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CASE REPORT

Apert syndrome: what prenatal radiographic findings should prompt its consideration?

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Apert syndrome was diagnosed in a newborn with typical facial and digital features whose only detected prenatal abnormality had been agenesis of the *corpus callosum*. This prompted a review of the central nervous system findings in all cases of Apert syndrome treated at the Craniofacial Center Boston Children's Hospital between 1978 and 2004. Two of 30 patients with Apert syndrome had prenatal identification of mild dilatation of the lateral cerebral ventricles and complete agenesis of the *corpus callosum* (ACC) documented with both ultrasound and MRI. Both had the common S252W mutation of *FGFR2*. Though cranial and orbital malformations typical of Apert were eventually seen in these fetuses in the third-trimester, even in retrospect, these were not detectable at mid second-trimester, ultrasound screening for congenital malformations. Hand malformations also went undetected in the second-trimester despite extensive imaging by experienced radiologists. We conclude that prenatal ultrasonographic identification of mild ventriculomegaly or ACC should stimulate a careful search for features of Apert syndrome and prompt follow-up imaging to look for bony abnormalities that have later onset. Prenatal molecular testing for Apert mutations should be considered in cases of mild ventriculomegaly and ACC. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: agenesis *corpus callosum*; *FGFR2*; Apert syndrome; prenatal diagnosis

INTRODUCTION

Apert syndrome, which accounts for 4.5% of all patients with craniosynostotic syndromes (Hehr and Muenke, 1999), is characterized by coronal synostosis, midfacial hypoplasia, bilateral syndactyly and symphalangism (OMIM, 101 200). Once suspected, the diagnosis can be confirmed by DNA analysis for the S252W and P253R mutations in the *FGFR2* gene, which together account for 98% of Apert cases. Though the mutation is autosomal dominant, the vast majority of cases of Apert syndrome are due to new mutations. The incidence of *FGFR2* mutations increases exponentially with paternal age, probably due to an increase in the frequency of these mutations and a selective advantage in the male germ line (Glaser *et al*., 2003; Goriely *et al*., 2003).

Apert syndrome has been diagnosed early in pregnancies in affected families, using a variety of modalities, including fetoscopy (Leonard *et al*., 1982), sonography (Narayan and Scott, 1991), and, more recently, molecular analysis (Chan and Thorogood, 1999). Nevertheless, despite the striking physical features seen in newborns with Apert syndrome, *de novo* cases are often not diagnosed prenatally, or are only identified in the third-trimester.

Central nervous system (CNS) anomalies in patients who have Apert syndrome have been previously documented (Cohen and Kreiborg, 1990; Renier *et al*., 1996; Yacubian-Fernandes *et al*., 2004). We found CNS findings in 27 of the 30 Apert patients seen at the Craniofacial Center of Children's Hospital, Boston (Quintero-Rivera *et al*., 2006) (see Table 1). We present clinical and radiologic details of two patients with Apert syndrome with agenesis of the *corpus callosum* (ACC) in whom CNS malformations were detected prenatally before the pathognomonic skeletal changes were visualized. Awareness of the fact that CNS abnormalities, including borderline ventriculomegaly and ACC, can be features of Apert syndrome, will increase opportunities for prenatal diagnosis in the second-trimester.

MATERIALS AND METHODS

Medical records and brain imaging of 30 patients with a postnatal diagnosis of Apert syndrome seen in

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Table 1—CNS anomalies in Apert syndrome compared with other studies

	Cohen and Kreiborg, 1990[a] ($N = 113$)	Renier *et al*., 1996 ($N = 60$)	Yacubian-Fernandes *et al*., 2004 ($N = 18$)	Quintero-Rivera *et al*., 2006 ($N = 30$)
Non-progressive ventriculomegaly	14	35	5	23
Hydrocephalus	6	8	—	4
Partial absence septum pellucidum	9	30	7	12
Complete ACC	15	3	5	2
Partial ACC	—	27	—	1

[a] Compilation from the literature.
ACC, agenesis of the *corpus callosum*.

the Craniofacial Centre at Children's Hospital, Boston, between 1978 and 2004, were reviewed with the approval of our Institutional Review Board for human research. Prenatal images, which were available for the two cases, are presented below. Prenatal sonograms were reviewed by a perinatologist (RR) and radiologist (CB), and prenatal MRI images were reviewed by a neuroradiologist (CR).

Clinical reports

Patient 1

A 37-year-old G3SAB2 had prenatal ultrasound imaging at 16 weeks that showed her fetus to have prominent lateral ventricles, measuring 9 mm in diameter at the level of the atrium (upper limit of normal 10 mm), and follow-up study was recommended. At 19-weeks' gestation,

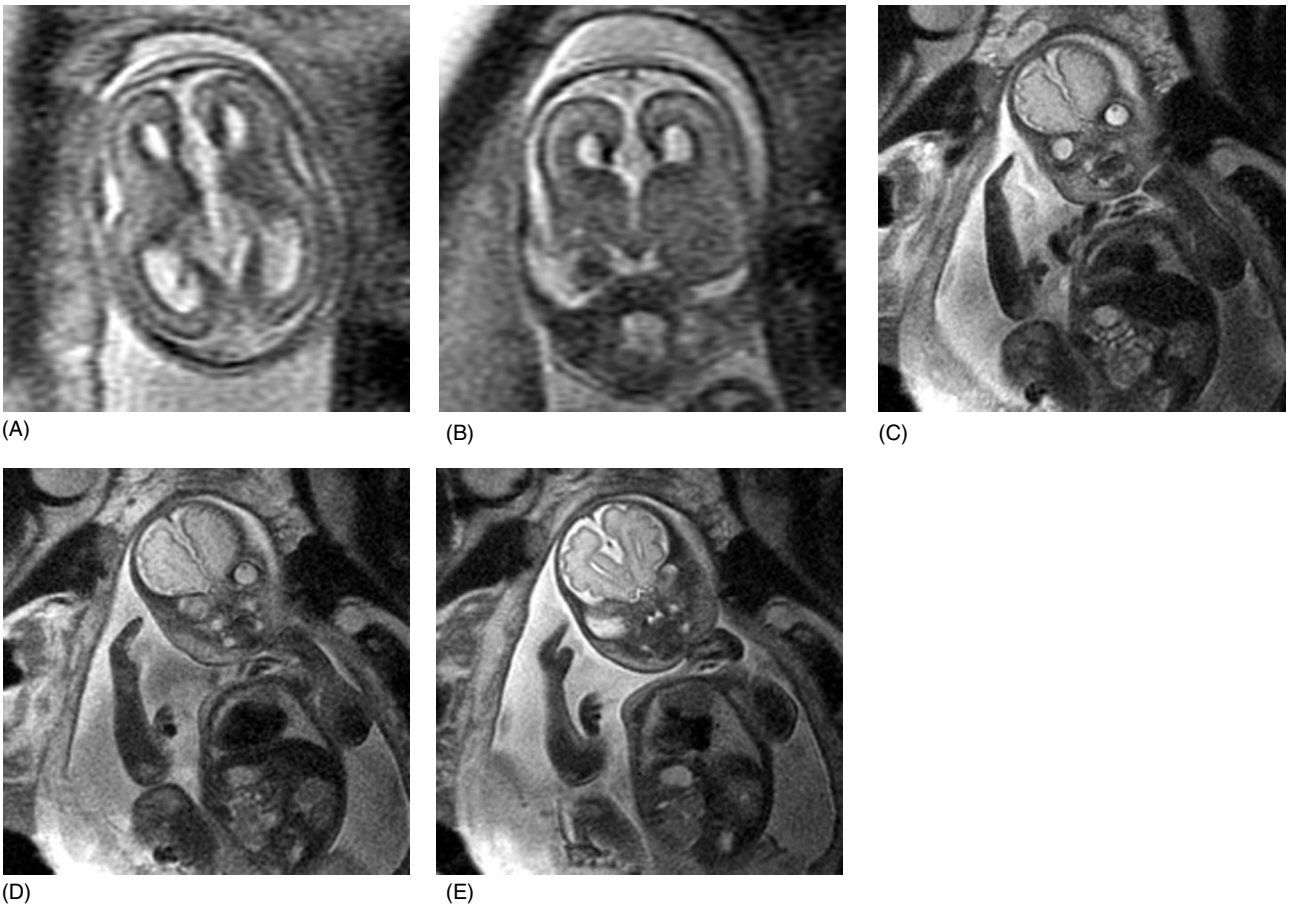

Figure 1—Prenatal MRI of patient 1. Axial (A) and coronal (B) T2 weighted single shot fast spin echo MR images at 19 weeks of gestational age demonstrate absence of the *corpus callosum* and associated colpocephaly. The third ventricle communicates with the interhemispheric fissure. The ventricles have a parallel orientation. There is a deficiency of callosal tissue across the midline. (C)–(E) Coronal images at 32 weeks of gestatio reveal malpositioned hands, with a broad thumb, and a spade-like hand and abnormal head shape. (A), (C), (D), (E) reproduced with permission from Levine D., ed. Atlas of Fetal MRI. Boca Raton, FL: Taylor & Francis Group, 2005. Copyright © 2005 From Atlas of Fetal MRI by Levine D, ed. Reproduced by permission of Routledge/Taylor & Francis Group, LLC

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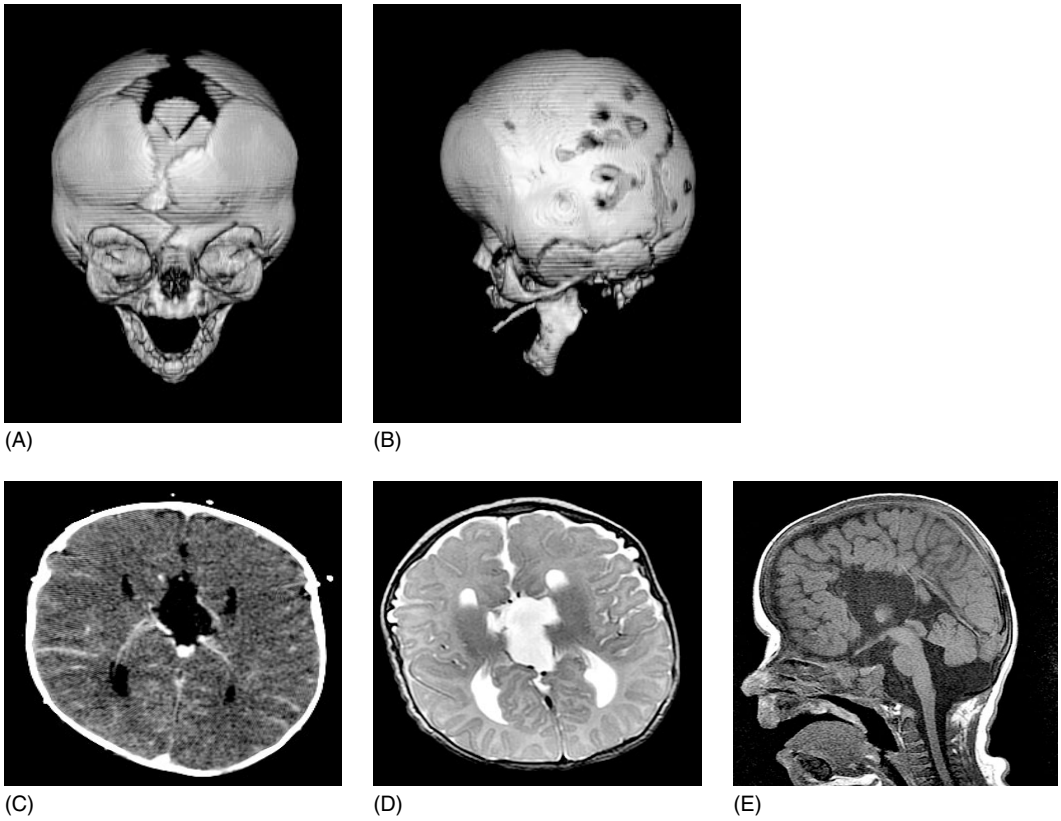

Figure 2—(A) Postnatal 3D CT scan of patient 1 confirms (1) bilateral coronal synostosis, (2) widely patent sagittal and metopic sutures, (B) (3) shallow orbits, (4) midfacial hypoplasia. (C) Axial CT with contrast, (D) axial FSE T2-weighted MRI and (E) sagittal T1 MRI image confirm agenesis of the *corpus callosum*

ACC was suspected based on parallel orientation of the lateral ventricles and colpocephaly. Magnetic Resonance Imaging (MRI) confirmed ACC. No other abnormality was detected at that time. Fetal echocardiogram at 20 weeks' gestation was normal. Amniocentesis showed a normal male karyotype (46,XY). The couple was counseled that ACC appeared isolated, but that some brain malformations might not be apparent in the second-trimester, and that a genetic syndrome might not be evident until after birth. They decided to continue the pregnancy. The subsequent MRI examination at 32 weeks demonstrated orbital hypertelorism, slightly oblong cranial shape and confirmed ACC with slit-like frontal horns, and nondilated lateral ventricles, measuring 7 mm at the ventricular atrium. In retrospect, abnormal hands were present as indicated by MRI, but were not detected at the time of the examination (Figure 1(C)–(E)). Other findings noted only retrospectively were a shallow anterior cranial fossa and exorbitism.

A male infant was delivered at 39 weeks by cesarean section. The infant had the typical facial appearance of Apert syndrome, including turricephaly, prominent downslanted eyes, hypertelorism and midfacial hypoplasia. He weighed 3485 g (75th percentile), his length was 55.5 cm (97th percentile), and the occipital-frontal circumference (OFC) measured 34 cm (fifth percentile). Other features included a beaked nose, depressed nasal bridge and widely patent fontanelles and sagittal suture. There was complex syndactyly of the four right fingers ('mitten hand') and, on the left, syndactyly of the middle three fingers. The toes were fused, with discrete toenails. On echocardiography the only abnormality was mild tricuspid regurgitation. Analysis of the *FGFR2* gene revealed the S252W mutation, the most common mutation associated with Apert syndrome.

Postnatally three-dimensional CT demonstrated bilateral coronal craniosynostosis and a wide midline calvarial defect, shallow orbits and midfacial hypoplasia, consistent with Apert syndrome (Figure 2(A) and (B)). Postnatal MRI and CT confirmed the prenatal finding of ACC. (Figure 2(A) and (B)).

Patient 2

A 32-year-old G2P1 had a prenatal ultrasound examination at 19 weeks that was interpreted as normal. Even upon retrospective review, cranial views appeared unremarkable. No images of the hands were available for review. Sonography at 29 weeks showed borderline ventriculomegaly (lateral ventricles measuring 11 mm) and mild polyhydramnios. Ultrasound examination at 35 weeks revealed typical findings of ACC with parallel teardrop shaped ventricles, a dilated third ventricle communicating with the interhemispheric fissure, and abnormal cerebral gyral pattern (Figure 3(A)–(B)). The profile was notable for frontal bossing and midfacial hypoplasia. Exophthalmos exorbitism was present. The hands were abnormally postured with indistinct

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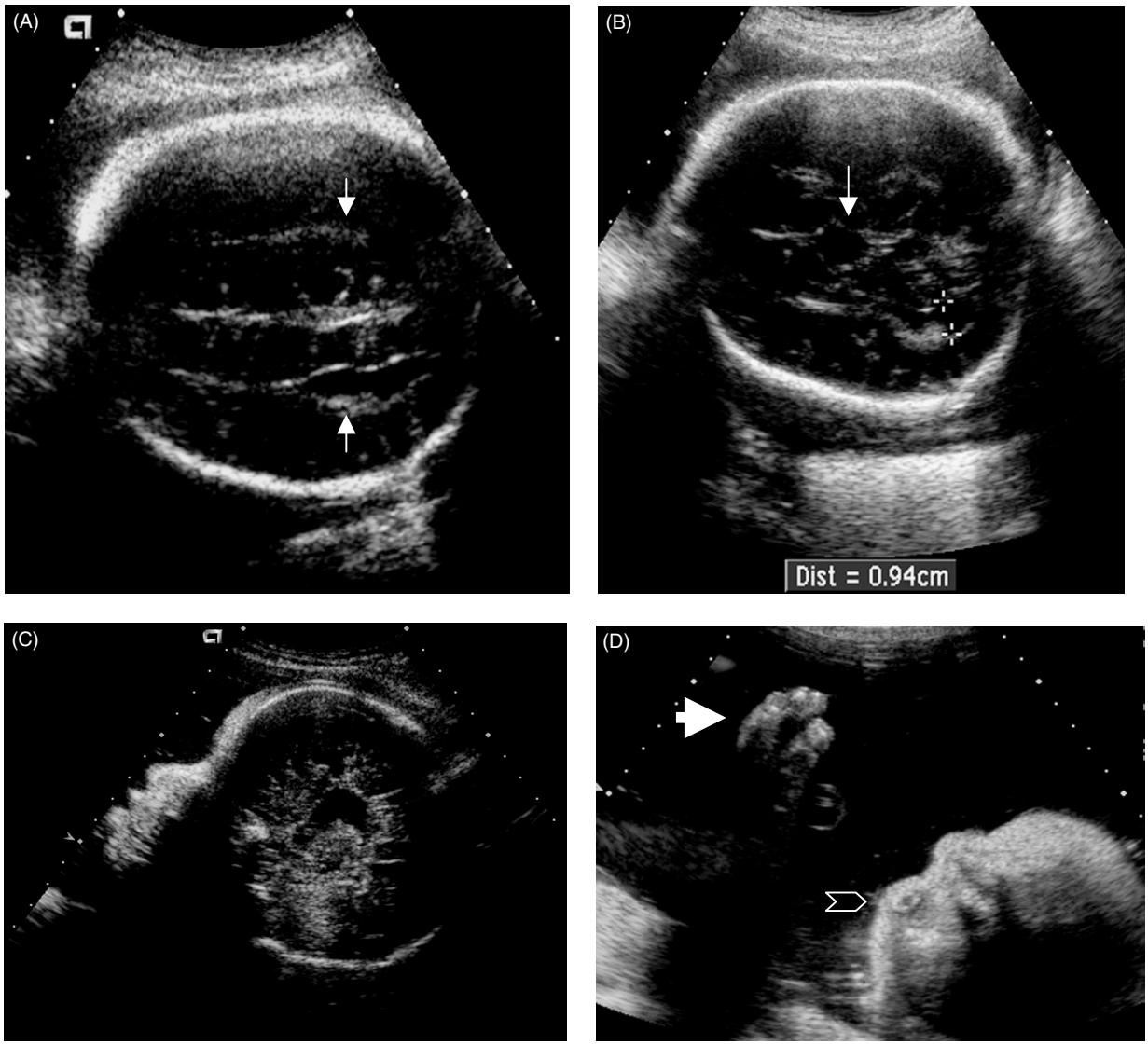

Figure 3—Prenatal ultrasound images of patient 2 at 35 weeks. (A) Axial view through the fetal head showing parallel lateral ventricles (arrows) with teardrop shape characteristic of agenesis of the *corpus callosum*. (B) Axial view through the fetal head at the plane of the biparietal diameter showing oblong cranial shape, dilated high rising third ventricle (arrow) and lateral ventricle measurement at the upper limit of normal for gestational age (calipers). (C) Fetal profile (midline sagittal view) showing frontal bossing and depressed nasal bridge. Cerebral sulci are seen radiating from the roof of the third ventricle. (D) Axial views through left hand and fetal head. Arrow indicates cross-sectional view through the digits of the left hand. Despite fetal movement distal digits including the thumb remained in constant apposition consistent with soft tissue syndactyly. Open arrowhead indicates prominent orbit (with lens visible)

digits (Figure 3(C)–(D)). Polyhydramnios persisted on follow-up examinations. Pulmonary artery stenosis with poststenotic dilatation was suspected. An amniocentesis documented a normal karyotype (46,XY). The family declined formal genetic counseling.

A male infant was delivered vaginally at term. He weighed 3500 g (75th percentile), with length 49.5 cm (50th percentile) and OFC 34 cm (fifth percentile). Physical findings included brachycephaly, bilateral coronal synostosis, midfacial hypoplasia and symmetrical syndactyly of fingers and toes. Apgar scores were one at 1 min and six at 5 min. He required intubation in the delivery room, and repeated episodes of airway obstruction prompted tracheostomy on the second day of life. Cranial CT scan revealed craniosynostosis, stenosis of the external auditory canals and bilateral jugular foraminal stenosis. There was diffuse narrowing of the nasal passages associated with midfacial hypoplasia. Postnatal MRI confirmed ACC (Figure 4). Echocardiogram demonstrated a secundum atrial septal defect, aneurysm of the septum primum and pulmonary stenosis. The clinical diagnosis was Apert syndrome and the common mutation S252W of *FGFR2* was identified.

DISCUSSION

Prenatal sonographic diagnosis of Apert syndrome has relies upon detection of the triad of abnormal cranial shape, midfacial hypoplasia and bilateral syndactyly of

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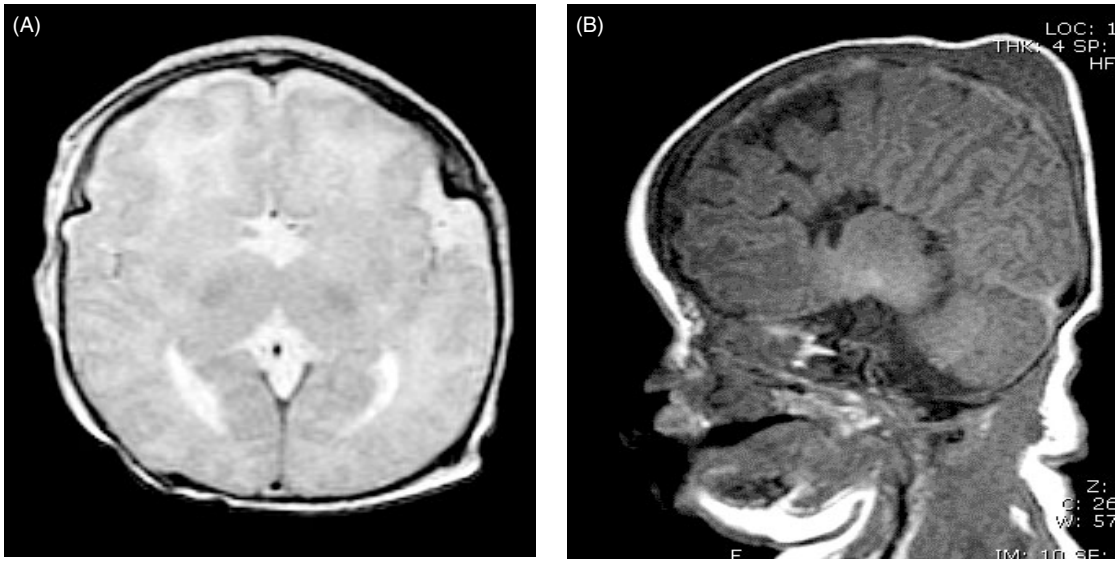

Figure 4—MRI of the brain in newborn patient 2. Axial (A) FSE T2-weighted and sagittal (B) T1 spin echo MR images show characteristic finding of agenesis of the *corpus callosum* with colpocephaly and absence of the cingulate gyrus. The head, and brachycephalicy

Table 2—Ultrasound findings that eventually have led to the prenatal diagnosis of Apert syndrome

Ultrasound findings (initial findings)	Reference
(Cupped fingers)	Leonard *et al*., 1982[a]
(Polyhydramnios)	Hill and Thomas, 1987
Mitten hands, irregularly shaped skull	Narayan and Scott, 1991[a]
Thickened nuchal folds	Chenoweth-Mitchell and Cohen, 1994 Parent *et al*., 1994
(Polyhydramnios)	Kaufman *et al*., 1997
(Polyhydramnios)	Filkins *et al*., 1997
(Mitten hands), craniosynostosis, frontal bossing, reduced foot length bilaterally with abnormal toes	Ferreira *et al*., 1999
(Abnormal appearance of skull) Deformed occipital part of cerebrum and lateral ventricles, frontal bossing, low nasal bridge, abnormal appearance of fetal hands and feet	Pooh *et al*., 1999
(Turribrachycephaly and syndactyly of hands and feet)	Boog *et al*., 1999
(Arthrogryposis)	Mahieu-Caputo *et al*., 2001
(Cardiovascular abnormalities)	Mahieu-Caputo *et al*., 2001
(Mild dilation of lateral cerebral ventricles, choroid plexus cysts, clenched hands) cloverleaf skull, proptosis, midfacial hypoplasia	Skidmore *et al*., 2003
(Hypoplastic left heart), cloverleaf cranium, dilated cerebral ventricles	Skidmore *et al*., 2003

[a] Family history of Apert syndrome.

the hands and feet. Ocular hypertelorism and exorbitism are also important associated features that alert the sonologist to the possibility of Apert syndrome or one of the other craniosynostosis syndromes. Targeted ultrasonography in families at risk has identified mitten hands as early as 16–17 weeks' gestation (Narayan and Scott, 1991). Ferreira *et al*. (1999) reported the first sporadic case diagnosed in second-trimester prompted by fetal ultrasonographic observation of 'mitten hands' and changes related to craniosynostosis at 20 weeks' gestation. However, the changes in cranial and orbital shape are often not marked until late in the second-trimester and become gradually more apparent during the third. Routine second-trimester ultrasonographic examination, which is most commonly performed at 17–18 weeks of gestation, may not reveal the cranial abnormalities. In the literature, as in our cases, often various nonspecific ultrasound findings prompt more detailed follow-up studies that lead to identification of the pathognomonic findings.

In reviewing 14 reported cases of prenatally diagnosed Apert syndrome, we found 12 in families without a prior family history of the disorder (Table 2). At 17.3 weeks one of the *de novo* cases found by Skidmore and colleagues showed slight dilation of the lateral cerebral ventricles, choroid plexus cysts and clenched appearing hands leading to an initial suspicion of aneuploidy. At follow-up ultrasound at 19.5 weeks the triad of syndactyly, cloverleaf skull, and exophthalmos was appreciated leading to *FGFR2* analysis and discovery of the

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S252W mutation. In their second case, ultrasonography at 21 weeks revealed a hypoplastic left heart, cloverleaf cranium and dilated cerebral ventricles. Other nonspecific prenatal findings that have eventually led to the diagnosis of Apert syndrome include thickened nuchal folds (Chenoweth-Mitchell and Cohen, 1994), polyhydramnios (Hill and Thomas, 1987; Filkins *et al*., 1997; Kaufman *et al*., 1997), extremity abnormalities (Boog *et al*., 1999; Mahieu-Caputo *et al*., 2001) and cardiovascular abnormalities (Mahieu-Caputo *et al*., 2001). We propose that prenatal identification of ACC or borderline ventriculomegaly should also lead to consideration of Apert syndrome.

Cerebral malformations including ACC and ventriculomegaly were first described in Apert syndrome by de Leon *et al*. (1987) and have been frequently described in Apert patients since documented (Table 1). Cohen and Kreiborg reviewing the literature in 1990 found 15 cases of ACC among 113 postnatally diagnosed Apert patients. They included complete and partial absence of the corpus callosum for an overall incidence of 13%. Renier *et al*. (1996) reported complete ACC in 5% and partial ACC in 45% of a series of 60 cases. Yacubian-Fernandes *et al*. (2004) reported hypoplasia of the corpus callosum in 5/18 patients. In our series, in addition to the two cases we describe here of complete callosal agenesis (7%), partial ACC was present in one case (1%) (Quintero-Rivera *et al*., 2006). Gershoni-Baruch *et al*. (1991) present a case report of Apert syndrome with occipital encephalocele and ACC.

The abnormal cranial shape and orbital hypertelorism so typical of Apert syndrome and the other craniosynostoses may be absent or very subtle in the second-trimester of pregnancy, becoming obvious only in the third-trimester, as in our second patient and as noted by Pooh *et al*. (1999). Complete assessment of the corpus callosum is difficult before 19–20 weeks of gestation, because of incomplete development prior to this time. However, evaluation of the lateral cerebral ventricles and documentation of presence of the septum pellucidum in the biparietal diameter view is part of a routine second-trimester obstetric ultrasound evaluation (ACOG, 2004) and may be useful in the early diagnosis of ACC, as illustrated by our patients and several other prenatally detected cases. Agenesis of the corpus callosum is associated with changes in the position and shape of the lateral and third ventricles and with absence of the septum pellucidum. Subtle abnormalities in the ventricles should thus be reassessed after 19 weeks, and fetal MRI may be useful in this setting. Detailed evaluation of the fetal hands is not part of standard obstetrical ultrasonographic protocols, but should be performed in high-risk cases, such as those with ventriculomegaly or ACC. Although sometimes difficult, evaluation of the digits is usually possible in the second-trimester (Reiss *et al*., 1995), and can aid in the detection of many craniosynostotic syndromes, including Apert and Pfeiffer, and should be attempted during a targeting scan once other anomalies are identified.

Prenatal diagnosis of Apert syndrome is challenging. Although molecular testing is now available to confirm the diagnosis once suspected, early detection in families with no prior affected children requires recognition of prenatal sonographic findings, which can be subtle until the third-trimester. Absence of the septal leaflets or borderline dilatation of the ventricles are nonspecific findings with diverse associations such as septooptic dysplasia, holoprosencephaly, ACC, or can be apparently isolated findings. Our series suggests that Apert syndrome should also be considered in the differential diagnosis of these findings particularly if there is associated ocular hypertelorism or hand anomalies. Intracranial abnormalities may precede the development of cranial changes in Apert syndrome, and can be detected before development of the corpus callosum is complete. Since these findings have a wide differential diagnosis, amniocentesis for karyotype chromosome analysis is routinely recommended to evaluate for the presence of associated cytogenetic abnormalities. We propose consideration of specific testing for the two missense mutations associated with Apert syndrome on amniocytes of fetuses with these anomalies if the karyotype proves normal.

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REFERENCES

American College of Obstetrics and Gynecology. 2004. ACOG practice bulletin: ultrasonography in pregnancy. *Obstet Gynecol* **104**: 1449–1458.

Boog G, Le Vaillant C, Winer N, David S, Quere MP, Nomballais MF. 1999. Contribution of tridimensional sonography and magnetic resonance imaging to prenatal diagnosis of Apert syndrome. *Fetal Diagn Ther* **14**: 20–23.

Chan CT, Thorogood P. 1999. Pleiotropic features of syndromic craniosynostoses correlate with differential expression of fibroblast growth factor receptors 1 and 2 during human craniofacial development. *Pediatr Res* **45**: 46–53.

Chenoweth-Mitchell C, Cohen GR. 1994. Prenatal sonographic findings of Apert syndrome. *J Clin Ultrasound* **22**: 510–514.

Cohen MM, Kreiborg S. 1990. The central nervous system in the Apert syndrome. *Am J Med Genet* **35**: 36–45.

de Leon GA, de Leon G, Grover WD, Zaeri N, Alburger PD. 1987. Agenesis of the corpus callosum and limbic malformation in Apert syndrome (type acrocephalosyndactyly). *Arch Neurol* **44**: 979–982.

Ferreira JC, Carter SM, Bernstein PS, *et al*. 1999. Second-trimester molecular prenatal diagnosis of sporadic Apert syndrome following suspicious ultrasound findings. *Ultrasound Obstet Gynecol* **14**: 426–430.

Filkins K, Russo JF, Boehmer S. 1997. Prenatal ultrasound and molecular diagnosis of Apert syndrome. *Prenat Diagn* **17**: 1081–1084.

Gershoni-Baruch R, Nachlieli T, Guilburd JN. 1991. Apert's syndrome with occipital encephalocele and absence of corpus callosum. *Childs Nerv Syst* **7**: 231–232.

Glaser RL, Broman KW, Schulman RL, Eskenazi B, Wyrobek AJ, Jabs EW. 2003. The paternal-age effect in Apert syndrome is due, in part, to the increased frequency of mutations in sperm. *Am J Hum Genet* **73**: 939–947.

Goriely A, McVean GA, Rojmyr M, Ingemarsson B, Wilkie AO. 2003. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. *Science* **301**: 643–646.

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Hehr U, Muenke M. 1999. Craniosynostosis syndromes: from genes to premature fusion of skull bones. *Mol Genet Metab* **68**: 139–151.
Hill BD, Thomas RJ, Peterson CS. 1987. The ultrasonic detection of Apert syndrome. *J Ultrasound Med* **6**: 601–604.
Kaufman K, Baldinger S, Pratt L. 1997. Ultrasound detection of Apert syndrome: a case report and literature review. *Am J Perinatol* **14**: 427–430.
Leonard CO, Daikoku NH, Winn K. 1982. Prenatal fetoscopic diagnosis of the Apert syndrome. *Am J Med Genet* **11**: 5–9.
Mahieu-Caputo D, Sonigo P, Amiel J, *et al*. 2001. Prenatal diagnosis of sporadic Apert syndrome: a sequential diagnostic approach combining three-dimensional computed tomography and molecular biology. *Fetal Diagn Ther* **16**: 10–12.
Narayan H, Scott IV. 1991. Prenatal ultrasound diagnosis of Apert's syndrome. *Prenat Diagn* **10**: 187–192.
OMIM # 101 200. Online Mendelian Inheritance on Man, http://www.ncbi.nml.nih.gov/omim.
Parent P, Le Guern H, Munck MR, Thoma M. 1994. Apert syndrome, an antenatal ultrasound detected case. *Genet Couns* **5**: 297–301.
Pooh RK, Nakagawa Y, Pooh KH, Nakagawa Y, Nagamachi N. 1999. Fetal craniofacial structure and intracranial morphology in a case of Apert syndrome. *Ultrasound Obstet Gynecol* **13**: 274–280.
Quintero-Rivera F, Robson CD, Reiss RE, *et al*. 2006. Intracranial anomalies detected by imaging studies in 30 patients with Apert syndrome. *Am J Med Genet* **140**: 1337–1338.
Reiss RE, Foy PM, Mendiratta V, Kelly M, Gabbe SG. 1995. Ease and accuracy of evaluation of fetal hands during obstetrical ultrasonography: a prospective study. *J Ultrasound Med* **14**: 813–820.
Renier D, Arnaud E, Cinalli G, Sebag G, Zerah M, Marchac D. 1996. Prognosis for mental function in Apert's syndrome. *Neurosurgery* **85**: 66–72.
Skidmore DL, Pai AP, Toi A, Steele L, Chitayat D. 2003. Prenatal diagnosis of Apert syndrome: report of two cases. *Prenat Diagn* **23**: 1009–1013.
Yacubian-Fernandes A, Palhares A, Giglio A, *et al*. 2004. Apert syndrome: analysis of associated brain malformations and conformational changes determined by surgical treatment. *J Neuroradiol* **31**: 116–122.

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