abnormalities of chromosome 7(7q11.2-q21.3) it is referred to as EEC syndrome type 1 (EEC1). A disorder formerly designated as EEC syndrome type 2 no longer exists[21].

Genetic counselling should be offered to affected families informing them that the risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy regardless of the sex of the resulting child. Due to germline mosaicism, unaffected parents of a child with EEC syndrome have a 4% risk of having another affected child[22].

Management is multidisciplinary and requires evaluation by orthopaedic, physical medicine and rehabilitation specialist, plastic and dental surgeons, ophthalmologists, dermatologists, and speech therapists. Prognosis is good with a near to normal life expectancy. Hypohidrosis (reduction/absence of sweat glands) presents the most life-threatening complication, as it can cause seizures and coma when inadequately managed[14].

For the sufferer his/her life revolves around the exceptional clinical variability of EEC syndrome even though the clinician may feel it is a rare disease to deserve attention. Hence, we have described this rare, symptomatic and sporadic case to confirm the unpredictable expressivity of EEC syndrome with a firm belief that a proper diagnosis helps in searching for other hidden problems as well as in confident management of the disease.

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