Incomplete EEC Syndrome In A Patient with Mosaic Monosomy 21

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Chromosome anomalies in cases of ectrodactyly, ectodermal dysplasia and cleft of the lip and palate (*EEC syndrome*) have not been reported. We now report a child with the above syndrome and mosaic monosomy of chromosome 21.

Introduction

The syndrome of ectrodactyly, ectodermal dysplasia, and cleft of the lip and palate (EEC syndrome) is a rare developmental abnormality. Patients showing two of the three defects have been reported as specific syndromes or as examples of partial EEC syndrome (Martens, 1804). Both complete and incomplete forms of the syndrome have been reported in pedigrees suggestive of autosomal dominant and recessive modes of inheritance (Freire-Maia, 1970; Cockayne, 1936; Rosselli and Gulienetti, 1961; Walker and Clodius, 1963; Ahrens, 1967; Rapp and Hodgkin, 1968; Jaworska and Popiolek, 1968; Temtamy and McKusick, 1969; Brill et al., 1972; Kaiser-Kupfer, 1973; Penchaszadeh and DeNegrotti, 1976). In other families, the defect appears to occur sporadically. It is unclear if the syndrome is indeed one entity reflecting variable expression of a single mutant gene or if it is an example of multiple etiologic mechanisms resulting in the production of one apparent clinical entity. We have had the opportunity to study a child affected with the incomplete form of the EEC syndrome. A chromosomal abnormality was detected, suggesting that at least the incomplete form of the EEC syndrome may result from a structural chromosomal anomaly rather than from a single gene mutation.

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Case Report (4276)

A 1910-gram white male infant was born to a 26-year-old father and a 24-year-old gravida 3 para 0 abortus 2 mother after eight months gestation. There was no family history of congenital malformations or parental consanguinity. The mother had experienced irregular menses since the age of 13 years; oral contraceptives were prescribed at the age of 17 for regulation of the menstrual cycles. Two previous pregnancies terminated spontaneously at 5 and 4-1/4 months, presumably because of cervical incompetence. The mother had used oral contraceptive medication for two to three years prior to conception of the proband. During the first trimester, the mother received antibiotics for an upper respiratory tract infection and a vaginal discharge. Cervical suturing was performed during the second trimester for treatment of an incompetent cervix, and the mother was confined to bed for the third trimester.

The infant was delivered by spontaneous vaginal delivery without complications. The

placenta, cord, and fetal membranes were normal. Multiple congenital anomalies were immediately noted. Initial measurements demonstrated the length to be below the third percentile and the head circumference at the third percentile for gestational age. The infant did well initially, but developed fever at the age of 10 days, for which antibiotics were given. The child was discharged at the age of 10 days. At the age of one month his weight was 2170 grams.

The child was first admitted to the University of Illinois Hospital at the age of 26 months for evaluation of poor growth. Physical examination at that time revealed an alert, tremulous infant with a head circumference of 45 cm (less than third percentile), length 86 cm (tenth percentile) and weight 10.4 kilograms (less than third percentile). The neurocranium was normal in shape but microcephalic. The cranial sutures were closed. The eyes were normally set, with very long lashes. Lateral nystagmus was present bilaterally. No abnormality of the nasal puncta or blepharitis was noted. The ears were normally set, with a preauricular tag on the right. There was bilateral serous otitis media requiring myringotomy and insertion of polyethylene tubes. The alae nasi were flat with a deviated nasal septum. Bilateral cleft lip and cleft palate were noted. A Simonart's band was present on the left side. Constant drooling of saliva was noted on several occasions. The premaxilla protruded markedly and was shifted to the left. The scalp hair was sparse and blond. Examination of the chest, cardiovascular system and abdomen revealed no abnormalities. Undescended testes and a small penis were noted. Examination of the right hand revealed syndactyly of the first and second digits; a rudimentary third digit was present. The left hand demonstrated absence of the third digit. Examination of the feet revealed two digits on each foot, with a typical lobster claw configuration. The skin was dry and eczematous. Normal sweating was confirmed by dermatologic consultation. On neurological examination, the patient had increased muscle tone and brisk deep tendon reflexes. There was truncal ataxia. Figures 1, 2 and 3 show the findings discussed above.

A history of seizure-like activity at the age of five months was obtained for which the patient had been treated with Phenobarbital and Dilantin. Developmental assessment at 40 weeks, using the Gessel Development Score, indicated that the patient was functioning at a 16–24 week level in motor, language, personal, social and adaptive behavior. At 26 months the patient was able to pull himself up but could not stand without support. He was able to say a few simple words.

Investigations

Hemoglobin, white blood cell count, erythrocyte sedimentation rate, prothrombin time and platelet count were within normal limits. Urinalysis revealed a specific gravity of 1.014 and a pH of 5.5. A urine culture grew E. coli for which the child was treated with antibiotics. The serum sodium ranged from 150–180 mEq/L, while the chloride, potassium and CO_2 were within the normal range. Further

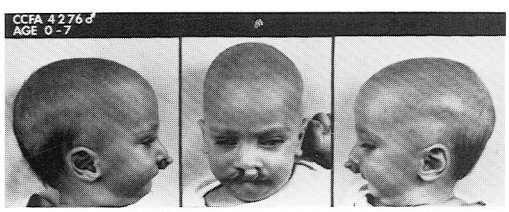

FIGURE 1. Seven month old male with unoperated bilateral cleft lip and palate.

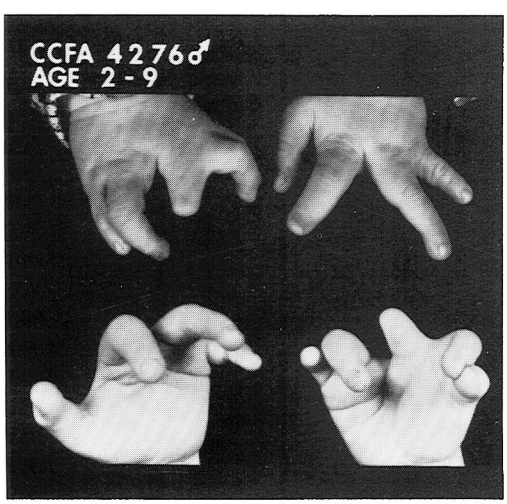

FIGURE 2. At age 2 years and 9 months, the right hand shows syndactyly of thumb and forefinger and missing middle and distal phalanges of the third finger. The third finger is absent on the left hand.

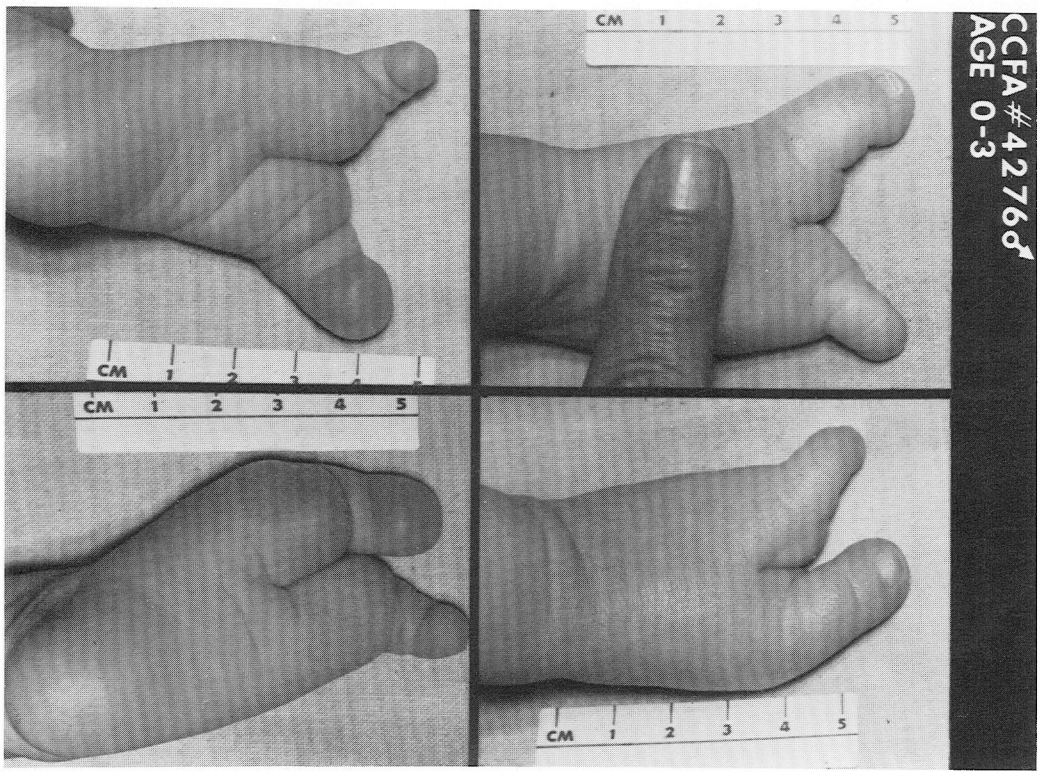

FIGURE 3. The feet show typical ectrodactyly configuration with only two toes on each foot.

investigations of renal function will be reported separately.

Radiographs of the skull and chest revealed no abnormalities. Computerized tomography of the skull demonstrated atrophy of the lower brain stem. Symmetrical areas of density were present periventricularly and were thought to represent small arteriovenous malformations or ectopic gray matter.

An electroencephalogram obtained during spontaneous sleep showed low voltage 20–25/sec. activity and normal spindle activity, maximal in the frontal area. Brain scan with technetium 99 perfusion revealed an abnormal concentration of medium in the posterior temporal area close to the midline.

An intravenous pyelogram demonstrated hydronephrosis of the left kidney with a moderate degree of pelvic caliectasis. There was normal filling of ureters and bladder, and the right kidney appeared to be normal. Renal perfusion scanning with ^{131}I Hippuran revealed slow perfusion bilaterally. Both kidneys were irregular in outline. Hippuran was taken up promptly by the left kidney, but urinary drainage was slow. The right kidney was small but cleared the medium more rapidly. No reflux was noted.

Cytogenetic Analysis

Chromosome analysis of cultured peripheral lymphocytes with Giesma banding revealed a 46XY/45,XY - 21 mosaicism (Figure 4). Of sixty cells analyzed, six (10%) were missing a G group chromosome. Further analysis with Q-banding confirmed that the missing G-group chromosome was indeed a chromosome 21. Analysis of chromosomes obtained from cultivated skin fibroblasts revealed a 46,XY normal pattern in all cells examined.

Discussion

The association of the EEC syndrome with mosaic monosomy of chromosome 21 is unique and provocative. Interpretation of such a finding is complicated, however, by the confusion in the medical literature regarding definition of the EEC syndrome. The interesting anomaly of "lobster claw" or ec-

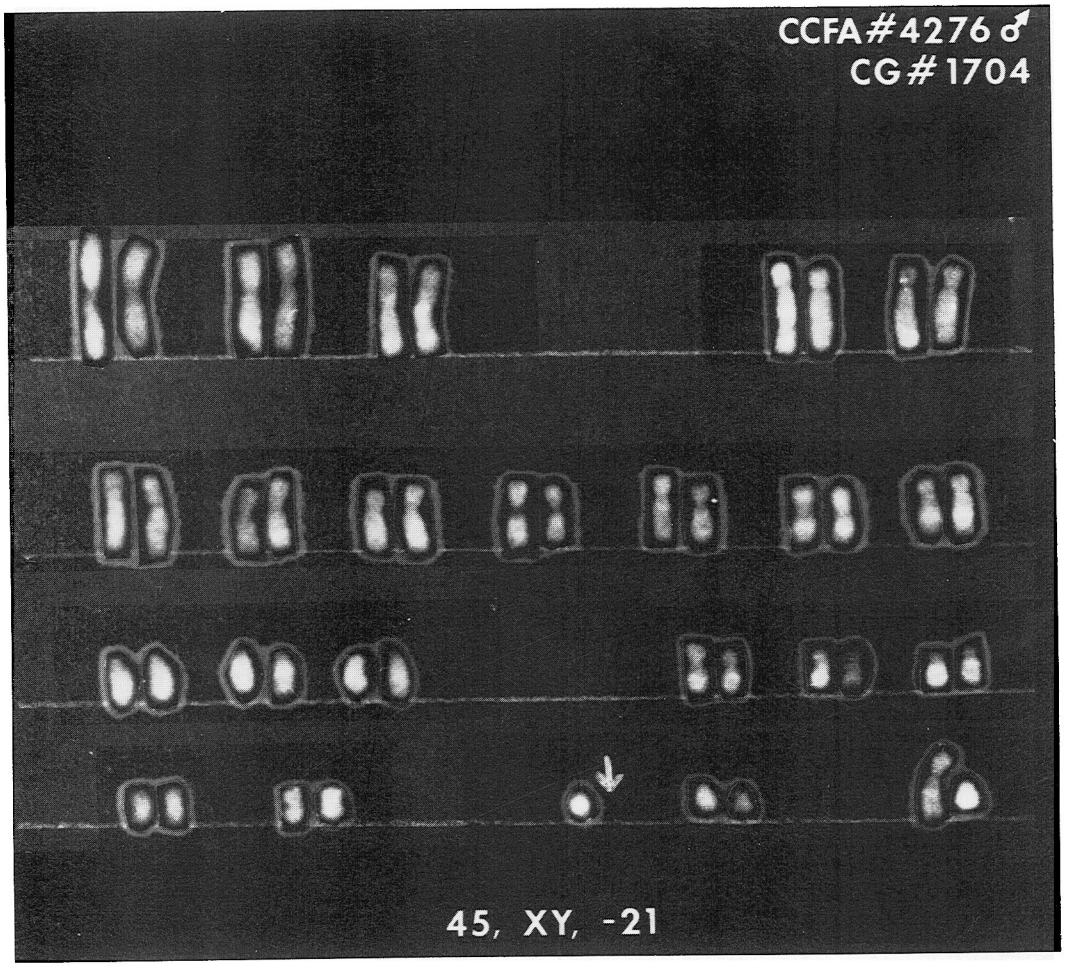

FIGURE 4. Karyotype 46XY/45XY—21 mosaicism.

trodactyly has been known since at least 1575; its relatively rare association with cleft lip and palate was documented in 1804 by Martens. The addition of ectodermal dysplasia of an atypical form to the constellation of anomalies occurred in 1970 (Freire-Maia, 1970). At the outset, it was clear that pedigrees existed in which some family members exhibited all components of the syndrome, and other family members exhibited only two components (Freire-Maia, 1970). In some families, two siblings were affected with both parents being phenotypically normal. For other pedigrees, direct parent to child transmission could be documented (Cockayne, 1936; Rapp and Hodgkin, 1968; Temtamy and McKusick, 1969; Robinson, 1973; Penchaszadeh and DeNegrotti, 1976).

Attempts at a complete literature review on the subject of EEC syndrome were frustrated by the many incompletely reported cases. It appeared, however, that at least 37 families have been described with the EEC syndrome (Table 1). In this context, the EEC syndrome was assumed to be present in any patient exhibiting two or more of the three components of ectrodactyly, ectodermal dysplasia and cleft lip and palate. Of these 37 families, 22 had a single affected member. Fifteen families demonstrated two or more affected individuals, with parent to child transmission evident in at least six such families. In six families, affected individuals within a single pedigree demonstrated different components of the syndrome. While chromosomal abnormalities have not been reported in association

TABLE 1. Review of reported cases of EEC syndrome

author and year	*family #*	*syndrome components*	*chromosome findings*	*mode of inheritance*
Kompe (1903)	1	E, C*	Not reported	Positive family history
Kellner (1934)	2	E, C	Not reported	Sporadic
Fuss (1935)	3	E, C	Not reported	Sporadic
Cockayne (1936)	4	E, ED, C	Not reported	**AD
Birch-Jensen (1949)	5	E, C	Not reported	Sporadic
Schonenberg (1955)	6	E, C	Not reported	Sporadic
	7	E, C	Not reported	Sporadic
Roselli (1961)	8	E, ED, C	Not reported	Sporadic
Walker and Clodeius (1963)	9	E, C	Not reported	Possible AD
	10	E, C	Not reported	Possible AR
	11	E, C	Normal	Possible AD
Ahrens (1967)	12	E, ED,C	Normal	***AR
Rapp (1968)	13	E, C	Not reported	AD
Jaworska and Popiolek (1968)	14	E, C	Not reported	Possible AD
Temtamy and McKusick (1969)	15	E, ED	Not reported	AD
Hillman and Fraser (1969)	16	E, C	Not reported	Sporadic
	17	E, C	Not reported	Sporadic
Freire-Maia (1970)	18	E, ED,C	Normal	AR
Berndorfer (1970)	19	E, C	Not reported	Sporadic
	20	E, C	Not reported	Sporadic
Berndorfer (1970)	21	E, C	Not reported	Sporadic
Berndorfer (1970)	22	E, C	Not reported	Sporadic
Rüdiger (1970)	23	E, ED, C	Normal	Sporadic
Bixler (1971)	24	E, ED, C	Normal	Sporadic
	25	E, ED, C	Normal	Sporadic
Fried (1972)	26	E, ED, C	Normal	Sporadic
Brill (1972)	27	E, ED, C (variable in family)	Normal	AD
Kaiser Keipfer (1973	28	E, ED, C	Not reported	Sporadic
	29	E, ED, C	Not reported	Sporadic
Robinson (1973)	30	E, ED, C	Normal	Sporadic
	31	E, ED,C (variable in family)	Not reported	AD
Pries (1974)	32	ED, C	Not reported	Sporadic
	33	E, ED,C (variable in family)	Not reported	Possible AR
	34	E, ED, C	Not reported	Sporadic
	35	E, ED, C	Not reported	Sporadic
	36	E, ED, C	Not reported	Sporadic
Penchaszedek (1976)	37	E, ED,C (variable in family)	Not reported	AD

* E—ectrodactyly.
ED—ectodermal dysplasia.
C—cleft.
** AD—autosomal dominant.
*** AR—autosomal recessive.

with the EEC syndrome, such studies were not performed (or at least not described) in 14 patients reported since 1972.

The syndrome of monosomy 21 has been described in 31 living patients. Of these, 23 individuals exhibited chromosomal mosaicism, and six individuals demonstrated the chromosomal abnormality in all cells studied. Ten patients had unusual physical findings of the extremities, palate, or ectodermal structures (Table 2). While musculoskeletal abnormalities are not uncommon in the chromosome 21 deletion syndrome, ectrodactyly has not been previously described in patients with this chromosomal abnormality. Cleft palate has rarely occurred in infants with the chro-

TABLE 2. Review of selected cases of monosomy G syndrome

author and year	*sex*	*age*	*hands*	*feet*	*karyotype*	*cleft palate*	*genitourinary*
Al-Aish et al. (1967)	F	4½ yrs.	Small and spade-like	Normal	Monosomy G	No	Normal
Lejeune et al. (1964)	M	7½ mos.	Koilonychia	Normal	Mosaic: (45, XY −21/ 46XY)	No	Hypospadias, inguinal hernia
Thorburn & Johnson (1966)	M	1 year	Thumbs held flexed	Normal	Monosomy G (45, XY, −21)	No	Normal
Challacombe & Taylor (1969)	M	16 wks.	Hands tightly clenched; thumbs low-set; nails normal	Rocker-bottom feet	Mosaic: (45, XY, −21/45XY, −21 + ring)	Cleft palate	Hypospadias; both testes were in the inguinal canal; right inguinal hernia
Gripenberg et al. (1972)	F	18 mos.	Flexion deformity of the finger	Normal	Monosomy G (45, XX, −21)	High palate	Normal
Halloran, et al. (1974)	F	20 mos.	Contractures of the proximal interphalangeal joints of the L fourth and fifth fingers	Partial syndactyly of the second and third toes bilaterally	Monosomy G (45, XX, −21)	No	Normal
Dzibua et al. (1976)	F	4 mos.	Held thumbs between the second and third fingers	Normal	Monosomy G (45, XX, −21)	Cleft palate	Normal
Kaneko et al. (1975)	M	Infant	Malopposed thumbs, overlying fingers and koilonychia on both hands	Club foot	Monosomy 21 (45, XY, −21)	High-arched palate	The penis was hypoplastic and the scrotum was bifid in which no testes were palpable
Cooksley & Wallace (1973)	F	22 yrs.	Hands small with short tapering finger	Second toe shorter than both hallux and third toe	Monosomy G (45, XX, −21)	Normal	Normal
Greenwood & Sommer (1971)	F	24 mos.	Normal	Normal	Mosaicism: skin normal, Peripheral blood (45, XX, −21)	High-arched palate	Normal

mosome 21 deletion syndrome (Challacombe and Taylor, 1969; Dziuba et al., 1976).

The finding of a chromosomal abnormality in a patient with a "known syndrome" which has been presumed to occur as the result of a single gene mutation raises several questions: (1) What is the relation of the chromosomal abnormality to the clinical findings? Certainly it is well-known that structural re-arrangements and duplications of chromosomal material may be present in phenotypically normal individuals. The finding of a chromosomal abnormality in a patient with physical anomalies does not prove an etiologic relationship. Monosomy of chromosome 21, however, has not been reported in normal subjects. It seems likely, therefore, that the chromosomal abnormality is etiologically related to the clinical syndrome in this patient. (2) What diagnostic studies should be performed in the evaluation of a patient who appears to represent a well defined clinical entity? Clearly, the clinician must maintain a high index of suspicion in the evaluation of patients who appear to represent "known" syndromes. In the case of the EEC syndrome, it appears that chromosome evaluation should be part of the initial diagnostic work-up, at least in incomplete and sporadic cases. (3) What is the impact of a chromosomal abnormality on genetic counseling? In cases of the EEC syndrome with normal karyotypes, genetic counseling has been complicated by the apparent heterogeneity of the disorder. In the absence of an affected parent or sibling, it has been impossible to distinguish the sporadic from the autosomal recessive case. Where a chromosomal abnormality has been identified, autosomal recessive inheritance becomes highly unlikely, and the risk of recurrence in a given family, where the parents have normal chromosome complements, becomes remote.

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