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Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus

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KEYWORDS: abnormalities; corpus callosum; magnetic resonance imaging; pregnancy outcome; prenatal diagnosis; ultrasonography

ABSTRACT

Objectives *To report, in a population of fetuses diagnosed with partial agenesis of the corpus callosum (PACC), the sonographic characterization, incidence of cerebral, extracerebral and chromosomal anomalies, and outcome. In addition, in some of our cases a comparison was made between findings on ultrasound and fetal magnetic resonance imaging (MRI).*

Methods *This was a retrospective study of all cases of PACC seen at two referral centers for prenatal diagnosis of congenital anomalies over a 10-year period. The following variables were assessed: indication for referral, additional cerebral and extracerebral malformations, chromosomal abnormalities, and pregnancy and fetal/neonatal outcome.*

Results *Among 54 cases of fetal agenesis of the corpus callosum detected in the referral centers during the observation period, PACC was diagnosed at prenatal sonography in 20 cases and confirmed at pre/postnatal MRI and necropsy examinations in 19 cases (35%). These 19 constituted the study group. The diagnosis was made in the sagittal planes and in 12 cases it was made prior to 24 weeks. In most cases the indication for referral was the presence of indirect signs of callosal anomalies, such as colpocephaly. In 10 cases PACC occurred in association with other anomalies and in nine it was isolated. MRI was particularly useful for demonstrating some additional cerebral anomalies such as late sulcation, migrational pathological conditions and heterotopia. Regarding pregnancy outcome, of those diagnosed before 24 weeks which had associated anomalies, all except two were terminated. Of the nine cases with isolated PACC, all were liveborn. Follow-up was available in eight, and two of these (25%) showed evidence of significant developmental delay. In our series the outcome of isolated PACC was not better than that of complete agenesis of the corpus callosum reported in other series.*

Conclusions *PACC can be diagnosed reliably and characterized in prenatal life. The sonographic sign present in most cases is colpocephaly. Prenatal MRI can be performed to confirm the diagnosis. It is particularly useful to demonstrate some additional cerebral anomalies such as late sulcation, migrational pathological conditions and heterotopia. The relatively poor survival rate is due to the high rate of terminations and associated major anomalies. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Developmental abnormalities of the corpus callosum (CC) include hypoplasia, hyperplasia, agenesis, and dysgenesis. Agenesis of the corpus callosum (ACC) can be complete (CACC) or partial (PACC); the latter form is also called hypogenesis. Its prevalence varies in different studies, depending on the population studied and the diagnostic criteria: it ranges between 0.3% and 0.7% in the general population[1] and 2% and 3% in the developmentally disabled population[2]. ACC is often associated with other

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cerebral and/or extracerebral malformations including syndromes and metabolic diseases[3–8].

Although the overall prognosis of ACC remains controversial, several studies have reported a worse prognosis in the presence of additional anomalies[2,4]; in the less frequent cases of isolated ACC, it appears to carry a prognosis compatible with normal or borderline postnatal development in most cases[9–12]. However, only a few papers have reported the prenatal diagnosis and outcome of ACC[4,9–15], and these include mainly CACC cases. Here, we describe the prenatal diagnosis and outcome of 19 cases of PACC.

METHODS

This was a retrospective study of all cases ($n = 19$) of PACC seen at two referral centers for prenatal diagnosis of congenital anomalies over a 10-year period (March 1996 to March 2005). The following variables were assessed: indication for referral, gestational age at diagnosis, additional cerebral and extracerebral malformations, chromosomal abnormalities, and pregnancy and fetal/neonatal outcome.

Colpocephaly, dilatation of the occipital horn, was not considered as an associated anomaly, because it is one of the basic signs of ACC. Fetuses with holoprosencephaly were not included in the study.

All cases underwent a detailed anatomy scan and fetal echocardiography with high-quality ultrasound equipment (Prosound 5000 Aloka, Tokyo, Japan; Voluson 730, Kreztechnik AG, Zipf, Austria). The fetal central nervous system (CNS) was studied using, depending on the position of the fetus, transabdominal and/or transvaginal axial, coronal and sagittal planes, as described by Timor-Tritsch and Monteagudo[16]. In all but two cases color Doppler was performed to visualize the course of the pericallosal artery. When the CC appeared shorter (caudally or rostrally) or not entirely present on ultrasound (Figure 1), this was considered a direct sign of PACC[17]. We evaluated all the sonographic findings usually considered as indirect signs of CACC: absence of the cavum septi pellucidi (CSP), enlargement of the ventricular atria and the occipital horns (colpocephaly), marked separation of the bodies of the lateral ventricles, laterally positioned frontal horns with concave medial borders, elevation of the third ventricle and radial disposition of the sulci on the internal aspects of the hemispheres[11,13,18].

In all cases, pre/postnatal magnetic resonance imaging (MRI) and/or necropsy were performed in order to confirm the diagnosis (Figure 2) and/or evaluate the presence of more subtle brain anomalies, such as migration disorders. Postnatal MRI was available in 12 cases, and necropsy reports were available in five of the seven cases in which a postmortem examination had been performed (71.4%) (Tables 1 and 2). In the two cases lacking necropsy reports, fetal MRI was available. Karyotyping was performed in 18/19 cases.

For all but one of the live births, follow-up information about the outcome was available: clinical data, particularly those relating to neuropsychiatric development, were obtained from records at maternal care and delivery units, from post-neonatal hospitalization records, and from interviews with parents. No radiological imaging, laboratory or electrophysiological tests were performed at the time of the study, but most of the patients had previously undergone these evaluations.

RESULTS

Over the study period, 54 cases of ACC were diagnosed in the two units. PACC was diagnosed at prenatal sonography in 20 cases and confirmed at pre/postnatal MRI or necropsy in 19 cases (35%). In the case of the single false-positive diagnosis, the CC was not absent but featured a thinner posterior part, and this was excluded from the study. The study group therefore consisted of 19 cases.

Tables 1 and 2 summarize the study findings. The mean gestational age at diagnosis was 24.6 (range, 21–34)

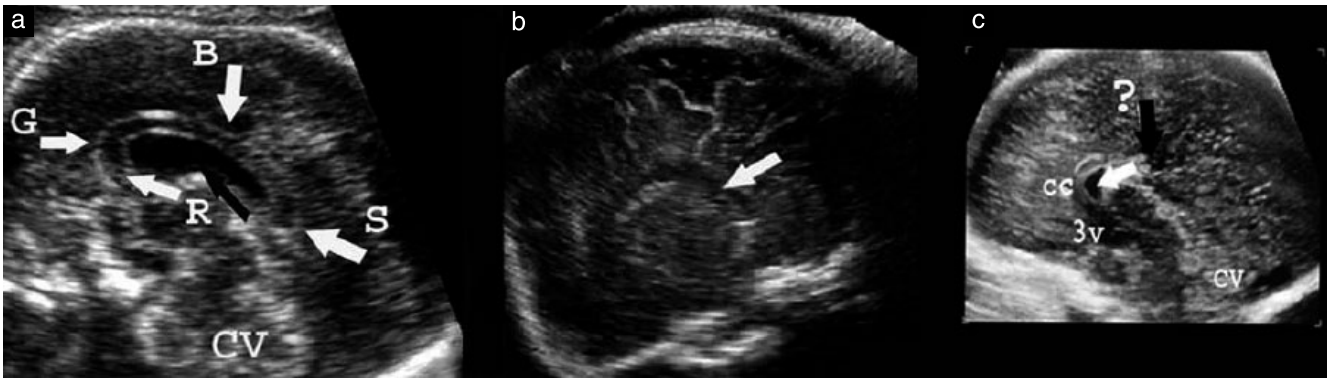

Figure 1 (a) Transabdominal two-dimensional (2D) ultrasound image (mid-sagittal plane) of a 23-week normal fetal brain showing the entire corpus callosum (CC). The black arrow indicates the cavum septi pellucidi. (b) Complete agenesis of the CC. Transvaginal 2D ultrasound image (mid-sagittal plane) of a 31-week fetal brain demonstrating absence (arrow) of the corpus callosum. (c) Partial agenesis of the CC. Transvaginal three-dimensional ultrasound image (mid-sagittal plane) of a 23-week fetal brain, showing partial formation of the CC, with the body stopping at the level of the unformed splenium. The white arrow indicates the cavum septi pellucidi. The black arrow (?) indicates the absence of the posterior part of the CC. 3v, third ventricle; ?, unformed splenium; B, body; CV, cerebellar vermis; G, genu; R, rostrum; S, splenium.

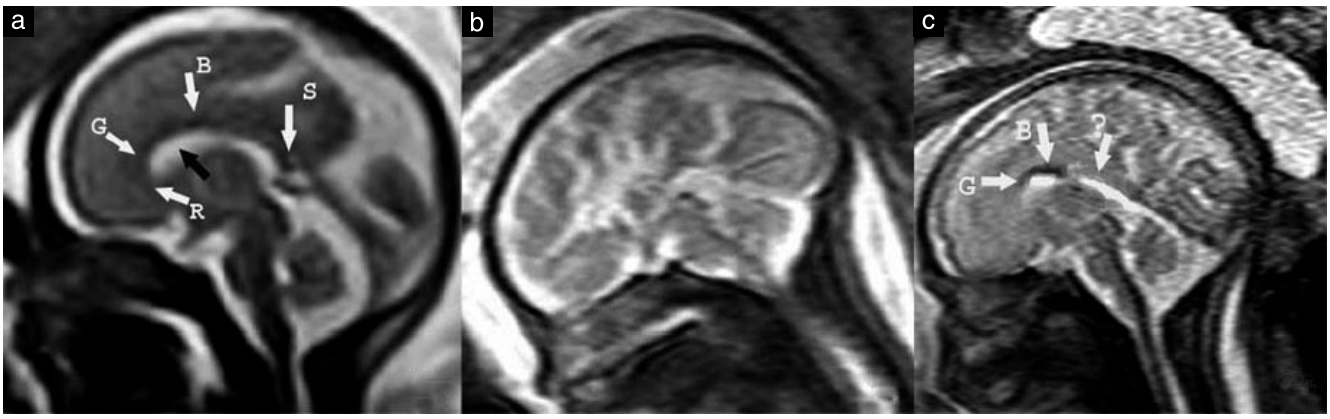

Figure 2 (a) Magnetic resonance image (MRI) (sagittal view) of a 25-week normal fetal brain (T2-weighted HASTE image). The corpus callosum (CC) is completely formed; it is evident as an intermediate signal due to the incomplete myelination. The black arrow indicates the cavum septi pellucidi. (b) Complete agenesis of the CC. MRI (sagittal view, T2-weighted HASTE image) of a 29-week fetal brain showing complete absence of the CC and the third ventricle communicating with the interhemispheric fissure. (c) Partial agenesis of the CC. MRI (sagittal view, T2-weighted HASTE image) of a 30-week fetal brain showing the absence of the posterior part of the CC (?) where cisternal enlargement is evident. B, anterior part of the body; G, genu; R, rostrum; S, splenium.

weeks), with 12/19 being diagnosed prior to 24 weeks of gestation. In nine cases, additional ultrasound scans were performed after the initial referral. In one case (Case 5), an associated brain anomaly was suspected at the second scan.

Indications for referral were: suspected isolated anomaly of the CC in 11 cases (Cases 5, 7, 8 and 11–18) (58%); diagnosis of cerebral and/or extracerebral anomalies, sometimes associated with a suspected callosal anomaly, in seven cases (Cases 1–4, 6, 9 and 10) (37%); a positive family history in one case (Case 19) (5%). When referral was based on indirect signs (Cases 1–4, 8, 11–15 and 17), colpocephaly was always present, often associated with marked separation of the bodies of the lateral ventricles (8/11 cases); of the remaining eight cases referred for other indications, it was present in five. Of note is the fact that indirect signs were not present in two of these cases.

Ten cases occurred in association with other malformations (Table 1), often in the context of a genetic anomaly. In this subset, the most frequently associated cerebral anomaly was the Dandy–Walker complex ($n = 3$). Extracerebral anomalies (including twin-to-twin transfusion syndrome) were detected in seven cases and were associated with chromosomal anomalies in three of them (two cases of trisomy 18 and one case of 5p deletion).

In the remaining nine cases (Table 2), the prenatal diagnosis of apparently isolated PACC was made and confirmed at postnatal MRI in all but one case (Case 11). In this case the postnatal MRI diagnosis also showed the presence of associated nodular periventricular heterotopia, which had been missed at prenatal ultrasound. This case was lost to follow-up.

In all 11 cases which underwent fetal MRI, the findings were concordant with the sonographic diagnosis of PACC. The only case with absence of the anterior part of the CC was correctly diagnosed at ultrasound and confirmed at MRI (Case 9). Associated CNS lesions diagnosed at fetal MRI included only polymicrogyria (Case 9) and nodular periventricular heterotopia (Case 7). In this case, the nodular periventricular heterotopia was missed on ultrasound examination and suspected on fetal MRI; however, it could not be confirmed or excluded at autopsy. This cerebral pathology was also the only misdiagnosed finding among the cases of prenatal diagnosis of apparently isolated PACC (Case 11). It was only demonstrated postnatally on MRI, although in this case prenatal MRI was not performed.

The occurrence of lissencephaly associated with PACC (Case 5) was not diagnosable at 21 weeks of gestation either by ultrasound or by MRI; at 27 weeks its presence was suspected at ultrasound and confirmed on MRI. Suspicion of lissencephaly was raised on ultrasound because the calcarine fissure and the parieto-occipital fissure were not visualized and the Sylvian fissure/insula was poorly formed.

As for pregnancy outcome, among the 12 fetuses diagnosed before 24 weeks, there were six terminations of pregnancy and one neonatal death, and eight showed additional anomalies. Among the seven remaining cases, there was one intrauterine death (Case 9). Of the 12 liveborn, one, who was delivered prematurely at 31 weeks, died during the neonatal period due to respiratory complications (Case 8). One case was lost to follow-up after the postnatal MRI (Case 11). Of the 10 survivors for whom we had follow-up information, eight had isolated PACC and two had associated brain anomalies (Case 5, lissencephaly and Case 10, Dandy–Walker malformation). In isolated cases, psychomotor evaluation was normal in six cases (median follow-up, 3 (range, 1–6) years), although the follow-up period was short in two of these cases (Cases 12 and 16; 12 and 19 months, respectively). In the remaining two cases (Cases 14 and 19), the prognosis was less favorable, with significant developmental milestone delay, associated in one case (Case 19) with hypotonia and feeding difficulties.

Table 1 Summary of cases with partial agenesis of the corpus callosum (PACC) in association with other malformations

Case	*Gestational age (weeks)*	*Referral reason*	*PACC type (on US)*	*Colpocephaly*	*Absent CSP*	*Associated anomalies on US*	*Karyotype*	*Fetal MRI*	*Postnatal MRI*	*Outcome*
1	21	ECA + suspected ACC (indirect signs)	Posterior	+	−	DORV + DW variant + hypotelorism	Trisomy 18	NP	NP	TOP
2	22	ECA + DWM + suspected ACC (indirect signs)	Posterior	+	−	TOF + DWM + vertebral anomalies	Trisomy 18	NP	NP	TOP
3	22	ECA + suspected ACC (indirect signs)	Posterior	+	−	Malaligned VSD + cleft lip and palate + club feet	5p deletion	PACC	NP	TOP
4	22	ECA + suspected ACC (indirect signs)	Posterior	+	−	Multicystic kidney	46,XY	PACC	NP	TOP
5	21	Suspected ACC (direct signs)	Posterior	+	−	Lissencephaly*	46,XX	PACC + lissencephaly*	PACC + lissencephaly	Live birth
6	22	Interhemispheric cyst + suspected ACC (direct signs)	Posterior	+	+	Interhemispheric cyst	46,XY	PACC + interhemispheric cyst	NP	TOP
7	23	Suspected PACC (direct signs)	Posterior	+	−	VSD	46,XX	PACC + nodular periventricular heterotopia	NP	TOP
8	22	Suspected ACC (indirect signs)	Posterior	+	−	VSD	46,XX	NP	PACC	Neonatal death
9	25	Twin-to-twin transfusion syndrome	Anterior	−	+	2 small porencephalic cysts	46,XX	PACC + 2 small porencephalic cysts + polymicrogyria	NP	Intrauterine death
10	30	DWM	Posterior	+	−	DWM	46,XY	NP	PACC + DW	Live birth

*Suspected at 27 weeks only. +, yes; −, no; ACC, agenesis of corpus callosum; CDH, congenital diaphragmatic hernia; CSP, cavum septi pellucidi; DORV, double outlet right ventricle; DW, Dandy–Walker; DWM, Dandy–Walker malformation; ECA, extracerebral anomalies; MRI, magnetic resonance imaging; NP, not performed; TOF, tetralogy of Fallot; TOP, termination of pregnancy; US, ultrasound; VSD, ventricular septal defect.

Table 2 Summary of cases with apparently isolated* partial agenesis of the corpus callosum (PACC)

Case number	*Gestational age (weeks)*	*Referral reason*	*PACC type (on US)*	*Colpocephaly*	*Absent CSP*	*Karyotype*	*Fetal MRI*	*Postnatal MRI*	*Outcome*
11	32	Suspected ACC (indirect signs)	Posterior	+	–	NP	NP	PACC + nodular periventricular heterotopia	Live birth
12	21	Suspected ACC (indirect signs)	Posterior	+	–	46,XX	PACC	PACC	Live birth
13	22	Suspected ACC (indirect signs)	Posterior	+	–	46,XX	PACC	PACC	Live birth
14	22	Suspected ACC (indirect signs)	Posterior	+	+	46,XX	PACC	PACC	Live birh
15	32	Suspected ACC (indirect signs)	Posterior	+	–	46,XY	NP	PACC	Live birth
16	26	Suspected ACC (direct signs)	Posterior	+	–	46,XX	PACC	PACC	Live birth
17	28	Suspected ACC (indirect signs)	Posterior	+	–	46,XY	NP	PACC	Live birth
18	34	Suspected ACC (direct signs)	Posterior	–	–	46,XX	NP	PACC	Live birth
19	21	Family history	Posterior	–	–	46,XX	PACC	PACC	Live birth

*The PACC was apparently isolated on prenatal sonography. ACC, agenesis of corpus callosum; CSP, cavum septi pellucidi; MRI, magnetic resonance imaging; NP, not performed.

In summary, 12/19 cases (63%) had a poor outcome (TOP, intrauterine death, neonatal death, associated cerebral malformations and/or neurological delay), while 6/19 cases (32%) had a good outcome (all isolated PACC), although two of these had a short follow-up period. (One of the nineteen cases was lost to follow up.)

DISCUSSION

The CC is the major commissure forming a junction between the cerebral hemispheres; it extends from the frontal lobe anteriorly to above the collicular plate posteriorly. The formation of the CC starts with the development of the genu in the 11th week; the body, isthmus and splenium develop at a later stage. If the normal developmental process is disturbed, the CC may be absent completely or partially ('hypogenetic'). Since the developmental process starts from the anterior part and progresses front to rear, when the CC is hypogenetic, it is usually the posterior portion that is affected (the posterior body and the splenium)[18]. The exception to this sequence is the late formation of the small frontal part, i.e. the rostrum corporis callosi, which develops at 18–20 weeks of gestation[18]. A knowledge of the organogenetic process involved in the formation of the CC helps in the differentiation between developmental damage (hypogenesia) and acquired damage (destruction). The latter had probably occurred in one of our cases, in which the absence of the anterior part of the CC was associated with small porencephalic cysts and polymicrogyria of the frontal region (Case 9); both these lesions are considered possible sequelae of hypoxic ischemic injury.

Usually, suspicion of callosal agenesis on routine obstetric sonography is based on indirect signs such as the absence of the CSP and/or the presence of colpocephaly. In our case series, colpocephaly was present in all but three cases of PACC (Tables 1 and 2; Cases 9, 18 and 19) and was almost always mild; conversely, the CSP was present in all but three cases. Its absence was related to the absence of the anterior part of the CC in Case 9; in the other two cases (Cases 6 and 14) the agenesis involved the majority of the body. In fact, the more the agenesis extends to the body of the CC, the more hypoplastic is the septum pellucidum. Hence, PACC can occur in the absence of indirect signs (Cases 18 and 19), which are what usually lead to its sonographic recognition in the fetus. It can be hypothesized that some PACC cases are overlooked *in-utero* due to the absence of indirect signs; this hypothesis is further supported by the observation that the number of cases of PACC appearing in the various fetal case series of ACC is a great deal lower than is the number of cases of CACC; this is in contrast to the situation in postnatal life, wherein the proportion of cases of PACC is not significantly different from that of cases of CACC[8,15].

Direct sonographic visualization of the CC in both the sagittal and the coronal planes, and the consequent diagnosis of callosal anomalies, requires an experienced operator and is generally obtained only by referring the mother to a specialized center. As for the difficulty in differentiating at prenatal ultrasound between complete and partial forms of ACC, reported by some investigators who advocate the constant employment of MRI to resolve the issue[19], it must be underscored that we found only 1/20 cases to be diagnosed incorrectly at prenatal ultrasound as PACC, and this case was therefore excluded from our analysis. In the remaining 19 cases, the correlation between pre/postnatal MRI and prenatal sonography was complete.

Interestingly, in most cases of PACC, on color Doppler the pericallosal artery followed closely the anterior part of the CC but lost its normal course where the CC disappeared, being absent at its posterior part; at this level it took an upward posterior oblique direction (Figure 3). In our experience this sign is of great value.

When associated anomalies were present in our case series, other brain abnormalities were found in eight of 10 cases. Fetal MRI identified brain malformations not detected on sonography in two of 11 cases (18%): one case of polymicrogyria (Case 9) and one of nodular periventricular heterotopia (Case 7). These results are rather different from those reported by Glenn *et al.*[15], who detected on fetal MRI additional brain anomalies that had been overlooked on ultrasound examination in five of eight (62.5%) cases. Another case of nodular periventricular heterotopia (Case 11) was not visualized on ultrasound but was demonstrated postnatally on MRI. These data agree with those of other authors[13,20] but differ from those of Glenn *et al.*[15], who detected no cases of heterotopia on fetal MRI that had not been suspected on prenatal sonography.

Regarding the case of lissencephaly associated with PACC (Case 5), this was the most recent case of PACC in our series. Although there have been recent reports describing sonographic criteria for the diagnosis of lissencephaly[21,22], it must be stressed that there is a wide spectrum of cerebral involvement in lissencephaly and only the severe forms can be suspected on ultrasound; milder degrees of cerebral involvement such as subcortical band heterotopia and pachygyria are very difficult, if not impossible, to diagnose. As reported by several authors[20,23], gyral anomalies and neuronal heterotopia are the anomalies most commonly missed on prenatal sonography.

The clinical relevance of callosal agenesis has yet to be fully determined. It is not unusual for individuals with agenesis of the CC to have no neurological problems, despite the absence of callosal fibers[24], whereas a case series of children with postnatally diagnosed ACC reported that most of them suffered from developmental delay and often developed seizures[25]. However, in this study there was a referral bias since children without developmental anomalies were not studied. Several postnatal case series suggest a direct relationship between the occurrence of associated brain abnormalities and poor neurodevelopmental outcome[12,14,25]. In our study, two fetuses with associated brain anomalies survived. Clinically, the child with lissencephaly (Case 5), who was 4 months old at the time of writing, had already developed epilepsy in the neonatal period. The other child (Case 10) developed seizures at the age of 7 months.

As for isolated PACC, caution must be adopted when assessing the fetal/neonatal prognosis. In fact, considering the paucity of PACC cases reported in the literature, no general conclusions can be drawn, though some interesting points can be discussed. The first point is that other CNS or extra-CNS malformations can be present even when PACC is apparently isolated at prenatal sonography, as demonstrated in one of our cases (Case 11). This patient was lost to follow-up, although the presence of nodular periventricular heterotopia in association with PACC makes an unfavorable prognostic impact on mental status and psychomotor development highly probable. It may be assumed, however, that with the increasing development and use of prenatal diagnostic imaging techniques, the identification of other associated anomalies will improve significantly.

Regarding the prognosis of isolated PACC confirmed by postnatal examination, in the literature, few PACC cases have been reported postnatally, and those that have were in the context of more extensive series including CACC cases[14,25]. The large series described by Goodyear *et al.*[14] comprised 10 isolated PACC cases, with clinical

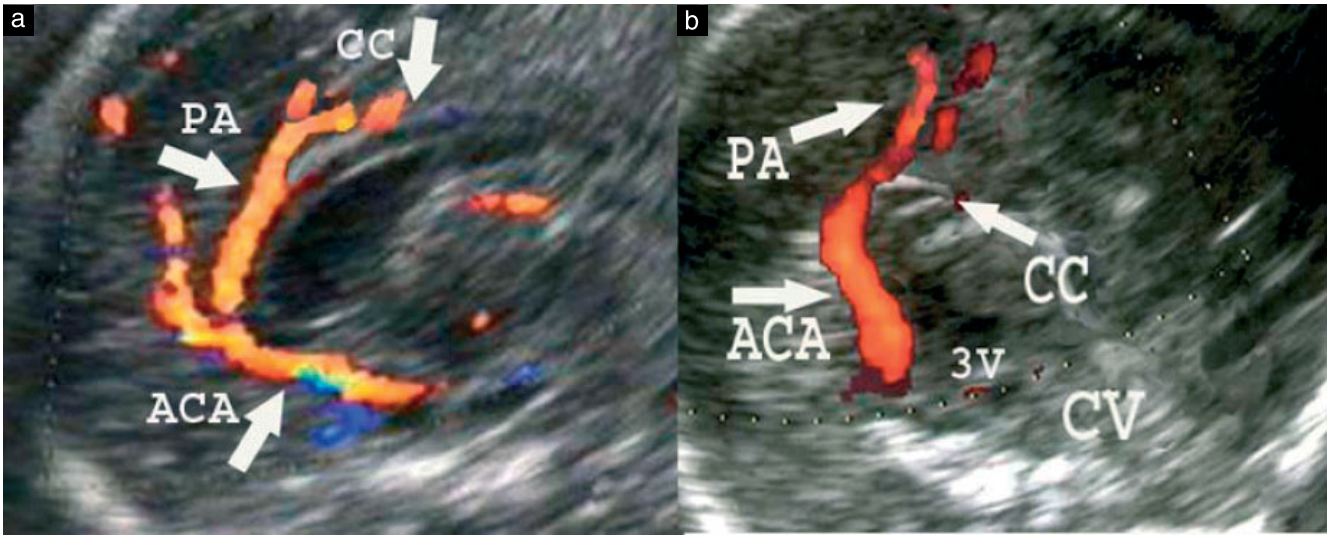

Figure 3 (a) Doppler image (mid-sagittal view) of a normal fetal brain demonstrating the anterior cerebral artery (ACA) and the pericallosal artery (PA) that closely follows the entire corpus callosum (CC). (b) In a fetus with partial agenesis of the corpus callosum, the PA closely follows the genu and the anterior part of the CC body but loses its normal course where the CC disappears; it takes an upward posterior oblique direction. CV, cerebellar vermis; 3V, third ventricle.

signs present in six (60%). This high percentage reflects a selection bias, as the patients identified in postnatal life presented neurological problems which were the reason for the scan in nearly all cases, while the information offered on the prenatal group was limited due to the paucity of the cases (only 2/10 in the PACC subset).

In our series, the psychomotor evaluation of the eight isolated cases of PACC was normal in six (median follow-up, 3 (range, 1–6) years) and there was neurodevelopmental delay in two (Cases 14, 19). Therefore, when isolated PACC was diagnosed prenatally, a significant neurodevelopmental delay was present in a consistent proportion of cases (2/8, 25%); this is similar to the outcome of isolated CACC, reported to be poor in 15–28% of cases[9,11,12]. This similarity is in accordance with the study of Moutard *et al.*[9], which reported no significant differences between complete and partial ACC, but our conclusion apparently conflicts with other reports[14] which came to very different conclusions, as considered above. The presence of feeding difficulties in Case 19 is interesting, indicating that this disorder, described previously in CACC patients[26], can be extended to PACC cases.

A final consideration is that even when the outcome is good, other subtle neuropsychological, perceptual and motor defects can emerge much later, since all individuals with CACC/PACC also have some other neuropsychological symptoms. Considering the presence of defects in the transfer of information, no differences seem to exist between PACC and CACC in terms of the performance accuracy of the somatosensory function, while response time was significantly shorter in PACC than in CACC children[27]. However, in our opinion, the clinical relevance of such deficits should not be exaggerated because CC functions are not completely understood[28,29], and it is difficult to assess correctly the neuropsychological status of individuals with CACC/PACC and normal-range IQs, and the role of possible compensatory mechanisms[30]. At the same time, a protracted follow-up (until around 6 years of age) is important to update the neurodevelopmental status of these patients, especially with regards to social interactions and school admission, in order to provide better prognostic information to families.

In conclusion, our study confirms that PACC can be diagnosed reliably and characterized at referral centers; fetal MRI is particularly useful in demonstrating some additional cerebral anomalies such as late sulcation, migration anomalies and heterotopia. However, in most cases these anomalies can be evaluated only in the late second trimester and during the third trimester. There is a consistent association with other major anomalies (more than half of the cases). The relatively poor survival rate is due to the high rate of terminations and associated major anomalies. Although this finding is of limited value due to the small number of cases, in this series the outcome of isolated PACC was not better than that of CACC reported in other series.

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