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New Syndrome

Multiple Congenital Malformations in Two Sibs Reminiscent of Hydrolethalus and Pseudotrisomy 13 Syndromes

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We report on two sibs, born to consanguineous parents, with defects of the midline including cleft lip and palate, flat nose, hypotelorism, and dysgenesis of corpus callosum, in addition to short limbs, radiolucent tibial notch, digital anomalies, ambiguous genitalia, and hypopituitarism. In spite of the similarities between this condition and the hydrolethalus and pseudotrisomy 13 syndromes, our patients had neither preaxial nor postaxial polydactyly, but had previously undescribed bilateral radiolucent tibial notch, which is not known to be part of those two syndromes. The cases presented here may very well represent a new autosomal recessive syndrome.

KEY WORDS: **cleft lip and palate, holoprosencephaly, dysgenesis of corpus callosum, hypopituitarism, hepatic dysfunction**

INTRODUCTION

The close relationship between the developing midline facial structures and Rathke pouch in early embryonic life, and the clinically recognized link between midline facial and cerebral defects (as depicted in the assertion, "the face predicts the brain"), should direct the pertinent inquiries toward the details of intracranial defects once a facial defect is observed [Cohen and Sulik, 1992]. However, information is needed regarding the recognition and detailed delineation of syndromic forms of interrelated entities, particularly hereditary ones [Cohen, 1989b]. We report here on two sibs of unlike sex with a similar multiple congenital malformation syndrome, born to a consanguineous Saudi Arabian couple.

CLINICAL REPORTS

Case 1

The proposita, a female infant with multiple congenital malformations, was born at term to a 24-year-old gravida 5, para 2, and abortion 1 mother after an emergency cesarean section prompted by vaginal bleeding and lack of progress in labor. She had Apgar scores of 5 and 7 at 1 and 5 min, respectively. She required resuscitation and intubation in the delivery room. She was transferred to King Khalid University Hospital at the age of 9 days because of respiratory distress with cyanosis, aspiration pneumonia, hypocalcemia, and feeding difficulties. The parents were first cousins, in good health, and had 2 healthy daughters. The mother had no diabetes mellitus, and gave a history of a spontaneous abortion at 13 gestational weeks (the abortus was not examined). She previously gave birth to a male infant with congenital malformations, not unlike the one described here, who died shortly after birth. Congenital malformations of a similar type including the single central incisor in close relatives were denied.

Examination on admission showed a jaundiced infant with multiple congenital anomalies. The weight was 3,750 g (90th centile), length 48 cm (50th centile), occipito-frontal head circumference (OFC) 33.5 cm (50th centile), temperature 38.5°C, and blood pressure 50/34 mmHg. She had sternal retractions, tachypnea, coarse rales, hyperdynamic precordium, 2/6 systolic murmur, intermittent cyanosis, mottled skin, poor tissue perfusion, generalized nonpitting edema, hepatomegaly, low umbilical attachment, large anterior fontanel, widely separated cranial sutures, generalized muscular hypotonia, and normal deep tendon

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reflexes. Multiple congenital anomalies included bilateral microphthalmia, micrognathia, median cleft lip and palate, flat nose, apparent hypotelorism (Fig. 1), bilateral camptodactyly and overlapping fingers with flexion deformity of fingers, syndactyly of first and second toes, short limbs, and hypoplastic female genitalia. She had no pre- or postaxial polydactyly.

Hospital course was complicated by intermittent episodes of cyanosis, and respiratory distress and failure which required ventilatory assistance. She tolerated several attempts at extubation for a few days, followed by development of lobar atelactasis and emphysema requiring the resumption of mechanical ventilation. She developed seizures at the age of 10 days concurrent with hypoglycemia, and hypocalcemia, and was treated with a short course of phenobarbital, glucose, and calcium without further recurrence. The diagnosis of congenital hypopituitarism was suspected and subsequently confirmed by hormonal studies. She received albumin, hydrocortisone, and dopamine infusion followed by replacement doses of hydrocortisone, l-thyroxine, and growth hormone. This was followed by an improvement of her muscular activity, respiratory drive, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. However, she continued to exhibit intermittent respiratory distress and hypoventilation associated with the aforementioned atelectasis. Later in her hospital course, she developed septicemia and respiratory tract infections, and was treated with ventolin nebulizer and antibiotics. Terminally, she developed a bronchiolitis-like illness with presence of respiratory syncythial virus in her tracheal secretions, and died at the age of 102 days in respiratory failure. Autopsy was denied.

Laboratory investigations disclosed the following: anemia, hypoglycemia, hyponatremia, hyperkalemia, hypochloremia, hypocalcemia, conjugated and unconjugated hyperbilirubinemia, elevated serum enzyme activities of alkaline phosphatase, ALT, AST, and gamma glutamyltransferase, low serum fibrinogen levels, prolonged PT and activated PTT, low urine osmolality and potassium, and high urinary sodium excretion. Prior to hormonal replacement therapy, endocrine studies disclosed serum levels of TSH, 0.01 μU/ml; free T_4, 1.7 μg/ml; free T_3, 0.3 μg/ml; cortisol, 0.1 μg/dl; prolactin, 0.1 ng/ml; plasma aldosterone, 74 ng/dl; FSH, 0.14 mIU/ml; and LH 0.01 m IU/ml. Levels of TSH, free T_4, free T_3, cortisol, and prolactin were thought to be low for the age.

Results of the following tests were either negative or within normal limits: sweat electrolytes, alpha-1 antitrypsin, TORCH studies, serum immunoglobulins and T-cell function, lipoprotein electrophoresis, HBsAg, serum and urine amino acid chromatography, stool-reducing substances, urinary-reducing substances, and dinitrophenylhydrazine. Chromosomes were normal (46,XX). Series of chest films showed normal heart and thymus, and recurrent episodes of lobar atelectasis involving almost all the lobes except for the left upper lobe, which appeared to be always emphysematous. A skeletal survey demonstrated symmetrical short limbs, a well-demarcated anteriorly located bilateral radiolucent tibial notch (Fig. 2), and no occipitoschisis. She had normal ECG and an ostium secundum type atrial septal defect, and large patent ductus arteriosus documented by heart ultrasound. Ultrasound examination of the adrenals, kidneys, and liver was unremarkable. Cranial ultrasound and CT scans showed deep facial cleft, dysgenesis of corpus callosum (Fig. 3), poorly differentiated eyeballs and optic nerves, although identified, whereas the leaves of septum pellucidum were divergent. The biliary radioisotope HIDA scan showed a good hepatic uptake and the appearance of activity in the gallbladder at 4 min and in the bowel around 2 hr.

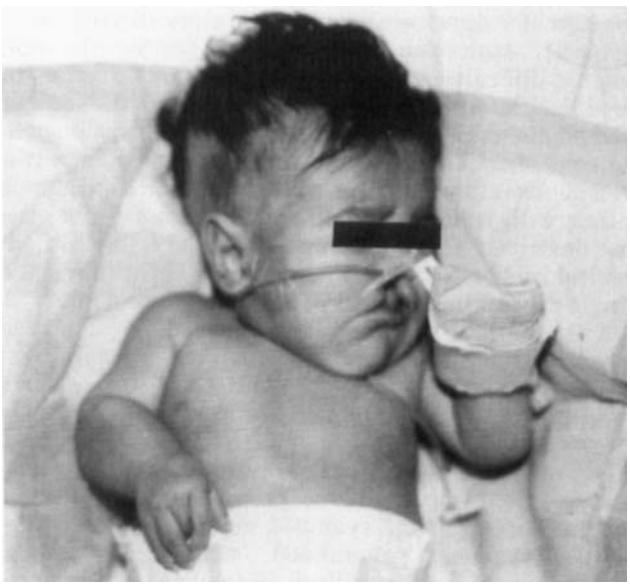

Fig. 1. Case 1. Complete midline cleft lip and palate, camptodactyly, and overlapping and flexion deformity of fingers.

Case 2

The brother of case 1, a full-term infant with breech presentation, was delivered by cesarean section at gestational age 41 weeks. A prenatal ultrasound study 2 days prior to delivery showed polyhydramnios, short femoral bones, unilateral cerebral ventricular dilatation, and a posterior fossa cyst consistent with Dandy-Walker anomaly. The Apgar scores were 3 and 6 at 1 and 5 min, respectively. He was resuscitated and intubated in the delivery room.

On admission, his temperature was 35.5°C, respiratory rate 80/min, heart rate 103/min, blood pressure 36/13 mmHg, weight 4,150 g (>90th centile), length 44 cm (<10th centile), and OFC 52.5 cm (>90th centile). He had a large head with positive translumination, enlarged fontanels, and widely separated sutures. An excess of loose and edematous skin was hanging over the orbital region, obliterating the eyes. He had a complete median cleft lip and palate, flat nose, apparent hypotelorism, chubby-looking short limbs with limited joint movement, bilateral ulnar deviation of hands, single palmar creases, and overlapping fingers. The case notes mention no pre- or postaxial polydactyly. He

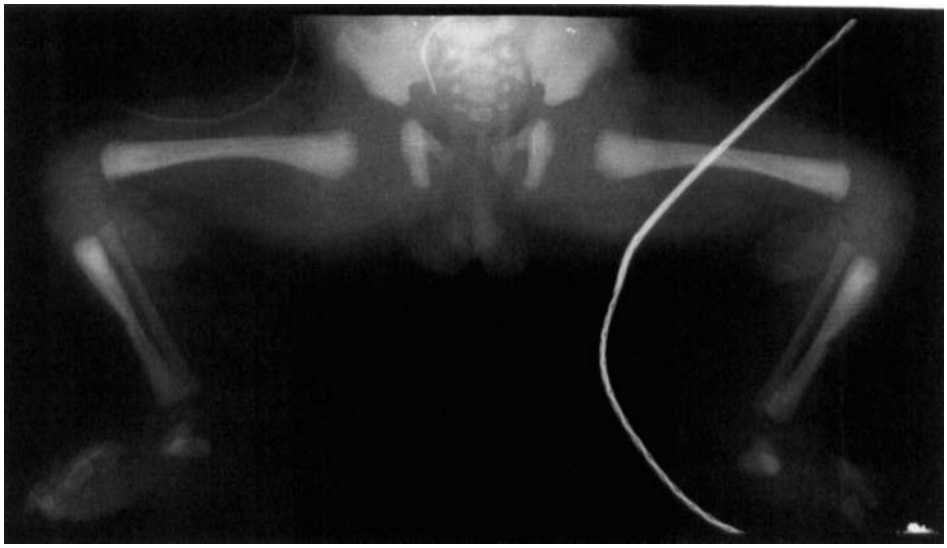

Fig. 2. Case 1. Short lower limbs and anteriorly located bilateral radiolucent tibial notch.

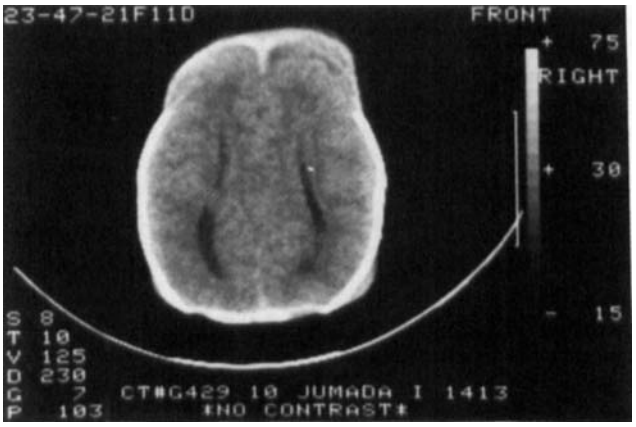

Fig. 3. Case 1. CT scan showing parallel lateral ventricles with mild dilatation of occipital horns consistent with callosal agenesis.

exhibited cyanosis, tachypnea, poor skin perfusion, hyperdynamic precordium, 2/6 systolic murmur at the left sternal border, and distended and prominent abdomen. Genitalia were ambiguous, with fused, hypoplastic, and wrinkled labio-scrotal folds, no palpable gonads, and a midline tag-like nonerectile microphallus (0.5 cm in length) with a small pinpoint opening underneath (perineal hypospadias), from which a total of 7 ml urine was obtained.

Shortly after admission, because of continuing tachypnea, intermittent cyanotic episodes, bradycardia, severe hypotension, and low blood dextrostix values, he was given increased ventilatory support, fresh-frozen plasma, and dopamine infusion. He developed repeated episodes of bradycardia and then cardiac arrest shortly after the completion of CT scan, and died at age 22 hr. Chromosomes were normal (46,XY). Skeletal survey disclosed symmetrical short limbs and a well-demarcated bilateral single radiolucent notch over each tibia anteriorly, identical in appearance to that observed in case 1. There was no occipitoschisis. Chest films showed normal-looking thymic shadow, lung fields, and heart. Cranial ultrasound and CT scans disclosed holoprosencephaly with a thin cerebral cortex and markedly dilated left lateral ventricle crossing the midline toward the less dilated right lateral ventricle, connected through a defect in the septum (Fig. 4). The corpus callosum was hypoplastic, and the third ventricle was not dilated. A large posterior fossa cyst resembling a Dandy-Walker malformation was observed, together with cerebellar hypoplasia. Optic nerves and eyeballs were identified, but the contents were not well-differentiated.

DISCUSSION

The common findings in the 2 sibs presented here include a complete median cleft lip and palate, flat nose, hypotelorism, dysgenesis of the corpus callosum, septo-optic dysplasia, digital anomalies, short limbs, radiolu-

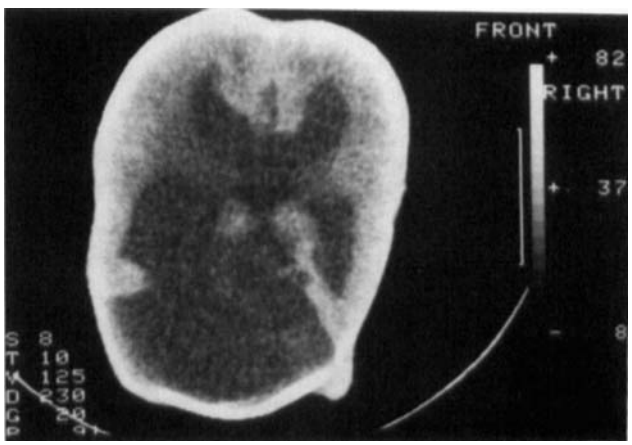

Fig. 4. Case 2. CT scan showing thin brain parenchyma and markedly dilated lateral ventricles. The ventricles are connected through a defect in the septum. A large posterior fossa cyst resembling Dandy-Walker anomaly is noted, together with dysgenesis of corpus callosum.

cent tibial notch, hypotension, hypoglycemia, and abnormal genitalia. Hypopituitarism was confirmed by hormonal studies in case 1 and strongly suggested in case 2, a male infant with microphallus, perineal hypospadias, and cryptorchidism. The discrepancy in severity of CNS involvement observed between the cases presented here is not an unexpected phenomenon in midfacial-brain malformations [Cohen and Sulik, 1992]. Autosomal recessive inheritance was predicted because of affected sibs of unlike sex, parental consanguinity, and a lack of similar cases among ancestors.

In recent reviews, Cohen [1989a] and Cohen and Sulik [1992] elaborated on the nosology of syndromic forms of midfacial-brain malformations and discussed the role of environmental, chromosomal, and monogenic causes. An unrecognized environmental influence is a remote possibility because of the similarity of phenotypic findings in our cases. There is also a possibility that a parent may segregate a small piece of translocated chromosome, resulting in chromosome imbalance in the offspring. A high-resolution chromosome analysis would have been most helpful: unfortunately, we have neither cells nor DNA available from our patients and the parents.

However, most relevant to our cases is the category of midfacial-brain malformations with monogenic inheritance. Autosomal recessive inheritance seems to be likely, considering the particulars of the family history and the high consanguinity rate (54.6%) in Saudi Arabia [Al Rajeh et al., 1993]. Among the possible entities pertinent to our discussion are the syndromes of hydrolethalus, pseudotrisomy 13, Meckel, Pallister-Hall, Smith-Lemli-Opitz, acrocallosal, and familial alobar holoprosencephaly [Cohen, 1989a; Cohen and Sulik, 1992; McKusick, 1994]. Our 2 patients were discordant for holoprosencephaly, despite the fact that they were concordant for septo-optic dysplasia. Some workers think that septo-optic dysplasia may represent a mild end of the holoprosencephalic spectrum [Johnson, 1990]. Generally, the syndromic forms of holoprosencephaly include digital anomalies, congenital heart defects, and abnormal genitalia [Cohen, 1989b], and it has been stated that "when holoprosencephaly is combined with severe facial anomalies and postaxial polydactyly, pseudotrisomy 13 syndrome should be considered" [McKusick, 1994]. Several phenotypic traits of the above entities were discordant with those of our patients, although one can identify some overlapping with the syndromes of hydrolethalus and pseudotrisomy 13 (Table I).

The hydrolethalus syndrome was first described by Salonen et al. [1981] and is characterized by very high intrauterine and early neonatal mortality, polyhydramnios, occipitoschisis, hydrocephalus, keyhole-shaped foramen magnum, agenesis of corpus callosum, defects of lung lobulation, anomalies of bronchus, trachea, and larynx, folded and overlapping loose skin, short limbs, ambiguous genitalia, and pituitary involvement [Salonen et al., 1981; Aughton and Cassidy, 1987; Krassikoff et al., 1987; Anyane-Yeboa et al., 1987; Bachman et al., 1990; Salonen and Herva, 1990]. The syndrome of

TABLE I. Comparison of Phenotypic Findings in the Present Cases With Those of Hydrolethalus and Pseudotrisomy 13 Syndromes*

			Syndromes[a]	
	Case 1	Case 2	Hydrolethalus	Pseudotrisomy 13
Cleft lip and palate	+	+	+	+
Hypotelorism	+	+	+	+
Corpus callosum agenesis	+	+	+	+
Holoprosencephaly	−	+	+	+
Septo-optic dysplasia	+	+	+	+
Hydrocephalus	−	+	+	+
Cerebellar hypoplasia	−	+	+	
Other CNS anomalies	−	+	+	+
Seizures	+	−	+	+
Apneic episodes	+		+	+
Hypopituitarism	+	+	+	
Ambiguous genitalia	+	+	+	
Micrognathia	+	+	+	
Airway anomalies	+		+	
Lung anomalies	+	−	+	+
Congenital heart disease	+	+	+	+
Gastrointestinal anomalies	−		+	+
Hepatobiliary dysfunction	+	−		
Renal anomalies	−		+	+
Tibial notch	+	+		
Short limbs	+	+	+	+
Digital anomalies	+	+	+	+
Skin, loose/redundant	−	+	+	
Polyhydramnios	−	+	+	
High mortality	+	+	+	+

* +, present; −, absent; empty space, not mentioned.

[a] Based on references of Anyane-Yeboa et al. [1987], Aughton and Cassidy [1987], Boles et al. [1992], Cohen and Gorlin [1991], Herva and Seppänen [1984], Hewitt et al. [1989], Krassikoff et al. [1987], Salonen et al. [1981], Salonen and Herva [1990], Seller et al. [1993], and Verloes et al. [1991].

pseudotrisomy 13, on the other hand, was described by Young and Madders [1987] to designate cases of multiple malformations including holoprosencephaly, severe facial anomalies, and postaxial polydactyly consistent with trisomy 13 yet with no demonstrable chromosomal defect [Hewitt et al., 1989; Cohen and Gorlin, 1991]. Those authors also emphasized the necessity of excluding the syndromes of hydrolethalus, Meckel, Smith-Lemli-Opitz, and Pallister-Hall in diagnostic attempts of pseudotrisomy 13 syndrome, and pointed to a need of further delineation of this entity. The phenotypic overlap between the syndromes of pseudotrisomy 13, hydrolethalus, and Smith-Lemli-Opitz was also stressed by Verloes et al. [1991]. In most cases, the lack of chromosomal abnormalities, affected sibs, and parental consanguinity suggested an autosomal recessive type of inheritance [Bachman et al., 1990; Hennekam et al., 1991; Seller et al., 1993].

Although some overlap, including "short limbs," is observed between our cases and the syndromes of hydrolethalus and pseudotrisomy 13 (Table I), our patients did not have renal and gastrointestinal anomalies. Furthermore, we observed no preaxial polydactyly, which is said to be characteristic of hydrolethalus syndrome in addition to postaxial polydactyly. Boles et al. [1992] reported a case of pseudotrisomy 13 with short upper limbs and radial hypoplasia. In a radiological study of hydrolethalus syndrome [Herva and Seppänen, 1984], proximal tibial shortness was found to be one of the most important characteristics of the entity; however, there is no mention of a tibial notch. The presence of bilateral radiolucent tibial notch in our patients and the absence of it in all the entities mentioned in the previous paragraph, including the hydrolethalus and pseudotrisomy 13 syndromes, make one wonder whether this radiolucency may ultimately prove to be as distinctive a trait in the syndrome reported here as the "keyhole-shaped" foramen magnum appears to be in the hydrolethalus syndrome.

In summary, the patients presented here may very well represent cases of a new autosomal recessive syndrome, distinct from other similar conditions, yet probably belonging to the same spectrum. There seems to be a compelling need for more detailed information in this area, which should include the involvement of hypothalamic, endocrine, hepatic, and skeletal systems. Further understanding may also come from molecular studies, starting from studies of chromosome 13 as the most likely candidate to carry genes responsible for these conditions.

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