Prenatal Diagnosis of Acro-Dermato-Ungual-Lacrimal-Tooth Syndrome, a Dominantly Inherited Ectrodactyly

Karen E. O'Brien, MD, Julie Shorrock, RDMS, Diana W. Bianchi, MD

As part of an assessment for preeclampsia, a prenatal sonogram performed on a pregnant woman at 33 weeks 4 days' gestation showed ectrodactyly in all 4 fetal extremities. The woman's husband had a history of hand abnormalities but was unaware that his condition was genetic. His examination was notable for ectrodactyly, small, peg-shaped teeth, microretrognathia, nail dysplasia, and a history of lacrimal duct blockage in infancy, consistent with a diagnosis of acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome. Acro-dermato-ungual-lacrimal-tooth syndrome is inherited as an autosomal dominant condition. Many of the inherited ectrodactyly syndromes are now known to be due to mutations in the p63 gene. This case, in which a prenatal sonographic diagnosis of ADULT syndrome was made, illustrates the importance of following up on a history of paternal hand anomalies.

Case Report

A 29-year-old primigravid woman with a single intrauterine pregnancy at 33 weeks 4 days was referred to the Maternal-Fetal Medicine service for treatment of severe preeclampsia. Up until that point, her pregnancy was uncomplicated. Results of a sonographic examination performed at 20 weeks' gestation in the primary physician's office were reportedly within normal limits. On admission to the hospital, a sonographic examination was performed. Abnormal numbers of digits on the fetal hands and feet were suspected. On a more detailed sonographic examination, the estimated fetal weight was 2080 g (38th percentile). The amniotic fluid index was 19.7 cm. Head, abdominal, and femur measurements were all appropriate for gestational age. The left foot was remarkable for the absence of several middle toes; the right foot could not be seen because of fetal positioning. The left hand appeared to have 4 fingers, and the right hand had 3 fingers.

Abbreviations
ADULT syndrome, acro-dermato-ungual-lacrimal-tooth syndrome; EEC, ectrodactyly, ectodermal dysplasia, and cleft lip and palate

Received March 14, 2002, from the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (K.E.O.), and Department of Radiology (J.S.), Women & Infants Hospital of Rhode Island, Providence, Rhode Island; and Division of Genetics, Department of Pediatrics, New England Medical Center, Boston, Massachusetts (D.W.B.). Revision requested March 20, 2002. Revised manuscript accepted for publication April 18, 2002.

Address correspondence and reprint requests to Karen E. O'Brien, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Women & Infants Hospital of Rhode Island, 101 Dudley St, Providence, RI 02905.
At the time of the sonographic examination, the patient reported that her 42-year-old husband had some form of hand abnormality but that she was unaware that it was “genetic.” Before delivery of the neonate, the husband was examined by a medical geneticist. In addition to bilateral foot and right hand ectrodactyly, he had small, peg-shaped teeth, microretrognathia, nail dysplasia, and a history of lacrimal duct blockage requiring surgery during infancy (Fig. 1). He never had difficulty with speech or hearing and denied skin sensitivity and excessive freckling. He was of normal intelligence, did not have clefting of the lip or palate, and denied renal or urologic problems. His nipples were normal, and his ability to sweat was unremarkable. He weighed 165 pounds and was 5 ft 8 in tall. On the basis of his physical examination, a clinical diagnosis of ADULT syndrome was made.

After the patient had received dexamethasone and had reached 34 weeks’ gestational age, labor was induced because of preeclampsia. She had a vaginal delivery of a 2300-g live male neonate with Apgar scores of 8 at 1 minute and 9 at 5 minutes.

Physical examination showed that the neonate’s left hand lacked a third finger, and the second and fourth fingers were fused (Fig. 2). The bony structures of the first, second, fourth, and fifth digits showed no abnormalities on radiography. Five metacarpal bones were visualized. The proximal phalanx of the third finger was bifid, and the middle phalanges articulated with each of the bifid portions of the proximal phalanx. The third finger had no distal phalanges. Soft tissue syndactyly was evident between the second finger and the radial portion of the third finger and between the fourth finger and ulnar portion of the third finger.

Externally, the third finger of the right hand was absent (Fig. 3). Radiographs of the right hand showed the presence of 5 metacarpals and normal although flexed bony structures in the thumb and second, fourth, and fifth digits. The proximal phalanx of the third finger was present but oriented transversely.

On physical examination, the findings for the left foot were notable for apparent absence of the second toe and syndactyly of the third and fourth toes (Fig. 4). Radiographs of the left foot showed the presence of 5 metatarsals. The first toe was normal. The second metatarsal was bowed and lacked associated phalanges. The proximal and distal phalanges of the third and fourth digits were fused. The fifth toe was normally aligned, with small proximal and tiny distal phalanges.

On general inspection of the right foot, the second and third toes appeared to be missing. Radiographs showed that 5 metatarsals were present. The first toe had normally associated proximal and distal phalanges. The second toe had 3 associated phalanges, but these were involved in soft tissue syndactyly with the first toe. A proximal phalanx was attached to the

Figure 1. A, Hypodontia in the father. B, Right hand of the father. Note onychodysplasia. C, Right foot of the father.
third metatarsal, but this was angled laterally. The fourth and fifth toes contained small but normal phalanges.

Other than the abnormalities of the hands and feet, the neonate's physical examination was unremarkable. An abdominal sonographic examination and radiographic studies of the chest and abdomen showed no abnormalities. He was vigorous and was discharged home on his sixth day of life.

Discussion

Ectrodactyly is a specific hand or foot malformation with partial or total absence of distal segments and normal proximal segments, resulting in missing digits, a median cleft, and fusion of the remaining digits.1 Ectrodactyly may occur as part of the split hand–split foot malformation, an autosomal dominant single-gene defect. Alternatively, it may appear as part of a syndrome with the split hand–split foot malformation being one component of a group of anomalies. The incidence of ectrodactyly is 1 in 90,000 live births.2

Various types of syndromic ectrodactyly exist. The most well known of these is the ectrodactyly, ectodermal dysplasia, and cleft lip and palate (EEC) syndrome. Several other disorders overlap the EEC syndrome, including the ectrodactyly and ectodermal dysplasia syndrome, the ectrodactyly and cleft palate syndrome, and the ectrodactyly and hearing loss syndrome. Tear duct abnormalities, nasolacrimal duct obstruc-

Figure 2. A, Radiograph of the left hand of the neonate. B, Left hand of the neonate. C, Prenatal sonographic view of the fetal left hand.

Figure 3. A, Radiograph of the right hand of the neonate. B, Right hand of the neonate. C, Prenatal sonographic view of the fetal right hand.
tion, ear anomalies, deafness, hypodontia, and renal anomalies are present in the lacrimoauriculo-dento-digital syndrome. The limb mammary syndrome is remarkable for hypoplasia or aplasia of the nipples and mammary glands, ectrodactyly, lacrimal duct atresia, nail dysplasia, hypohidrosis, cleft palate, bifid uvula, and hypodontia. These syndromes are all inherited in an autosomal dominant fashion. Goltz-Gorlin syndrome is an X-linked dominant condition, lethal in boys, in which affected girls have ectodermal dysplasia, facial clefts, lacrimal duct and genitourinary abnormalities, and hearing loss. Limb abnormalities in Goltz-Gorlin syndrome typically do not include ectrodactyly.

In the present case, the father’s findings were most consistent with a diagnosis of ADULT syndrome, another syndromic ectrodactyly, which was first described in 1992. Acro-dermato-ungual-lacrimal-tooth syndrome is an autosomal dominant disorder characterized by hypodontia, early loss of permanent teeth because of weak fixation, ectrodactyly, obstructed lacrimal ducts, onychodysplasia, and excessive freckling. The diagnosis of ADULT syndrome is made clinically, and the neonate’s father had most of the findings described in ADULT syndrome. Given the father’s diagnosis, the neonate’s ectrodactyly must be considered in light of a positive family history of ADULT syndrome. Not all of the components of ADULT syndrome are manifested in the neonatal period. Furthermore, as an autosomal dominant disorder, it is common to have variation in expression of the phenotype. For these reasons, the neonate’s anatomic findings, in association with the father’s clinical diagnosis of ADULT syndrome, made the diagnosis of ADULT syndrome in the neonate highly likely.

Prenatal sonographic diagnosis of ectrodactyly was first reported in 1980, when Henrion et al noted that a 16-week fetus had 1 hand with syndactyly and both feet with claw-like deformities. Prenatal sonographic diagnosis of EEC syndrome has been reported in the literature, but to our knowledge, this is the first prenatal diagnosis of ADULT syndrome.

The neonate in our case was delivered vaginally. There is no indication for cesarean delivery solely because of the diagnosis of ectrodactylic syndromes, and the route of delivery should be determined by standard obstetric criteria. Neonates with the split hand–split foot malformation or one of the ectrodactyly syndromes must undergo a thorough postnatal physical examination. Because the cardiopulmonary system is generally not impaired, these neonates are not at high risk of requiring neonatal resuscitation. The palate should be examined for clefting. Some neonatologists recommend administration of prophylactic antibiotics until the renal anatomy can be studied, because these neonates may have genitourinary abnormalities. Early audiologic testing should be performed, because these infants may have hearing loss. Artificial tears may need to be administered in case of decreased lacrimal secretion.
The infant will require follow-up with a clinical geneticist and an orthopedic surgeon. Generally, the hands of patients with ectrodactyly are not functionally impaired, provided they can oppose 2 digits. Surgical treatment for individuals with ADULT syndrome may include functional improvements of the hands and feet and repair of lacrimal duct blockage.2

The major long-term difficulties associated with the split hand–split foot malformation and the ectrodactyly syndromes include visual difficulties from corneal scarring brought about by meibomian gland dysfunction and recurrent blepharitis.2 There is no evidence that intelligence is affected in patients with the syndromic split hand–foot malformation. Buss et al5 followed 24 Welsh patients with EEC syndrome and found no evidence of mental retardation or developmental delay.

With regard to the genetic aspects of ADULT syndrome, the neonate’s parents were counseled regarding a 50% recurrence risk in future pregnancies, regardless of fetal sex. In 2000, Propping et al6 mapped the ADULT locus to chromosome region 3q27. The split hand–split foot and limb mammary syndromes share the same disease locus on chromosome 3q27, suggesting that these conditions may be allelic.6 In 2001, Van Bokhoven et al7 analyzed mutations of the p63 locus of chromosome 3q27 in 43 patients with EEC syndrome, 35 patients with the split hand–split foot malformation, and 3 families with limb mammary syndrome. p63 gene mutations were detected in almost all patients with EEC syndrome and a small proportion of patients with split hand–split foot malformation. In 2 families with limb mammary syndrome, frameshift mutations were detected in exons 13 and 14 of the p63 gene.7 Because of clinical overlap between ADULT and limb mammary syndromes, it is reasonable to explore the hypothesis that mutations in the p63 gene are involved in the pathogenesis of ADULT syndrome. DNA was collected from the affected infant and his parents for p63 mutation studies, which are in progress.

In summary, we describe the third-trimester prenatal sonographic diagnosis of fetal ectrodactyly. The fact that the parents did not perceive the father’s condition as genetic led to a diagnosis relatively late in life for the father. This case illustrates the importance of following up on a history of paternal hand anomalies.

References