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Case Report

Four cases with ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome: Clinical evaluation and management and literature review

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ABSTRACT

A rare syndrome is ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome, which may present with lobster claw deformity. The main clinical characteristics indicate involvement of ectodermal and mesodermal tissues, including mesoaxial and longitudinal defect of distal extremity, cleft lip and palate, and developmental defects of ectoderm derives. Renal anomalies and hormonal disorders may be seen in EEC patients. This article discusses endocrine problems in 4 EEC patients diagnosed based on clinical characteristics.

Keywords: Ectrodactyly, ectodermal dysplasia cleft lip, lobstarclow, adipsic hypernatremia

INTRODUCTION

Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome is a rare autosomal dominant disorder that also develops de novo in most cases. It displays decreased genetic makeup penetrance and variability.[1-3] The syndrome has 2 types: Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 1 (EEC1, OMIM **%** 129900); Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3). The EEC3 is the most common (90%), and the EEC1 (10% of cases). EEC syndrome-3 (EEC3) is caused by a heterozygous mutation in the gene encoding p63 (TP63) (OMIM; *603273) on chromosome 3q28. EEC1 has been linked to chromosome 7q11.2-q21.3(OMIM **%** 129900). It is part of "split hand foot malformation", a group of disorders including distal extremities in varying degrees.[1,3] Although symptoms may vary widely between patients, it most commonly presents with an absence of digits or anomaly in hand and foot (ectrodactyly, split hand/foot), cleft lip/palate, ectodermal dysplasia, anomalies of hair and sweat glands, as well as distinctive facial characteristics, ocular and urinary anomalies.[1,3]

Here, we presented 4 EEC patients diagnosed with clinical characteristics for their rarity and comorbid endocrine anomalies.

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CASE 1

A 6-years and 10 months old girl was the second live birth in the third pregnancy of a 31-years old mother. The birth weight was 3140 g. There was no consanguinity between parents. In the first examination at 13 months of age, weight was 4850 g (-5.3 SDS), and height was 67 cm (-3.3 SDS). In addition, there was a cleft lip and palate, low-set ear, flat nasal bridge, prominent frontal process, agenesis in the middle finger and metacarpal bone of the right hand, syndactyly between the fourth and fifth digits in the left hand, and bilateral total hearing loss. Pituitary hormone screening was performed due to the midline defect, T4 was 0.7 ng/dl (N:0,86-1,4), TSH was 0.4 µIU/mL (N:0,6-5,5 µIU/mL), revealing central hypothyroidism. MR imaging of the pituitary was as expected. In addition, echocardiography and abdominal sonography were also found to be as expected. The patient was diagnosed with EEC syndrome by phenotypic characteristics and was scheduled for a follow-up. In control visits at 2 years and 8 months of age, genital hair growth was observed in the physical examination. Bodyweight and height were 10 kg (-2.3 SDS) and 83 cm (-2.49 SDS), respectively. Thelarche and pubarche were rated as Tanner stages 1 and 2, respectively. The hormonal evaluation revealed the following results: ACTH, 20.3 pg/mL (normal range 10-60 pg/mL) and 17-hydroxyprogesterone, 14.1ng/mL (reference <2 ng/mL), cortisol was 15.5 µg/dl. Bone age was compatible with calendar age. The patient was diagnosed with non-classical congenital adrenal hyperplasia and prescribed hydrocortisone after genetic testing revealed Val281L homozygous mutation in exon 7 on CYP21A1. Informed consent was obtained from the patient's parents.

CASE 2

A 10-years and 5-month-old boy presented to the pediatrics outpatient clinic with micro-penis. He was referred to our clinic due to hypernatremia. In his medical history, it was found that his birth weight was 3000 and that he underwent surgery for cleft lip/palate at 8 months of age and bilateral cryptorchidism at one year of age. In addition, it was found out that he underwent columella and dentoalveolar surgery at 1 year of age. There was no consanguinity between parents. In physical examination, weight and height were 35.6 kg (50-70p) and 140.2 cm (50-75p), and mental development was normal. There were bilateral split hand deformity and syndactyly in two fingers on the right and two fingers and the fourth and fifth accessory fingers on the left. There was a scar from cleft lip/palate surgery on the face and a scar from cryptorchidism surgery on the bilateral inguinal regions. Penis length was within normal limits according to age (stretched penile length: 4.9 cm, normal was: >4.83 cm according to his age group), and testicles were within the scrotum but found to be atrophic (TV:<1 ml, normal was 2.67±0,98 ml according to his age) then verified with USG. Repeated sodium measurement was 153 mmol/L, whereas urine density was 1035, and urine output was calculated as 0.71 cc/kg/hour. The findings were consistent with adipsic hypernatremia, thus orally replacing the free fluid gap. The sodium level and urine density were normalized with increased urine output (the urine osmolarity device was faulty). In the hormonal assessment for pituitary causes, the patient was diagnosed with central adrenal insufficiency (ACTH was <15 pg/ml, cortisol was 2 µg/dl, and cortisol peak was 7 µg/dl in the IV ACTH test); thus, hydrocortisone was prescribed. The remaining

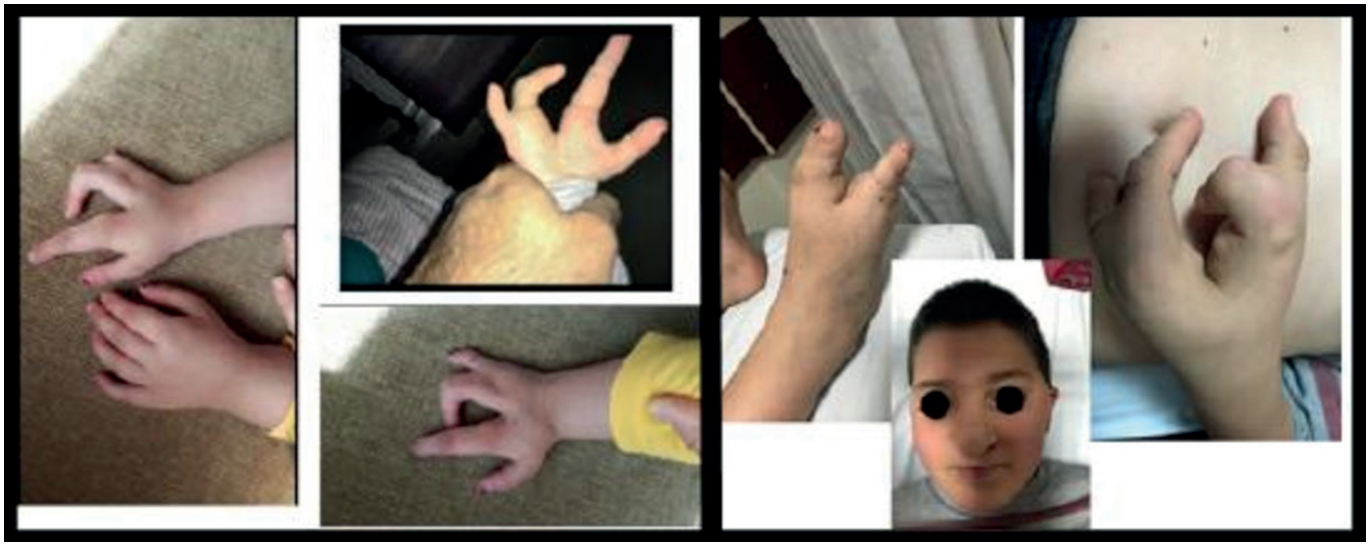

Figure 1. The photograph of case 1 is presented in the left box, and of case 2 is in the right box

pituitary hormones were found to be expected. The patient underwent a brain MRI due to central adrenal insufficiency and adipsic hypernatremia, revealing lobar holoprosencephaly. The consent form was obtained from the patient parents.

CASE 3

A 20-days old boy was referred to our clinic for further assessment of a midline defect. In his medical history, he was born from the first pregnancy of a 28-years old mother (birth weight: 2920 g) and admitted to the neonatal intensive care unit due to multiple malformations. In physical examination, his body weight and height were 2902 g (1.67 SDS) and 51 cm (-0.24 SDS), and his head circumference was 36 cm (-0.06 SDS). In addition, there was a cleft lip/palate, a split hand/foot anomaly, syndactyly at the fourth and fifth accessory fingers in both feet, a low-set ear, and a 1/6 systolic murmur along the left side of the sternum. No intracranial abnormality was detected on transfontanelle sonography, ostium secundum atrial septal defect (ASD) on echocardiography, and grade 1-to-2 pelvicalyceal ectasia in the left kidney on renal sonography. In the hormonal assessment of the hypothalamic-pituitary axis, the growth hormone level was 5.6 ng/ml(N:>7 ng/ml (4), indicating a low level for the neonatal period. No hypoglycemia, a finding of GH deficiency, was observed. A follow-up was scheduled for GH deficiency. Informed consent was obtained from the patient's parents.

CASE 4

The patient consulted our department for hypocalcemia, hypomagnesemia, decreased parathyroid hormone, and extremity anomalies on postnatal day 8. In the medical history, the patient was born from the fourth pregnancy of a 32-years old mother. The gestational age was 37 weeks at birth and the birth weight was 3630 g. The patient was admitted to the neonatal care unit due to multiple malformations. It was found that there was cerebellar hypoplasia in intracranial assessment, ureteropelvic stricture at left in renal assessment, and in cardiac evaluation double-outlet right ventricle and findings compatible with transposition of great vessels during the antenatal examination. In physical examination at presentation, weight was 3630 g (0.37 SDS), height was 46 cm (-1.86 SDS), and head circumference was 37 cm (1.43 SDS). There was a low-set ear, flat nasal bridge, split hand and foot deformity, 6 fingers in the right foot with syndactyly in the second and third fingers, syndactyly in the first and second fingers at the left foot, and pectus excavatum deformity. A clamp at the umbilicus and a single umbilical artery were observed in the umbilicus. In the cardiac examination, a marked 2/6 systolic murmur was recorded at the aortic region. In the genital examination, bilateral scrotal hypoplasia was observed and stretched penile length was measured to be 1.8 cm (normal was: 3.64±0.36 cm according to his age group). No gonad was detected in the right inguinal canal, and gonad-like tissue was detected in the left inguinal canal during palpation. There was facial asymmetry on the left side during crying. On transfontanelle assessment, the lateral ventricles were bilateral asymmetric and dilated, while the corpus callosum was thinner than expected. A subependymal cyst was observed at the level of the caudothalamic sulcus on the right. Based on a prenatal cardiac examination, findings compatible with double-aortic arch anomaly were detected on CT angiography. This finding was confirmed by a postnatal echocardiogram. The hepatic

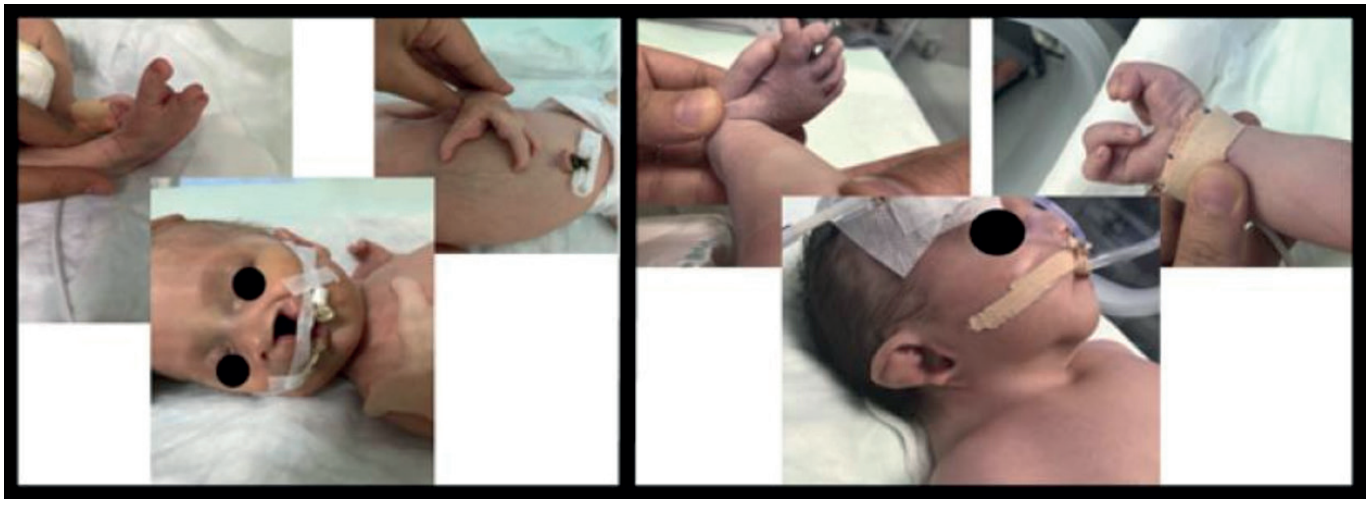

Figure 2. The photograph of case 3 is presented in the left box, and of case 4 is in the right box

artery branches were dilated and tortuous on abdominal sonography, while the renal assessment was regular. In the hormonal assessment for the hypothalamic-pituitary axis on day 15 of life, GH was 15 ng/ml. At the same time, LH, FSH, and total testosterone were <0.1 mIU/L(N:>0.3 mIU/L for mini puberty), 0.3mIU/L, and 31 ng/dL(N:70-400 ng/dL), respectively. It was found that mini puberty failed in the patient; thus, a follow-up was scheduled for hypogonadotropic hypogonadism. Informed consent was obtained from the patient's parents.

Table 1. Clinical features of cases

Features	Case 1	Case 2	Case 3	Case 4
Cleft lip	+	+	+	-
Cleft palate	+	+	+	-
Ectrodactyly	+	+	+	+
Syndactyly	+	+	+	+
Nail hypoplasia	-	-	-	+
Teeth defects	-	+	-	-
Genitourinary defects	-	+	+	+
Malformed auricles	-	+	-	+
Flat nasal tip	-	+	-	+
Micropenis	-	-	-	+
Cryptorchidism	-	+	-	+
Sparse eyebrows	+	-	+	+
Mental retardation	+	+	-	-
Semilobar holoprosencephaly	-	+	-	-
Growth hormone deficiency	-	-	+	-
Hypogonadotropic hypogonadism	-	-	-	+
Adipsic hypernatremia	-	+	-	-

DISCUSSION

The EEC is the most common split hand and foot deformity syndrome. Rudiger first described a girl with ectrodactyly in both hands and one foot, severe keratitis, ectodermal dysplasia, and cleft lip and palate deformity in 1970. Rudiger was also the first author to propose the acronym EEC. Similar findings were reported in a case by Cokayne in 1936. Although several studies have been carried out to elucidate EEC's genetic and clinical characteristics, it remains one of the rare syndromes. Findings related to the renal, cardiac, and other systems have been well-defined; however, the number of cases assessed by endocrine findings is relatively limited. Phenotypic characteristics were compatible with EEC syndrome in all cases presented here, and a detailed assessment was performed regarding endocrine disorders.

Ectrodactyly, also known as split hand-foot deformity, involves the hand and feet midline. Cleft lip, which is variably associated with cleft palate, is one of the fundamental findings seen in 68-100% of cases. Ectodermal dysplasia affects structures derived from embryonic ectoderms such as the epidermis, pituitary gland, hypothalamus, sweat glands, enamel, nail, lens, and ear, resulting in developmental defects. In addition, neuroectodermal and meso-ectodermal development defects are also common. The association of cleft lip/palate with ectrodactyly distinguishes EEC syndrome from other split hand and foot malformations.[2,3] Ectodermal dysplasia findings such as malformations of the ear and hair, dystrophic nails, and tooth anomalies are also present in 77% of patients with EEC syndrome.[4-6] Microcephaly and mental retardation were reported in 5-10% of EEC patients.[7,8] In addition to the classic triad of EEC, there was a dentoalveolar defect, prominent ear, and lobar holoprosencephaly detected by MRI in case 2, a low-set ear, and ear rotation anomaly in case 4. There was mental retardation in cases 1 and 2. However, there was no hair and nail defect in our patients.

Renal anomalies are also common structural changes in patients with EEC syndrome. Although it was previously considered a minor component, subsequent studies have shown that its incidence is underestimated. In 24 patients with EEC, Buss et al. found urinary anomalies such as glandular hypospadias, ureteral reflux, hydronephrosis, and decreased bladder volume in one-fourth of patients.[5,9-11] In addition, voiding problems such as dysuria or pain were present in family members of a patient with EEC, and abnormal bladder epithelization was detected in this family.[12] Among our cases, grade 1-to-2 pelvicalyceal ectasia was present in the left kidney in case 3. No other urinary problems were detected, but the parents were warned about voiding problems.

In patients with EEC, hormonal alterations may be present, mainly due to the involvement of the hypothalamic-pituitary axis. Firstly, Van Maldergem et al. reported a boy with hypogonadism. In subsequent reports, hypothalamic-pituitary disorders such as hypogonadotropic hypogonadism, pituitary hypoplasia, GH deficiency, and diabetes insipidus were reported.[11-16] Adipsic hypernatremia was reported as a hypothalamic pathology in only one case with EEC.[17] Among our cases, central hypothyroidism was detected in case 1, while

Table 2. The detailed clinical features of our study patients and review of the literature

	Buss et al. (1995) (n=24)	Bigatà et al. (2003) (n=5)	Maclean et al. (2007) (n=6)	Hatipoğlu et al. (2009) (n=2)	Alves et al. (2015) (n=2)	Augello et al. (2015) (n=2)	This Study (n=4)
Cleft lip	13	1	-	2	1	2	3
Cleft palate	11	3	1	2	1	2	3
Ectrodactyly	20	3	1	2	2	2	4
Syndactyly	7	2	1	1	-	1	4
Nail hypoplasia	19	3	1	1	2	1	1
Teeth defects	24	5	4	-	1	-	1
Genitourinary defects	6	1	5	2	-	-	3
Malformed auricles	-	1	3	1	-	-	2
Flat nasal tip	-	-	2	-	2	2	2
Micropenis	-	-	-	2	-	-	1
Cryptorchidism	-	1	-	2	-	-	2
Sparse eyebrows	-	-	1	-	2	-	3
Mental retardation	-	-	-	-	-	-	2
Semilobar holoprosencephaly	-	-	-	-	-	-	1
Growth hormone deficiency	-	-	1	1	-	-	1
Hypogonadotropic hypogonadism	-	-	-	2	-	-	1
Adipsic hypernatremia	-	-	-	1	-	-	1

central adrenal insufficiency and adipsic hypernatremia were detected in case 2. Moreover, GH deficiency was detected in case 3, while a follow-up for hypogonadism was scheduled in case 4. The central hypothyroidism in case 1 and the central adrenal insufficiency in case 2 were secondary to the brain abnormality and are expected but rare hormonal disorders.

Interestingly, congenital adrenal hyperplasia was detected during evaluations for premature pubarche at 3 years of age in case 1. To the best of our knowledge, there is no case report on the association of EEC and congenital adrenal hyperplasia. There are 2 forms of congenital adrenal hyperplasia inherited in an autosomal recessive manner: classical and non-classical. The classical form includes a life-threatening salt-wasting type and a simple-virilizing type causing ambiguous genitalia. This form shows a delayed onset of symptoms and is seen in 1: 13,000-1: 15,000 live births. The non-classical form is more prevalent than the other.[18,19] The non-classical form can either be asymptomatic or present with premature pubarche, hirsutism, menstrual disorders, and infertility. Although the actual frequency is unknown, it is not surprising that non-classical congenital adrenal hyperplasia is more common than expected in our Turkish community due to the frequency of consanguinity.[20] The non-classical congenital adrenal hyperplasia detected as an endocrine pathology in our EEC patient was considered a co-incidence due to its higher prevalence in the population since there seems to be no genetic association between these entities.

As our cases show, EEC syndrome involving many symptoms can present with a broad spectrum of clinical manifestations. The EEC syndrome should be kept in mind in cases with ectrodactyly and cleft lip/palate, and comprehensive evaluations, including water metabolism, should be undertaken regarding the hypothalamic-pituitary in particular. Diagnosing secondary adrenal insufficiency, which can be life-threatening, water metabolism disorders, and GH deficiency is essential. Moreover, other congenital endocrine problems, such as congenital adrenal hyperplasia, should be considered in these patients.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Concept: GT, ÜGŞ, ZUT, MNH, LA, NH; Design: GT, ÜGŞ, ZUT, MNH, LA, NH; Data Collection or Processing: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Analysis or Interpretation: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Literature Search: GT, ÜGŞ, ZUT, MNH, LA, NH, TG; Writing: GT, ÜGŞ, ZUT, MNH, LA, NH, TG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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