

EEC syndrome: A rare entity

Aftab Ahmed RANA ¹, Suresh CHANDRAN ¹, Joshua GEORGE ²

¹ Department of Paediatric and ² Department of Ophthalmology, RIPAS Hospital, Brunei Darussalam

ABSTRACT

Ectrodactyly, Ectodermal dysplasia and Cleft lip/palate (EEC) syndrome is a rare combination of multiple congenital anomalies. Although the anomalies are diverse, the underlying problem arise from early embryonic ectodermal tissue defects or insults. We report a case of a baby boy who was born at 33 weeks of gestation with EEC syndrome. He died five months later of aspiration pneumonia. The management requires a multidisciplinary approach and proper parental counseling which should include risk of recurrence in future pregnancies. Prenatal diagnosis is possible by antenatal ultrasound scan at 14-16 weeks of gestation.

Keywords: Cleft lip, cleft palate, ectodermal dysplasia, ectrodactyly

INTRODUCTION

The rare combination of ectrodactyly (lobster-claw deformity), ectodermal dysplasia and cleft lip with or without cleft palate comprises EEC syndrome, ¹ also referred to as 'Split hand-split foot-ectodermal dysplasia-cleft syndrome'. ² Abnormalities that characterise EEC syndrome include those ectodermal dysplasia, manifesting as hyperkeratosis, hypoplastic nipples, sparse thin and wiry hair and nail dysplasia; cleft lip and /or cleft palate, including maxillary hypoplasia and dental defects like missing or abnormal dentition, There may be abnormalities of the kidney and

eye (i.e. blephritis, dacryocystitis, blepharophthalmosis and absent punctae in lower eyelids), and occasionally, cognitive impairment and hearing loss. ² Fifty percent or more of those affected by this syndrome also have genitourinary anomalies. ³ Although the anomalies are diverse in EEC syndrome, the underlying problems arise from early embryonic ectodermal tissue defects or insults. It usually occurs as an autosomal-dominant trait and less commonly in a sporadic form. ^{2, 4} In this syndrome, any of the three cardinal manifestations may present with variable expressions. Genetics of EEC syndrome is complex and not completely known. ⁴ The exact prevalence of EEC syndrome is unknown. Affected individuals usually have normal intelligence and with appropriate and timely surgical interventions,

Correspondence author: Aftab Ahmed RANA
Department of Paediatric, RIPAS Hospital,
Bandar Seri Begawan BA 1710,
Brunei Darussalam
Tel+673 7125404 Fax: +673 2242690
E mail: draftabrana@hotmail.com

affected individuals can have normal life expectancy. We report a case of this rare syndrome in a premature baby boy in Brunei Darussalam.

CASE REPORT

A male infant was delivered at 33/40 weeks of gestation by normal vaginal delivery to a primigravida mother. He required bag and mask ventilation at birth and the Apgar score

was six and eight at one and five minutes respectively (Refer to supplementary text for APGAR score). He was stabilised and was immediately transferred to neonatal intensive care unit for further evaluation and management.

The mother, a 19-year-old housewife and the father, a 34-year-old military man, are second degree relatives. The father has two normal children from a previous mar-

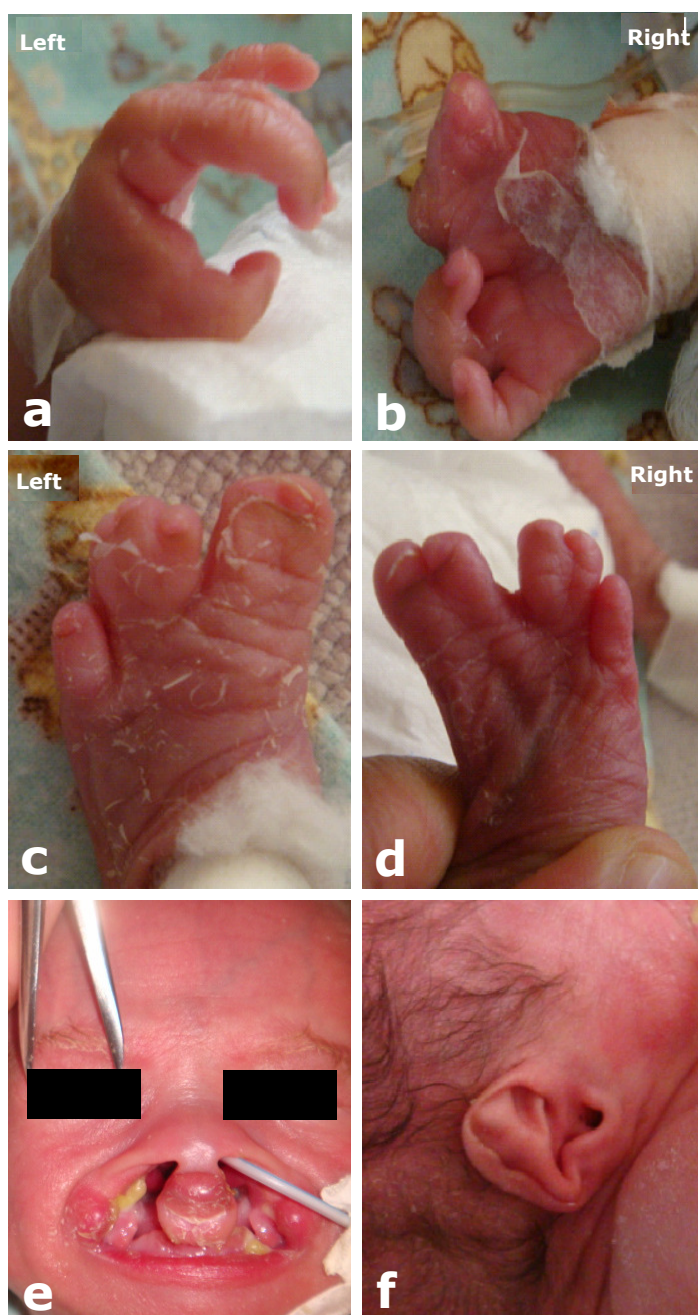


Fig 1: a and b) show ectrodactyly with absence of left index, right index and middle fingers, c and d) Polydactyly with complete syndactyly of the big and second toes, partial syndactyly of the third, fourth and fifth toes of the left foot and first and second toes and third and fourth toes with hypoplasia of the nails of the right foot, e) Cleft lip and palate, f) Low set malformed ears and g) Ambiguous genitalia with meconium seen at the urethral orifice.

riage. Both parents were found to be healthy without any medical co morbidities. During antenatal screening, the mother blood's was positive for Toxoplasma IgM antibody which was not treated until after the pregnancy. During the pregnancy, the mother had received regular antenatal care. She denied the use of any medications (traditional, prescribed or over the counter) during the pregnancy.

The baby was born with a weight of 660 grams and a head circumference of 26 cm indicating severe intrauterine growth retardation as both growth parameters were well below the 10th centile. Both his hands and feet had defects in the mid portion. Both hands showed ectrodactyly with absent index finger of the left hand and index and middle fingers of the right hand (Figures 1a and b). The left foot showed polydactyly with complete syndactyly of the 1st and 2nd toes, and incomplete syndactyly of the 3rd, 4th and 5th toes. The right foot showed partial syndactyly of the 1st and 2nd toes and the 3rd and 4th toes (Figures 1c and d). Both the hands and feet also showed varying degrees of hypoplasia of the nails (Figures 1c and d). Facial defects consisted of mid facial hypoplasia with complete bilateral cleft lip and palate (Figure 1e). The ears were low set and malformed with abnormal pinnae (Figure 1f). Both ear lobes were symmetrical but posteriorly rotated. There was generalised wrinkled, dry and scaly skin with hypopigmentation. Body hair was sparse and fine. He also had ambiguous genitalia (Figure 1g).

A skin biopsy reported findings shortened rete ridges of the epidermis and the dermis with hypoplasia of hair follicles and seba-

ceous glands. The sweat glands and the subcutaneous tissue appeared normal. The histopathological findings were consistent with a diagnosis of ectodermal dysplasia.

A detailed ophthalmological examination showed agenesis of lacrimal puncta, epiphora, blepharophimosis, palpebral fissure length of 45mm (normal 47-63mm), width of 6mm (normal 8-8.5mm), and lacrimal duct blockage. Genitourinary evaluations revealed small bilateral dysplastic kidneys, rectourethral fistula and ambiguous genitalia (labioscrotal fold and small phallus with hypospadiasis).

Toxoplasma IgM was negative and routine blood investigations that included full blood count and renal functions, revealed normal findings. Ultrasound scan of the head and echocardiography also revealed normal results. Chromosomal karyotyping was normal (46 XY).

The baby was maintaining oxygenation on air from the seventh day after birth and on full feeds by the fourteenth day. Ophthalmology examination at four week showed retinopathy of prematurity (stage III /zone II) in both eyes which required laser therapy. The baby died of aspiration pneumonia at five months.

DISCUSSION

EEC syndrome was first described by Cockayne in 1936.⁵ Although the association of ectrodactyly and cleft lip had been noted, it was not until 1970 that Rudiger *et al.* appreciated that some patients also had features of ectodermal dysplasia and named the disorder as EEC syndrome.¹ This condition is auto-

somal dominant with low penetrance and variable expressivity although sporadic and autosomal recessive traits have been reported.^{2, 4} There can be great variability in the clinical manifestations of EEC syndrome in affected members of the same family.^{6, 7}

The underlying genetics of EEC syndrome is complex and still not completely known. Chromosome 19 has been postulated as the locus for the abnormalities found in EEC syndrome. This is supported by reports on the association of cleft lip with or without cleft palate on locus 19q, which suggests that EEC could be an allelic variant.⁸ Transcription factor p63 is a key regulator of ectodermal, orofacial, and limb development. Mutations in the p63 gene can cause syndromes of ectodermal dysplasia, ectrodactyly, and orofacial clefting. Interestingly, the p63 gene is a homologue of the tumour suppressor gene p53, though this is not indicative that patients with EEC are more likely to develop tumours. More recently, the p63 gene has been targeted in numerous studies.⁹⁻¹² It is possible that there is more than one genetic locus involved in the actual manifestation of this syndrome in any single individual.¹² Other proposed sections of the involved chromosome include 3q27^{9, 11, 12} and 7q11.2-q21.3.^{8, 12}

Prenatal diagnosis can be made by transvaginal ultrasonography performed at 14 to 16 weeks of gestation demonstrating a bilateral cleft lip and/or palate with lobster-claw hand deformities.^{13, 14} Differentiation from the other ectodermal syndromes can be difficult in the absence of lip/palate and limb deformities. However, full gene sequencing is recommended for fetuses with prenatal ultrasound findings suggestive of EEC or related syn-

dromes. Mutation-specific testing is recommended if there is a family history of a known p63 mutation.

There is no cure for EEC syndrome but many treatments are available to address the symptoms secondary to the multiple deformities or abnormalities. It requires a multidisciplinary team approach and should include paediatricians, plastic surgeons, dental surgeons, ophthalmologists, dermatologists, nephrologists and speech therapists. Surgical corrections of cleft lips, cleft palates, and abnormalities in the hands and feet are usually done at an early stage. Corrections of cleft lips or palates are important for feeding and for speech. Early audiology assessment is mandatory. These patients also require much dental management. Urology review is essential if there are genitourinary abnormalities. Other supportive measures such as saliva substitutes for severe xerostomia, simple emollient for dry skin and artificial tears for dry eyes will be essential.

Early and correct diagnosis is important so that timely and appropriate counseling for the parents can be arranged. They should be reassured that corrective surgeries can be performed and be counseled for early corrective surgeries for cleft lips/palates as the cosmetic results are better. It also avoids complications such as difficulty in feeding and aspirations. They should be reassured that the prognosis for most patients with EEC syndrome is generally good with normal intelligence and life span. Any serious medical problems are usually minimal and manageable. Successful social adaptation also plays an important role in the quality of life of an individual with EEC syndrome. Great effort

should be made to encourage early parental involvement in the management of these cases for the improved outcomes. Although management of these cases is difficult, early involvement of the multidisciplinary team is required.

REFERENCES

- 1:** Rudiger RA, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia and cleft lip-palate-the EEC syndrome. *Am J Dis Child* 1970; 120:160-3.
- 2:** Sybert VP. Ectodermal dysplasias. In Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York: McGraw-Hill; 2003. p. 515-22.
- 3:** Rollnick BR, Hoo JJ. Genitourinary anomalies are a component manifestation in ectodermal dysplasia, ectrodactyly, cleft lip/palate (EEC) syndrome. *Am J Med Genet*. 1988; 29:131-6.
- 4:** Penchaszadeh VB, de Negrotti TC. Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome: dominant inheritance and variable expression. *J Med Genet*. 1976; 13:281-4.
- 5:** Cockayne EA. Cleft palate-lip, hare lip, dacryocystitis, and cleft hand and foot. *Biometrika* 1936; 28:60-3.
- 6:** Roelfsema NM, Cobben JM. The EEC syndrome: a literature study. *Clin Dysmorphol*. 1996; 5:115-27.
- 7:** Zonana J. Ectodermal dysplasia. In: Rimoin DL, Connor JM, Pyeritz RE, editors. *Principles and Practice of Medical Genetics*. New York: Churchill Livingstone; 1996. p. 1279-91.
- 8:** O'Quinn JR, Hennekam RC, Jorde LB, Bamshad M "Syndromic ectrodactyly with severe limb, ectodermal, urogenital, and palatal defects maps to chromosome 19". *Am J Hum. Genet*. 1998; 62:130-5.
- 9:** Celli J, Duijf P, Hamel BC, et al. "Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome". *Cell*. 1999; 99:143-53.
- 10:** Ramirez D, Lammer EJ. "Lacrimoauriculodentodigital syndrome with cleft lip/palate and renal manifestations". *Cleft Palate Craniofac J*. 2004; 41:501-6.
- 11:** Brunner HG, Hamel BC, Van Bokhoven H. "The p63 gene in EEC and other syndromes". *J Med Genet*. 2002; 39:377-81.
- 12:** Barrow LL, van Bokhoven H, Daack-Hirsch S, et al. "Analysis of the p63 gene in classical EEC syndrome, related syndromes, and non-syndromic orofacial clefts". *J Med Genet*. 2002; 39:559-66.
- 13:** M Bronshtein, R Gershoni-Baruch MD. Prenatal transvaginal diagnosis of the ectrodactyly, ectodermal dysplasia, cleft palate (EEC) syndrome. *Prenat Diagn*. 1993; 6:519-22.
- 14:** Annerén G, Andersson T, Lindgren PG, Kjartansson S. Ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC): the clinical variation and prenatal diagnosis. *Clin Genet*. 1991; 40:257-62.



Breast Cancer Day 24th October 2011

- Breast cancer is the most common cancer in women in Brunei Darussalam
- The incidence continue to increase over the years