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Congenital Contractures, Ectodermal Dysplasia, Cleft Lip/Palate, and Developmental Impairment: A Distinct Syndrome

Roger L. Ladda, Jonathan Zonana, Jeanette C. Ramer, Maria J. Mascari, and Peter K. Rogan

The Pennsylvania State University College of Medicine, Department of Pediatrics, Division of Genetics (R.L.L., J.C.R., M.J.M., P.K.R.), Hershey, Pennsylvania; Departments of Molecular and Medical Genetics and Pediatrics, Oregon Health Sciences University, Portland, Oregon (J.Z.)

Brothers were affected with severe congenital contractures, multiple cutaneous manifestations of ectodermal dysplasia, cleft lip/palate, and psychomotor and growth impairment. High resolution prometaphase chromosomes were normal. Molecular studies of DNA markers, closely flanking the X-linked hypohidrotic ectodermal dysplasia locus, did not show evidence of a submicroscopic deletion from the Xq12-q13 region. The parents and a normal sister exhibited none of these findings. This constellation of anomalies appears to represent a unique AR or XLR syndrome.

KEY WORDS: congenital contractures, ectodermal dysplasia, cleft lip, cleft palate, retardation

INTRODUCTION

Congenital contractures (arthrogryposis) are not uncommon and may be associated with over 140 malformation complexes [Hall, 1990]. The association of congenital contractures and ectodermal dysplasia is unusual and has been reported in only 3 instances [Goldsmith, 1990]. Rosselli and Gulienetti [1961] first reported the association of hypohidrotic ectodermal dysplasia, cleft lip and palate, and limb deformities in 4 patients. Côté et al. [1982] described arthrogryposis and ectodermal dysplasia in a 16-year-old girl who also had short stature and low-normal intelligence. In their classical text, Freire-Maia and Pinheiro [1984] described a patient with arthrogryposis and ectodermal dysplasia with normal mentation. They also observed an individual with ectodermal abnormalities limited to the head with cleft lip/palate. We have cared for two brothers with severe congenital contractures, ectodermal dysplasia, hypopigmentation, clefts of the lip and/or palate and psychomotor impairment. A similar syndrome has not been reported previously.

CLINICAL REPORTS

Patient 1

This infant, born at term, had extensive contractures along with cleft lip and palate. Scalp hair and eyebrows were sparse. Weight was 3,525 g (80th centile); length was 52 cm (90th centile); head circumference (OFC) was 36.5 cm (>90th centile). He had poor suck and required feeding by nasogastric tube. Gastroesophageal reflux to the level of the oropharynx was documented by "milk scan" and barium swallow, necessitating Nissen fundoplication and placement of gastrostomy. At age 2 months, obstructive and central apnea were confirmed. Nasal oxygen was required to maintain appropriate saturation. Evaluations included a normal skeletal survey, normal CT and MRI scans of the brain, and a normal electroencephalogram. Bilateral hip dislocation was identified radiologically and was treated with bracing.

Physical findings at 2 months are shown in Fig. 1a–f. Hair was brittle and thin with little pigmentation. Scalp was dry and scaly with multiple flat nevi. Small capillary hemangiomata were found over the glabella and occiput. The infant had brachycephaly, mild frontal bossing, deep-set eyes, prominent superior orbital ridges, narrow palpebral fissures (blepharophimosis), bilateral ptosis, angular face with micrognathia, cleft of lip and palate, and flexion contractures at elbows, knees, wrists, and digits. Right testis was undescended and glandular hypospadias was evident.

This child has been evaluated for ability to produce sweat several times by a qualitative method employing a powder mixture containing bromphenol blue 2 g; sodium carbonate 6 g; corn starch 16 g; gum tragacanth 16 g sprinkled on patches of skin in different areas. Individual sweat pores were detected by the intense punctate blue stain. There appeared to be normal numbers of pores using one of us (R.L.L.) and several age-matched

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Address reprint requests to Roger L. Ladda, M.D., The Pennsylvania State University College of Medicine, Department of Pediatrics, P.O. Box 850, Hershey, PA 17033.

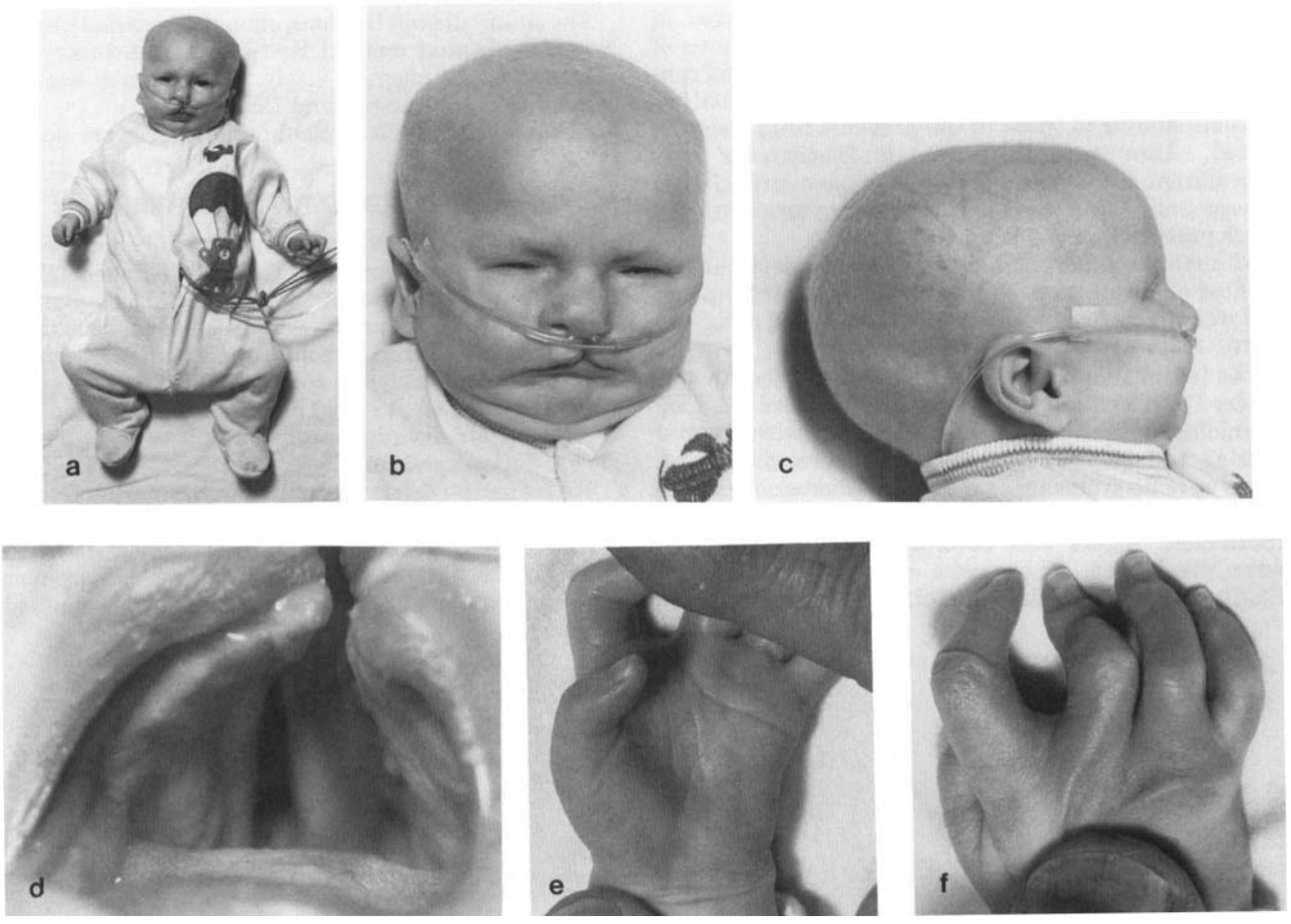

Fig. 1. **a,b:** Patient 1 has deeply set eyes, micrognathia and small bulbous nose. **c:** Scalp shows scant brittle light hair with scaling; ears are posteriorly rotated. **d:** Lip and palate clefts. **e,f:** Digital flexion contractures and aberrant flexion creases are noted.

clinic patients as control individuals. The infant has never had a documented episode of hyperthermia. He has been noted to form sweat about the head.

Psychomotor delay was apparent by 6 months, and at 28 months his developmental skills were at the 4–6 month level. By 42 months, he had limited language and motor function at a 12 month level. Head circumference has grown along the 10th centile; length and weight have followed the 3rd and 5th centiles, respectively.

Ocular exam at 30 months documented hyperoptic astigmatism, refractive amblyopia, and intermittent exotropia. Spectacles were required to achieve visual acuity of 20/60 with either eye. Nasolacrimal ducts were hypoplastic.

Dental development was delayed with eruption of the first tooth at 15 months. Central mandibular incisors were conical and lateral mandibular incisors were absent; other teeth were small or displaced.

Extended chromosomes (at the 550 haploid band level) were normal (46,XY).

Parents and an 8-year-old sister were normal. There was no history of contractures or ectodermal dysplasia in any relative. Parents were not consanguineous.

Genetic Counseling

The couple was counseled that the risk of recurrence of this combination of malformations in another pregnancy could not be determined with precision. If the condition was caused by a single gene, the chance of having an affected child (male or female) could be as great as 1 in 4 for an autosomal recessive trait or 1 in 2 for an affected male if the trait was X-linked recessive and the mother a carrier. The issue of germline mosaicism for an X-linked or autosomal dominant trait remained a further concern. Serial fetal assessments by ultrasound scan were recommended to search for malformations, in particular, palate defects and contractures based on abnormal fetal positioning and movement in any subsequent pregnancy.

Patient 2

At 19 weeks gestation the fetus was studied carefully by diagnostic ultrasound. Biparietal, chest, and femur measurements correlated well with gestational age based on the date of the last menses. The fetus appeared well-formed and active, but during extended observa-

tion, the digits of the hands appeared to be fixed in flexion and never opened as expected. Contractures of other joints could not be confirmed. Recurrence of congenital contractures with the risk of additional malformations similar to those in the previous child was suspected. After reviewing the implications of this information, the couple elected not to have further fetal assessments. The pregnancy proceeded to term with the development of polyhydramnios.

At birth the infant had anomalies virtually identical to those of his affected sib (Fig. 2a–e). He was limp and had weak respiratory efforts. Death occurred at age 10 hours. A limited autopsy was permitted.

The infant weighed 3.5 kg (60th centile); length was 51 cm (75th centile); OFC was 31 cm (<3rd centile). Craniofacial profile was brachcephalic with frontal bossing and deep-set eyes. Hair was sparse and blond; there were no eyelashes or eyebrows. Micrognathia was severe and the palate had a cleft. All major joints were contracted; fingers were severely fixed in flexion and were overlapped. There was metatarsus adductus. Phallus was small with glandular hypospadias.

The infant did not live long enough to assess sweating by our qualitative method. Sections of the skin were not obtained for histological study. Skin biopsies were obtained for chromosomal and DNA analyses.

Chromosomes (450 haploid band level) were normal (46,XY).

MOLECULAR ANALYSES

Both affected individuals in the family were males with unaffected parents, suggesting X-linked inheritance. In addition, two of the manifestations found in these brothers, cleft palate and dysplasia of ectodermal derivatives (X-linked hypohidrotic ectodermal dysplasia), have been mapped to Xq12-q21 [Zonana et al., 1992; Gorski et al., 1992]. The question was raised as to whether their disorder might be due to a contiguous gene deletion syndrome.

To test for the deletion of polymorphic markers closely flanking the X-linked ectodermal dysplasia (EDA) locus (Xq12-Xq13.1), several loci were examined. DNA extractions, restriction fragment length polymorphism, and microsatellite analyses were performed by methods

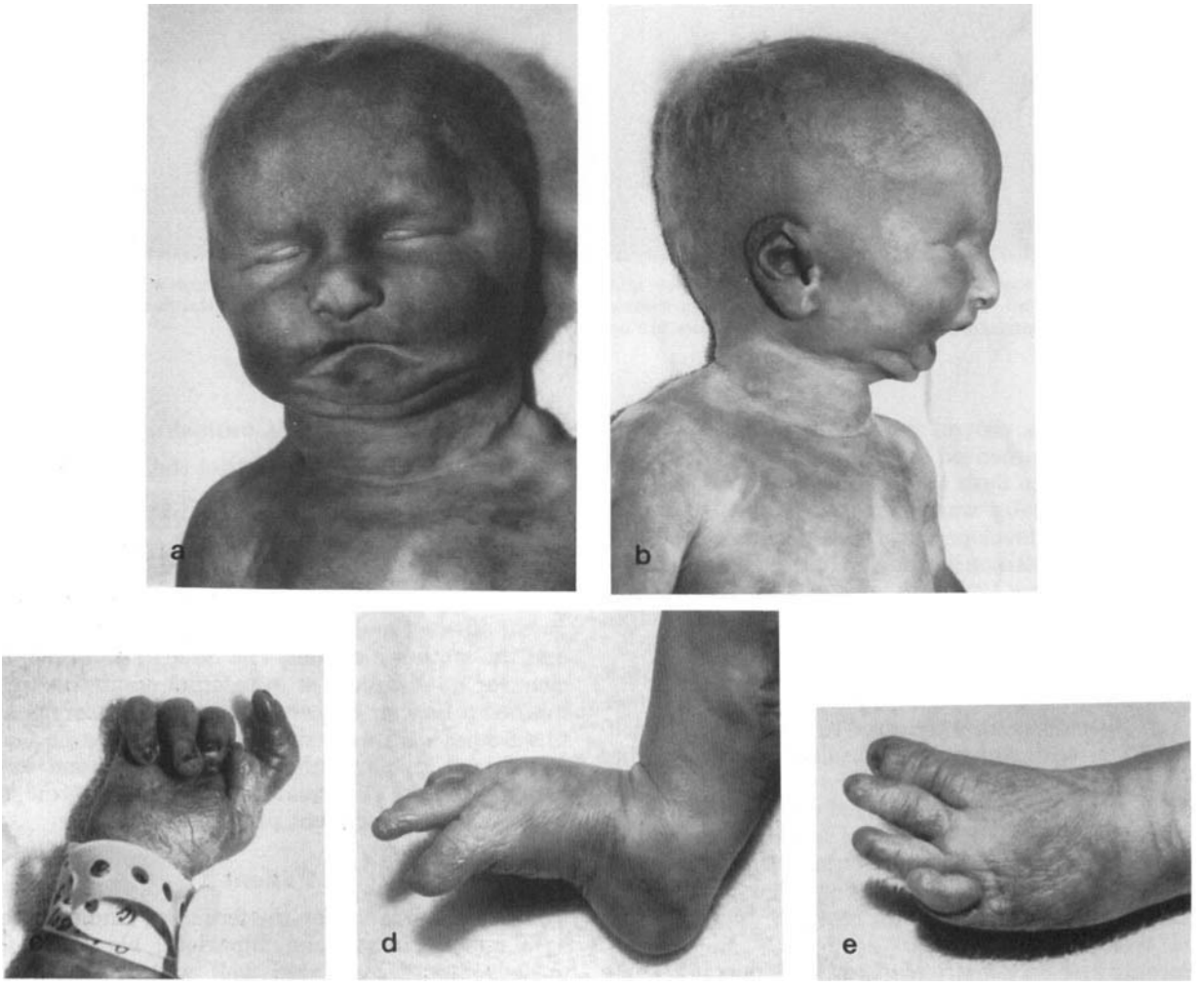

Fig. 2. **a,b:** Craniofacial features of Patient 2 are essentially identical to sibling (patient 1). **c–e:** contractures of fingers and toes are severe with nail hypoplasia.

TABLE I. Findings in Selected Ectodermal Dysplasia Syndromes Compared to Those of our Patients*

Phenotype	Roselli & Gulienetti [1961]	Bowen & Armstrong [1976]	Côté et al. [1982]	Freire-Maia & Pinheiro [1984]	Oğur & Yüksel [1988]	Rapp-Hodgkin syndrome	Hay-Wells syndrome	Present report
Skin								
Dry			+	+	+	+	+	scalp
Thickened	+				+	focal		
Thin		focal						+
Hyperpigmented	+							
Bruises easily		+						
Hair								
Sparse		+	+	+	+	+	focal	+
Coarse	+					+		
Curly	+				+			
Hypopigmented		+			+			+
Brittle								+
Pili torti			+			+		
Nails					N			N
Absent/small						+	+	
Thickened	+						±	
Brittle	+		+					
Pitted		+						
Teeth								
Absent/small	+	+			+	+	+	+
Enamel anomalies		+	+			+	+	
Conical					+	+	+	+
Miscellaneous								
Palatal cleft	+	+	−	+	+	+	+	+
Lip cleft	+	+	−		+	+	+	+
Sweat production	↓	N	N		↓	↓	N	N
Contractures	Pterygia	−	+		−	−	−	+
Growth deficiency	NR	−	+		+	+	−	+
Psychomotor development	NR	MR	N		MR	N	N	MD
Unique findings	Thumb aplasia; GU malformations	Adhesions between eyelids; absent vaginal orifice	Diabetes mellitus			Corneal opacities; atresia of lacrimal puncta	Adhesions between eyelids; recurrent scalp infection	Blepharophimosis; hip dislocation

* (+) present; (−) absent; (N) normal; (NR) not reported; (MR) mental retardation; (MD) moderate delay.

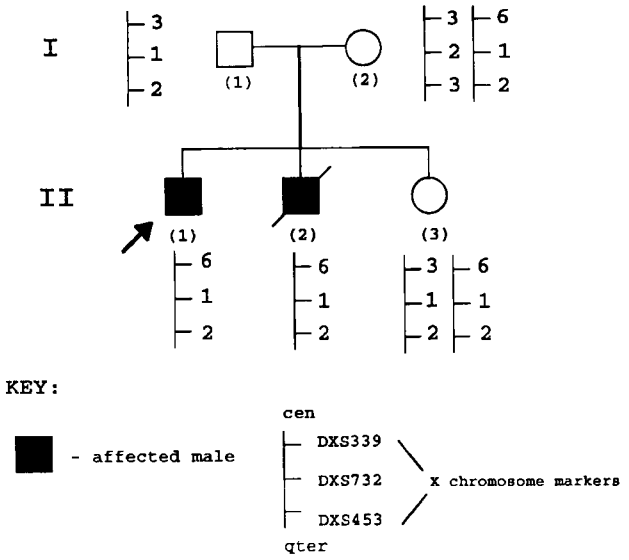

Fig. 3. Analyses of polymorphic marker loci flanking the EDA locus in the parents and normal sister of the affected male siblings.

previously described [Zonana et al., 1992]. The loci evaluated included the closely linked flanking loci DXS339 ($\hat{\theta}Z_{max.} = .00$; Z max. = 28.19) and DXS453 ($\hat{\theta} = 0.009$; $Z_{max.} = 22.94$) which contain highly polymorphic (CA)n dinucleotide repeat sequences [Zonana et al., 1992]. The DXS732 locus, which is closely linked to the EDA locus ($\hat{\theta} = 0.000$; Z max. = 22.94) was also tested. It contains a highly conserved DNA sequence that may be a part of the EDA gene itself, and recently it has been shown to be submicroscopically deleted in a male with EDA [Zonana et al., 1992]. The results are seen in Figure 3. Note that the mother (I-2) of the affected individuals is heterozygous at all 3 marker loci, and that her sons and daughter inherited the same maternal X-chromosome in the Xq12-q13.1 region.

DISCUSSION

These brothers have a unique syndrome of arthrogryposis with ectodermal dysplasia, cleft lip/palate and severe psychomotor delay. We approached the differential diagnosis in these brothers by extension from the primary abnormalities of arthrogyposis and ectodermal dysplasia. Review of the relevant reports documented several individuals with traits overlapping those of our patients (Table I). The 4 patients (2 males; 2 females) reported by Rosselli and Gulienetti [1961] had major anomalies of the digits including syndactyly, ectrodactyly and hypoplastic thumbs. Hair was coarse and white; nails were brittle and dysplastic. Popliteal pterygium were prominent. Unilateral renal agenesis was also found. These 4 children had a similar facial appearance which bears essentially no similarity to that of our patients. Richieri-Costa et al. [1992] described a young woman with abnormalities much like those reported by Rosselli and Gulienetti [1961]. The patient described by Côté et al. [1982] did not have cleft lip/palate, but there were mild digital contractures, pili torti and congenital absence of all nails. She was small for gestational age and continued to grow along the 3rd centile. At age 2 years, she developed diabetes mellitus which required high doses of insulin. Mental function was normal. Parents were normal. Freire-Maia and Pinheiro [1984] described 2 patients with arthrogryposis and ectodermal dysplasia, one without clefts and normal mentation, and another with ectodermal dysplasia confined to the head and bilateral cleft lip/palate. We asked Dr. Freire-Maia to review the clinical findings and photographs of our patients and he concurred with our impression that their changes were unique. Rapp-Hodgkin and Hay-Wells syndromes were also considered in the differential diagnosis for these infants and excluded (Table I). On the basis of our experience and review of the literature, we were also able to exclude the Marden-Walker syndrome [Ramer et al., 1993].

Ectodermal dysplasia, cleft lip and palate, syndactyly with abnormalities of skeletal growth and mental retardation have been reported in sibs in 2 unrelated families [Bowen and Armstrong, 1976; Oğur and Yüksel, 1988]. Parents were unaffected. Consanguinity was prominent in one family in which multiple urogenital tract anomalies also occurred [Oğur and Yüksel, 1988]. EEC syndrome (ectrodactyly-ectodermal dysplasia-cleft lip/palate) has some overlap with these conditions, but it clearly stands apart [Rüdiger et al., 1970; Freire-Maia, 1970]. Several forms of the distal arthrogryposis are associated with palatal clefts [Hall et al, 1982]. Robinow and Johnson [1981] described mother and daughter with distal arthrogryposis (type IIA) with cleft palate and short stature. Cleft lip was noted in the family reported by Reiss and Sheffield [1986] with type IIC distal arthrogryposis. A severe and usually lethal form of popliteal pteryguim syndrome has been associated with sparse hair, hypoplastic teeth, cleft lip/palate, and facial clefts [Bartsocas and Papas, 1972]. The phenotypes of these affected individuals bear little resemblance to our patients.

The syndrome we describe appears to have a genetic cause based on the similar phenotype in 2 sibs. The inheritance may be monogenic with autosomal recessive, X-linked recessive, or even autosomal dominant inheritance with parental gonadal mosaicism as possible alternatives. A microdeletion of several gene loci is yet another possibility, either on the X-chromosome, or on an autosome with one of the parents having a cryptic balanced translocation. The mother and the normal sister showed no evidence of hair, skin, nail, or dental abnormalities to suggest mild carrier manifestations.

Since both X-linked hypohidrotic EDA and cleft palate map to the proximal region of the long arm of the X-chromosome (Xq12-q21), anonymous DNA markers closely flanking the EDA locus were examined in this family. Even though there was no evidence of eccrine sweat gland abnormalities in the propositus, hypohidrosis can be quite variable in EDA. The molecular studies demonstrated that both sibs inherited the same haplotype of polymorphic markers from the Xq12-q13 region. If they had inherited different haplotypes in this region from the mother, it would have excluded a microdeletion involving the EDA locus. However, there is a 50% probability of their inheriting the same haplotype

in this region, unrelated to the underlying disorder. There was no evidence for deletion of marker loci proximal or distal to the EDA locus, ruling out a microdeletion involving the EDA locus.

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