Agenesis of the Corpus Callosum: An MR Imaging Analysis of Associated Abnormalities in the Fetus


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**BACKGROUND AND PURPOSE:** Anomalies associated with callosal agenesis (ACC) found postnatally have been well documented. However, to our knowledge, no detailed MR imaging analysis of associated anomalies has been reported in a large cohort of fetuses with ACC. This study will assess those anomalies and compare them with postnatal cohorts of ACC, to identify associated fetal brain abnormalities that may give insight into etiology and outcome.

**MATERIALS AND METHODS:** All cases of ACC diagnosed on fetal MR imaging during an 11-year period were retrospectively reviewed, including fetal MR imaging, postnatal MR imaging, and autopsy findings. Neurodevelopmental outcome was classified as poor in children with seizures and/or severe neurodevelopmental impairment or in cases of neonatal death.

**RESULTS:** Twenty-nine cases of ACC were identified. Median gestational age was 26.14 weeks (range, 19.71–36.43 weeks). Twenty-three fetuses had delayed sulcation and/or too-numerous cortical infoldings (abnormal morphology). Fifteen fetuses had cerebellar and/or brain stem abnormalities. Fetal MR imaging findings suggested a genetic syndrome in 5 fetuses and an acquired etiology or genetic/metabolic disorder in 2 fetuses. Findings were confirmed in 8 cases with postnatal MR imaging, except for delayed sulcation and small vermis, and in 4 cases with autopsy, except for periventricular nodular heterotopia and abnormalities in areas not examined by autopsy. Neurodevelopmental outcome was good in 7 and poor in 9 children. Abnormal sulcal morphology and/or infratentorial abnormalities were present in those with poor outcome and absent in those with good outcome.

**CONCLUSIONS:** ACC is infrequently isolated in fetuses. Abnormal sulcation is common and suggests more diffuse white matter dysgenesis in these fetuses.

The corpus callosum is the largest commissure connecting the cerebral hemispheres. It develops from the laminae reunions of His between 8 and 20 weeks. New insights into the formation of the corpus callosum have identified molecules secreted by midline glial populations that are involved in attracting and repelling axons so that they cross the midline and form the corpus callosum. Thus, formation of the corpus callosum is complex; this characteristic may explain why most cases of callosal agenesis (ACC) are not isolated.

ACC can be detected prenatally by routine sonography, for which the important signs include absence of the cavum septum pellucidum, colpocephaly, high-riding third ventricle, and widening of the interhemispheric fissure. Fetal MR imaging is clinically helpful in suspected cases of ACC because it can confirm that the callosum is absent. Moreover, additional abnormalities occur frequently with ACC and are best detected by fetal MR imaging. Although the prognostic implications of prenatally detected ACC are not fully understood, evidence suggests that the presence of additional brain abnormalities imparts a worse prognosis. We chose to review our experience with cases of ACC and compare them with postnatal cohorts with ACC, to identify associated fetal brain abnormalities that may give insight into the etiology and outcome.

**Materials and Methods**

We identified all cases of complete ACC diagnosed by fetal MR imaging performed at our institution between November 1996 and October 2007. All fetal MR imaging examinations were performed on a 1.5T magnet (GE Healthcare, Milwaukee, Wis) using a torso phased-array coil. All fetal MR imaging was performed without maternal or fetal sedation. Single-shot fast spin-echo T2-weighted images were acquired in the axial, sagittal, and coronal planes. In 24 cases, single-shot fast spin-echo T2-weighted images were acquired by using a new technique known as real-time imaging for the fetus, which allows the technologist to interactively control imaging parameters such as slice position, orientation, FOV, and thickness. All images were 3-mm thick with no skip, though in 1 case, the axial images were 4 mm thick, and in 1 case, the sagittal images were 5 mm thick. FOV ranged from 20 to 28 cm depending on gestational age. Whenever possible, imaging was repeated until at least 2 adequate axial, coronal, and sagittal sets of images were obtained, in order to decrease the effect of fetal motion on the study. Nineteen patients also had 5-mm axial fast multiplanar spoiled gradient-recalled T1-weighted images. MR images were retrospectively reviewed by 2 pediatric neuroradiologists who were blinded to the sonographic findings and clinical information. All patients had good- (n = 25) or fair- (n = 4) quality images; no patient had poor-quality images with severe fetal motion or poor signal intensity to noise.

The following structures were assessed on the fetal MR imaging and scored as normal, abnormal, or suspicious: sulcation pattern and developing cortex; morphology of the ventricles; supratentorial parenchymal signal intensity; supratentorial multilayered pattern; morphology and signal intensity of the deep gray nuclei; morphology of the ventricular walls; and morphology of the brain stem, cerebellum, and brainstem, and cerebellar vermis. All cases of ACC diagnosed on fetal MR imaging during an 11-year period were retrospectively reviewed, including fetal MR imaging, postnatal MR imaging, and autopsy findings. Neurodevelopmental outcome was classified as poor in children with seizures and/or severe neurodevelopmental impairment or in cases of neonatal death.
and vermis. A finding was considered suspicious if it was only visualized in 1 plane and could not be confirmed in another plane. Ventriculomegaly was not considered an additional finding because dilation of the posterior lateral ventricles can be attributed to ACC. Sulcation delay was assessed on the basis of published studies.\textsuperscript{17,18} Primary sulci were identified, and each fetus was assigned a sulcation score on the basis of the number of primary sulci present with a maximum score of 34 (17 sulci on each side).

A sulcation score was assigned in a similar manner to 37 control fetuses on the basis of review of their fetal MR images (median gestational age by last menstrual period, 22.71 weeks; range, 21–34 weeks). All control fetuses had normal fetal MR imaging findings and underwent fetal MR imaging for family history of neurologic abnormalities (n = 22); as volunteers recruited from sonography and/or obstetrics clinics (n = 8); for a maternal history of cerebellar arteriovenous malformation and hemorrhage (n = 1); or for suspected abnormality on sonography, including dilated bowel (n = 1), prominent posterior fossa fluid (n = 2), questionable small vermis on 17-week sonography with a normal vermis seen on 19-week sonography (n = 2), questionable prominent midline fluid collection (n = 1), a prominent choroid plexus (n = 1), and possible small head size on initial sonography, with normal head size on follow-up sonography (n = 1).

A logistic function was fitted by nonlinear least squares with the sulcation score as the outcome and gestational age by last menstrual period (LMP) and disease status (control versus ACC) as covariates.\textsuperscript{19} Thirteen patients had repeated measurements in the dataset. These were modeled as independent observations because there was not enough repeated data to support a longitudinal model. The fitted logistic curve for controls was compared against the curve for patients (4- to 6-mm section thickness, 0.5- to 2-mm skip) in all patients except 1; axial spin-echo T2-weighted images in all patients on the basis of review of their fetal MR images (median gestational age by last menstrual period (LMP) and disease status (control versus ACC) as covariates.\textsuperscript{19} Thirteen patients had repeated measurements in the dataset. These were modeled as independent observations because there was not enough repeated data to support a longitudinal model. The fitted logistic curve for controls was compared against the curve for patients (4- to 6-mm section thickness, 0.5- to 2-mm skip) in all patients except 1; axial spin-echo T2-weighted images in all patients (4- to 6-mm section thickness, 0.5- to 2-mm skip); sagittal spin-echo T1-weighted images (3- to 5-mm thickness; skip, 1 mm) in 5; and axial spin-echo T1-weighted images (4- to 5-mm thickness; skip, 1–1.5 mm) in 3. Autopsy reports of the fetal brain were also reviewed when available and compared with fetal MR imaging findings.

Neurodevelopmental outcome was assessed by a postnatal questionnaire administered to the parents (for living children), which included questions about attainment of neurodevelopmental milestones, presence of seizures, hospitalizations, and need for therapeutic interventions, and by review of medical records (for both living children and cases of neonatal death). Living children who had no seizures, motor, or cognitive impairment were classified as having a good neurodevelopmental outcome. Neonatal deaths or children with seizures, motor, and/or cognitive impairment were classified as having a poor neurodevelopmental outcome. Five cases have been previously published.\textsuperscript{5}

This study was approved by our institutional review board.

Results

Twenty-nine cases of ACC were diagnosed on fetal MR imaging during an 11-year period. Median gestational age based on LMP was 26.14 weeks (range, 19.71–36.43 weeks). Median gestational age based on sonographic measurements was 26.57 weeks (range, 19.86–37.00 weeks). There was an average interval of 5.38 days between the sonography and fetal MR imaging (range, 0–17 days). Twenty-seven cases were singleton pregnancies, and 2 cases were dichorionic diamniotic twin pregnancies in which 1 twin had ACC. Three fetuses also had a second antenatal MR exam obtained between 6 and 7.43 weeks (mean, 6.48 weeks) after the first fetal MR exam. Twenty-six fetuses were referred for fetal MR imaging for sonographically suggested ACC, 1 fetus was referred for isolated mild ventriculomegaly on sonography, 1 was referred for ventriculomegaly and a small cerebellum, and 1 was referred for a small vermis. Additional findings were detected by sonography in 13 fetuses and included the following: small or absent vermis (n = 4), small or absent cerebellum (n = 4), irregularity of the ventricular wall suggestive of periventricular nodular heterotopia (n = 6), choroid plexus cysts (n = 3), abnormal brain stem (n = 2), germinal matrix and intraventricular hemorrhage (n = 1), and a focal sulcal malformation (n = 1).

Fetal MR Imaging Findings

Sulcation abnormalities were present in 23 fetuses (on-line Table). Twelve patients had abnormal sulcal morphology characterized either by abnormal, too numerous infoldings (11 fetuses) or by absent sulcation (1 case). In 3 patients, the abnormal, too numerous cortical infoldings were unilateral, though there was delayed sulcation in the contralateral cerebral hemisphere (Fig 1A). A delay in sulcation was observed in 20 patients, including those with normal sulcal morphology. Interestingly, sulcation delay was detected only in those fetuses that were 29 weeks or younger; those 30 weeks or older did not have sulcal delay.

Abnormal morphology of the lateral ventricle was always seen in association with abnormal sulcal morphology (Fig 2A) and always involved at least the frontal horn, which was either incompletely formed, showed undulations along the margin, and/or was focally dilated (Fig 2B). The abnormality was unilateral in 5 of the 7 cases and occurred on the side with the abnormal cortical infoldings or more severe abnormal cortical infoldings (if both cerebral hemispheres were involved). In 5 fetuses, the atria were also enlarged. A total of 25 fetuses had enlargement of the ventricular atria, with a median size of 13.5 mm (range, 10–68.2 mm).

Abnormal signal intensity in the supratentorial parenchyma was characterized most often by T2 hypointensity underlying areas of abnormal cortical infoldings (Fig 1B) or diffusely in association with lissencephaly. Two patients had heterogeneous signal intensity in the parenchyma with areas of injury, hemorrhage, and/or necrosis (Fig 3). The multilay-
ered pattern (which is normally seen between the 20th and 29th gestational weeks) was absent in 9 fetuses and indistinct in 2 (Fig 2A). All had sulcation delay. In 7 fetuses, the affected hemisphere also had abnormal sulcal morphology, whereas 2 also had severe parenchymal destruction.

Three patients had dysplastic-appearing deep gray nuclei characterized by small size and abnormal shape, and all had associated abnormal sulcal morphology and posterior fossa abnormalities (Fig 4). The deep gray nuclei were small, with areas of mixed hypointense and hyperintense T2 signal intensity consistent with hemorrhage and necrosis in 2 fetuses with parenchymal signal-intensity abnormalities, sulcation delay, and posterior fossa abnormalities (Fig 3).

Periventricular nodular heterotopia (PVNH) were present in 4 fetuses (Fig 5). In 5 fetuses, nodularity along the ventricular wall was seen in only 1 plane and thus was considered suspicious. PVNH was usually seen in association with abnormal sulcal morphology, though it was seen only in association with delayed sulcation in 1 fetus and it was the only additional finding in 1 fetus.

Fifteen fetuses had infratentorial brain abnormalities. The cerebellum was abnormal in 13; suspicious in 1 with a small vermis, where the right cerebellum appeared small with abnormal orientation of the folia on 1 axial image; and suspicious in 1, with an asymmetric appearance of the fourth ventricle and right cerebellum appearing small on only 1 axial series. Both cerebellar hemispheres were abnormal in 10 fetuses, and unilateral involvement was seen in 3 (Fig 6A). The cerebellum was small in 7 fetuses, and abnormal morphology was identified in 6, 5 of which were also small. Two of the fetuses with a small cerebellum had evidence of compression of the posterior fossa structures by either a posterior fossa cyst or hydrocephalus. The vermis was absent in 2 fetuses and small in 10 and was usually associated with an abnormal cerebellum and brain stem. The brain stem was abnormal in 10 of the 13 fetuses with an abnormality of the cerebellar hemispheres and in 1 with a normal cerebellum but small vermis (Fig 6B). The
confirmed by autopsy. A diagnosis of Walker-Warburg syndrome was higher in those patients with abnormal sulcal morphology ($P = .00007$). The proportion of patients with abnormal deep gray nuclei compared with those with normal deep gray nuclei ($P = .03$). The proportion of patients with abnormal deep gray nuclei was higher in those patients with posterior fossa abnormalities compared with those with a normal posterior fossa ($P = .04$). There was a trend toward a greater proportion of patients with abnormal sulcal morphology in those with posterior fossa abnormalities compared with those with a normal posterior fossa ($P = .054$).

**Postnatal Follow-Up, Postnatal MR Imaging, and/or Autopsy Findings**

There were 16 live births. Postnatal MR imaging was performed in 8 patients (on-line Table). Postnatal MR imaging was performed between 2 days and 23 months of age. An autopsy was performed in 4 cases (on-line Table) and in 1 case, both a postnatal MR exam and neonatal autopsy were performed. Fetal autopsy was performed 5 days after the fetal MR exam in 1 case. In 3 cases, neonatal death occurred between 1 and 5 days of birth, and a postnatal autopsy was performed (interval between fetal MR exam and autopsy was 2.43 weeks, 3.71 weeks, and 11.28 weeks).

Fetal MR imaging findings were confirmed in all cases with postnatal MR imaging, except for delay in sulcation, which was not present on the postnatal MR images; 1 case of small vermis; and 2 cases of suspected PVNH. In all 3 cases with PVNH on fetal MR imaging, findings were confirmed on postnatal MR imaging. However, in 2 cases with fetal MR imaging findings suspicious for PVNH, there was no evidence of PVNH on postnatal MR imaging. Findings on postnatal MR imaging that were not detected on fetal MR imaging included a dorsal defect in the pons, small foci of white matter injury, germinal matrix hemorrhage, an area of deep cortical infolding consistent with cortical malformation (in a case in which fetal MR imaging was too limited to assess sulcal morphology), and dysplastic deep gray nuclei (in a case in which fetal MR imaging was too limited to assess the deep gray nuclei).

Fetal MR imaging findings were confirmed in nearly all cases with autopsy, except for 1 case of dysplastic deep gray nuclei in which postmortem did not examine the deep gray nuclei, 1 case of destructive/hemorrhagic changes in the posterior parietal and occipital lobes that were not clearly examined on autopsy (the postmortem report only commented on the normal frontal lobes and did not comment on the parietal, occipital, or temporal lobes), and 2 cases of PVNH not mentioned in the postmortem report. Interestingly, in 1 case with both postnatal MR imaging and neonatal autopsy, PVNH was confirmed by postnatal MR imaging but not mentioned on the postmortem report; this discrepancy likely reflects the limitations of autopsy. Neuroradiologic findings that were not seen on fetal MR imaging included heterotopia in the cerebellar white matter, ectopic neurons in the subcortical cerebral white matter, small/absent cranial nerves, absent olfactory bulbs, and 1 case of acute intraventricular and left cerebellar hemorrhage in which the new findings could possibly have been related to termination of pregnancy performed after the fetal MR imaging.

Of the 16 live births, 3 neonates died during the neonatal

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**Fig 4.** Patient 10: 23-gestational-week fetus. Axial image demonstrates small abnormally shaped deep gray nuclei [arrows]. The Sylvian fissures are absent, and there is diffuse thinning and hypointensity of the parenchyma. A diagnosis of Walker-Warburg syndrome was confirmed by autopsy.

**Fig 5.** Patient 29: 36.43-gestational-week fetus. Axial image demonstrates bilateral periventricular nodular heterotopia (black arrows) and mild ventriculomegaly.
period, 6 have seizures and/or severe neurodevelopmental dis-
abilities, and 7 are healthy or have only mild neurodevelopmental
delays (on-line Table). The causes of neonatal death were prema-
turity in the setting of Walker-Warburg syndrome, pneumotho-
rax and respiratory failure in the setting of brain stem dysfunc-
tion, and respiratory failure and minimal motor function in the
setting of brain stem compression from severe hydrocephalus. Of
the living patients, 1 has required placement of a ventriculoperi-
toneal shunt but has done well developmentally. The proportion
of patients with abnormal sulcal morphology was higher in those
with poor neurodevelopmental outcome compared with those
with good neurodevelopmental outcome ($P = .01$). In the pa-
tients with poor neurodevelopmental outcome, there was also a
higher proportion of cerebellar abnormalities ($P = .003$), ver-
mian abnormalities ($P = .003$), and brain stem abnormalities
($P = .001$), compared with those with good neurodevelopmental
outcome. Among those with good neurodevelopmental out-
come, 1 had PVNH, 1 had suspicion for PVNH (not confirmed
by postnatal MR imaging), 3 had sulcation delay, and 1 had an
indistinct multilayered pattern.

**Discussion**

We observed additional brain abnormalities in 27/29 of fe-
tuses with ACC. The most common findings were sulcation
abnormalities, followed by posterior fossa abnormalities. Ab-
normal sulcal morphology (12/28) could be detected as early
as 19 gestational weeks and was just as frequently detected in
fetuses less than 24 gestational weeks as it was in fetuses older
than 24 gestational weeks. Abnormal sulcal morphology was
nearly always associated with multiple brain abnormalities
and was associated with a specific syndrome in 42% of cases.
Moreover, abnormal T2 hypointensity was often seen in the
prenatal studies using fetal MR imaging4,5,10,28 and may be due to the younger gestational age and increased number of fetuses in our study. If we exclude sulcation delay, then 69% had additional findings on fetal MR imaging, which is more similar to findings in prior studies of fetal ACC using either fetal MR imaging and/or postnatal imaging.4,5,10,11,28,29 In addition, fetal MR imaging identified abnormalities not detected by prenatal sonography in most (83%) patients; this difference is in agreement with prior studies and further supports the need for fetal MR imaging in cases of sonographically suspected ACC.5,28,30,32,33

In most fetuses, the additional abnormalities were suggestive of a developmental etiology. In 5 fetuses (17%), there were extensive additional malformations identified by fetal MR imaging and suggestive of a genetic syndrome. These included 2 cases of Aicardi syndrome (1 confirmed postnatally), 1 case of Walker-Warburg syndrome (confirmed on autopsy), 1 case of clinically diagnosed oral-facial-digital syndrome (Type I), and 1 case of clinically diagnosed MASA syndrome. Interestingly, in 3/29 (10%) fetuses, there was evidence of destructive changes in the brain parenchyma, suggesting either an acquired etiology or genetic/metabolic abnormality, which can be associated with ACC.
Although nearly half of the cases resulted in termination of pregnancy, we did observe that the presence of additional abnormalities was associated with a poor neurodevelopmental outcome. In particular, abnormal sulcal morphology and/or infratentorial abnormalities were present in all patients with poor neurodevelopmental outcome and absent in all patients with good neurodevelopmental outcome. This is in agreement with findings in prior studies showing that the presence of additional brain abnormalities imparts a worse prognosis. 6-8,11-15 Interestingly, we did observe sulcation delay in many patients, including those with a good neurodevelopmental outcome, which suggests that the sulcation delay is actually a manifestation of the white matter dysgenesis that likely occurs in ACC, rather than a separate or additional abnormality. Longer term neurodevelopmental studies, however, are needed in these patients because developmental delays have been observed in children with prenatally diagnosed isolated ACC 7,10,12,34–35 and may not be detected until school age. 34

Our study is limited by the fact that fetal MR imaging was performed at many different gestational ages. It is likely that the sensitivity of fetal MR imaging for certain brain abnormalities might increase with increasing gestational age, given the increased head size and decreased fetal motion with increasing gestational age. Thus, performing fetal MR imaging at a consistent gestational age (and perhaps twice during the pregnancy) would probably give a better idea of the accuracy of the study, though it is not clinically practical. Postnatal MR imaging or autopsy was performed in only 38% of the cases, which limits our assessment of the accuracy of fetal MR imaging. In all cases in which a postnatal MR exam was performed, however, we were able to collect and view the images in a blinded manner. Our study is also limited by the short-term follow-up of many of our patients to younger than 2 years of age. Longer follow-up is needed, with more formal neurodevelopmental testing, because behavioral and cognitive difficulties may not be detected until the children reach school age. 34

Conclusions

Isolated ACC is infrequent, with sulcal and infratentorial abnormalities as common findings. Sulfation delay was present in most fetuses with ACC, including those with a good neurodevelopmental outcome, and suggests a more global white matter dysgenesis. Future studies using diffusion-weighted and diffusion tensor imaging in the fetus are needed to give insight into the structure of white matter in fetuses with ACC.

References