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Prenatal diagnosis and outcome of partial agenesis and hypoplasia of the corpus callosum

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KEYWORDS: callosal hypoplasia; corpus callosum; partial agenesis; prenatal diagnosis; ultrasound

ABSTRACT

Objective *To present antenatal sonographic findings and outcome of fetuses with hypoplasia or partial agenesis of the corpus callosum.*

Methods *The database of our ultrasound laboratory was searched retrospectively for cases of hypoplasia or partial agenesis of the corpus callosum suspected at antenatal neurosonography between 1998 and 2008 and confirmed by pathology or postnatal neuroimaging. In surviving infants, clinical follow-up had been arranged to assess neurodevelopmental outcome.*

Results *Nineteen fetuses with callosal underdevelopment were identified at a median gestational age of 22 (range, 21–33) weeks and confirmed at follow-up, including 14 with partial agenesis and five with hypoplasia. Among the 14 fetuses with partial agenesis, there were additional brain findings in 10, including two with absent cavum septi pellucidi, four with mild isolated ventriculomegaly and four with cerebellar abnormalities, two of which also had ventriculomegaly. Pregnancy was terminated electively in seven of the cases with partial agenesis and there was one neonatal death. Among the six surviving infants, neurodevelopmental outcome was appropriate for age in three at follow up, including two cases with isolated partial agenesis of the corpus callosum. Among the five fetuses with prenatally diagnosed callosal hypoplasia, additional anomalies were present in four. Two cases were terminated electively and three were alive at the time of writing, with a median age of 3 years. Among them, apparently normal neurological development was observed in only one case.*

Conclusions *An antenatal diagnosis of callosal underdevelopment is possible by expert sonography. There is often association with other major anomalies. However, even in fetuses with apparently isolated findings, the prognosis is uncertain. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The corpus callosum is the major junction between the cerebral hemispheres, extending from the frontal lobe anteriorly to above the quadrigeminal plate posteriorly. Congenital anomalies of the corpus callosum are commonly associated with other malformations, aneuploidies or genetic syndromes[1–4]. Furthermore, even in cases with isolated callosal anomaly there is a high risk of abnormal neurodevelopment[5–7]. Among callosal abnormalities, agenesis of the corpus callosum, which can be partial or complete, and callosal hypoplasia are included.

Prenatal diagnosis of complete callosal agenesis is feasible from the midtrimester onwards by expert sonography. At two-dimensional (2D) ultrasound in the axial view of the fetal head, suspicious findings are absent cavum septi pellucidi and teardrop configuration of the lateral ventricles with possible ventriculomegaly. Antenatal diagnosis is based upon the non-visualization of the corpus callosum at transfontanellar ultrasound in either the sagittal or the coronal plane[8,9].

More subtle findings, such as hypoplasia and partial agenesis of the corpus callosum, may also be recognized antenatally[7,10–12]. In these cases sonographic diagnosis is extremely difficult because the corpus callosum is detectable and, while it is atypical in appearance, the axial view of the fetal head is often unremarkable. In cases of callosal hypoplasia or partial agenesis ultrasound

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diagnosis is based, respectively, on the demonstration of a decreased thickness of the corpus callosum or a decreased thickness and abnormal shape, in the median view. Normative charts for fetal corpus callosal biometry have been established and are of critical importance in assisting the sonographer during subjective assessment to confirm either corpus callosal integrity or its underdevelopment[13,14]. Prognostic implications for fetuses with partial agenesis seem to be similar to those for fetuses with total agenesis[1,7,15], although some claim there to be a better outcome in the former group[6]. Prenatal diagnosis of callosal partial agenesis[7,10,11] or hypoplasia[12] has in fact been reported rarely. We therefore present the antenatal sonographic findings and outcome of a group of fetuses in which callosal hypoplasia or partial agenesis was recognized prenatally.

PATIENTS AND METHODS

The database of our ultrasound laboratory was searched retrospectively for cases of hypoplasia or partial agenesis of the corpus callosum suspected at antenatal sonography between 1998 and 2008. Ultrasound investigation was carried out using AU5 or Technos (Esaote, Genoa, Italy) or Voluson 730 Pro/Exp (GE Healthcare, Milwaukee, WI, USA) ultrasound machines equipped with multifrequency transabdominal and transvaginal probes. In some cases ultrasound examination was supported by three-dimensional (3D) and 4D technology. According to our standard policy, fetal head examination was performed transabdominally in the axial, coronal and sagittal planes and the corpus callosum was visualized in the median plane to permit its length and thickness to be measured and compared with the reference charts. Partial agenesis was suspected when the corpus callosum appeared to be shaped abnormally and to be short for gestational age posteriorly and was not overlying the quadrigeminal plate. Hypoplasia was suspected when the corpus callosum appeared to be thin for gestational age but of normal length. In these suspected cases, the maximum length of the corpus callosum and its widest thickness at the level of the body were measured, and if the callosal length or thickness was below the 10th centile for gestational age of the reference charts[13,14] a conclusive diagnosis of partial agenesis or hypoplasia of the corpus callosum, respectively, was established. In cephalic-presenting fetuses whose corpus callosum was suspicious or unclear in appearance, multiplanar neurosonography was further performed transvaginally using a high-frequency probe (7.5–10 MHz). In abnormal cases a more detailed scan of the fetal head was performed, including investigation of the aspect of the cavum septi pellucidi and the lateral ventricles. Furthermore, color flow mapping was used to visualize the course of the pericallosal arteries. A careful survey of the entire fetal anatomy including fetal echocardiography was then performed to rule out associated intra- or extracranial anomalies. Fetal karyotyping was offered if this had not been assessed previously. From 2001 onwards, antenatal magnetic resonance imaging (MRI) was offered to confirm the sonographic findings. This was carried out using a 1.5T system (Signa LX, GE Healthcare) with the fetal brain being examined in a multiplanar fashion by a sequence of T2-weighted, single-shot fast-spin echo images. The MRI examination was carried out by a pediatric neuroradiologist (G.T.) assisted by one of the sonographers.

When a fetal callosal anomaly was suspected, a detailed postnatal evaluation was carried out in order to confirm the antenatal findings. If pregnancy termination or postnatal death occurred, necropsy was carried out by an expert in perinatal pathology (P.B.). In surviving infants, postnatal neuroimaging techniques such as computed tomography and MRI were used to verify antenatal brain findings and neuropediatric follow-up was arranged in order to assess neurodevelopmental outcome.

RESULTS

During the study period 19 fetuses with callosal underdevelopment were identified antenatally, at a median gestational age of 22 (range, 21–33) weeks, and confirmed at follow-up by pathology or postnatal neuroimaging, including 14 with partial agenesis and five with hypoplasia. Most of these cases had been referred to our laboratory due to suspicious findings at routine ultrasound examination. In a few of them a detailed evaluation in our center had been arranged due to an increased risk for congenital anomalies or obstetric complications in the current pregnancy. Sonographic findings and outcome of all 19 cases are summarized in Table 1.

Among the 14 fetuses with partial agenesis, there were additional brain findings in 10, including two with absent cavum septi pellucidi, four with mild tear-drop isolated ventriculomegaly (< 15 mm), and four with abnormalities of the cerebellum-posterior fossa complex, two of which also had ventriculomegaly. In four fetuses there was also hypoplasia of the remaining portion of the corpus callosum which was associated with absence of the splenium. Of these, three were diagnosed prior to fetal viability and one was recognized at 33 weeks of gestation in a patient who had been referred on suspicion of fetal ventriculomegaly. Following sonographic diagnosis, fetal brain MRI was performed in four cases and in all it confirmed the ultrasound findings. In the whole group, additional extracranial anomalies were recognized in two fetuses, including one with a structural heart defect who was diagnosed postnatally with Cri du Chat syndrome (5 p- deletion) and one with apparently isolated polyhydramnios which turned out postnatally to be caused by choanal atresia in the setting of CHARGE (callosal hypoplasia, choanal atresia, micrognathia) syndrome.

Of the 14 cases with prenatally diagnosed partial agenesis of the corpus callosum, the pregnancy was terminated electively in half, including five cases with

Table 1 Summary of sonographic findings and outcome in 19 cases with callosal partial agenesis or hypoplasia

Case	*Week*	*Indication for sonography*	*Corpus callosum/CSP appearance*	*Additional sonographic findings*	*Outcome*
Partial agenesis of the corpus callosum					
1	22	Ventriculomegaly	Missing splenium, CSP present	Teardrop-shaped ventricles, mild ventriculomegaly	Live birth, at 10 years developed multiple intracranial lipomas and seizures
2	21	Ventriculomegaly	Missing splenium, CSP present	Ventriculomegaly, Dandy–Walker complex	TOP
3	22	Ventriculomegaly	Missing splenium, CSP present	Ventriculomegaly, Dandy–Walker complex	TOP
4	22	Ventriculomegaly	Missing splenium, CSP present	Teardrop-shaped ventricles, mild ventriculomegaly	TOP
5	21	Ventriculomegaly	Missing splenium, CSP present	Teardrop-shaped ventricles, mild ventriculomegaly	TOP
6	21	Previous preterm birth	Missing splenium, CSP present	None	Live birth, normal development at 8 years
7	22	Abnormal cardiac findings	Missing splenium, CSP present	DORV, IUGR, hypoplastic cerebellum	Live birth, chromosomal anomaly (5 p-), neonatal death at 1 month
8	21	Consanguineity	Missing splenium, CSP present	None	TOP
9	21	Drug consumption	Missing splenium, < thickness of CC, CSP absent	None	TOP
10	22	Polyhydramnios	Missing splenium, < thickness of CC, CSP absent	Polyhydramnios	Live birth, at 1 year CHARGE (callosal hypoplasia, choanal atresia, micrognathia) syndrome, mental delay
11	21	Enlarged cisterna magna	Missing splenium, < thickness of CC, CSP present	Dandy–Walker complex	Live birth, at 3 years motor development delay
12	33	Ventriculomegaly	Missing splenium, < thickness of CC, CSP present	Teardrop-shaped ventricles, ventriculomegaly	Live birth, normal development at 2 years
13	21	Previous pregnancy with IUGR	Missing splenium, CSP present	None	Live birth, normal development at 3 years
14	23	Increased nuchal translucency thickness	Missing splenium, CSP present	None	TOP
Hypoplasia of the corpus callosum					
15	33	Hydronephrosis	< thickness of CC, CSP present	Polyhydramnios, unilateral renal agenesis, hydroureteronephrosis and megacystis	Live birth, esophageal atresia, vescicoureteral reflux, normal development at 8 years
16	21	Maternal diabetes	< thickness of CC, CSP small	None	TOP
17	32	Reduced cranial circumference	< thickness of CC, CSP present	Hemimegalencephaly	Live birth, at 3 years severe neurodevelopmental delay and seizures
18	32	Consanguineity	< thickness of CC, CSP present	Ventriculomegaly, tetralogy of Fallot, unilateral renal agenesis	Live birth, at 3 years Pena-Shokeir type 2 syndrome
19	22	Suspicion of CHD	< thickness of CC, CSP present	Single umbilical artery, heart right–left ventricular disproportion, IUGR	TOP

<, decreased; CC, corpus callosum; CHD, congenital heart disease; CSP, cavum septi pellucidi; DORV, double outlet right ventricle; IUGR, intrauterine growth restriction; TOP, termination of pregnancy.

additional brain findings (two with abnormalities of the cerebellum–posterior fossa complex, one with absent cavum septi pellucidi and two with isolated ventriculomegaly). Of the remaining seven fetuses, six were delivered near term and were alive at the time of writing, with a median age of 3 (range, 1–10) years and the one suffering from 5p- deletion died shortly after birth. Among the six surviving infants, neurodevelopmental outcome was reported to be appropriate for age in three, while there were neurological abnormalities present in the other three, including one case with mild motor delay associated with Dandy–Walker complex, one case with seizures due to multiple intracranial lipomas detected after birth and one case with severe mental retardation in whom CHARGE syndrome was recognized postnatally because of associated findings (choanal atresia, micrognathia). In the two cases with isolated partial agenesis of the corpus callosum in which the pregnancy was not terminated, neurological outcome of the infant was reported to be normal at follow-up (one at 3 and one at 8 years).

Of the five fetuses with prenatally diagnosed callosal hypoplasia, there were additional findings in four, including a case with hemimegalencephaly and three with multiple anomalies involving either the brain or other systems (one with ventriculomegaly, tetralogy of Fallot and unilateral renal agenesis, one with esophageal atresia and one with single umbilical artery, congenital heart disease and intrauterine growth restriction). Notably, the cavum septi pellucidi appeared normal in the four cases with additional findings and was small in the only case in which callosal hypoplasia appeared isolated. Fetal MRI was additionally performed in three cases and confirmed the ultrasound findings. Of the whole group, two cases including the one with no additional findings were detected in the second trimester and were terminated electively. The other three were diagnosed sonographically in the third trimester; these were delivered near term and were alive at the time of writing, with a median age of 3 (range, 3–8) years. Among them, apparently normal neurological development was observed only in the infant with esophageal atresia, who underwent surgical repair. Both the infant with hemimegalencephaly and the one with tetralogy of Fallot showed severe neurological impairment at follow-up. In the latter, Pena–Shokeir type 2 syndrome was diagnosed after birth.

DISCUSSION

The corpus callosum may be imaged antenatally by targeted multiplanar sonography from the midtrimester[8,9]. Focusing the ultrasound beam on the sagittal suture of the fetal head, the entire length of the corpus callosum may be displayed as a sonolucent band demarcated superiorly and inferiorly by two echogenic lines (Figure 1). Recently the development of 3D ultrasound has provided several advantages in the study of the fetal central nervous system (CNS). Thanks to volume sonography, starting from an axial section of the fetal head, which is usually easy to obtain, it is possible to achieve a median view of the brain and to visualize antenatally anomalies of the corpus callosum or other midline structures. Moreover, since 3D ultrasound has been implemented by the static volume contrast imaging (VCI) modality, the image quality of reconstructed planes such as the sagittal one has greatly improved[16,17].

On this basis prenatal assessment of the corpus callosum has become part of expert fetal scanning, evaluation involving not only its presence, but also its size and aspect. At prenatal ultrasound a fully developed corpus callosum is seen to overlay the quadrigeminal plate of the mesencephalon in the median view of the fetal brain. However, when dealing with the suspicion of callosal underdevelopment, either partial agenesis or hypoplasia, normative charts of its length and thickness are available for comparison[13,14]. If these biometric parameters are below the normal range an objective diagnosis of callosal underdevelopment may be established prenatally. Moreover, a deviation in the normal course of the pericallosal arteries is reported to be an additional sign of corpus callosal partial agenesis[11]. In such cases the arteries closely follow the contour of the corpus callosum at its anterior part (the genu and the body), but take an upward direction at the level of the missing splenium. As previously suggested[11], those indirect sonographic findings, which are commonly reported in fetuses with complete callosal agenesis, were encountered inconsistently in this series of fetuses with partial agenesis or hypoplasia. A small or absent cavum septi pellucidi or colpocephaly were in fact detectable only in a small proportion of our cases, and we failed to demonstrate the other indirect signs of absent corpus callosum, such as an enlarged and upward displaced third ventricle, radial appearance of the medial sulci and incomplete cingulate gyrus[11]. A likely explanation is that in cases of absent corpus callosum most of these findings are due to defective or abnormally oriented interhemispheric bundles, whereas in cases with partial agenesis or hypoplasia, normal appearance of the cavum septi pellucidi or the lateral ventricles may reflect a minor disruption of the midline fibers.

Partial agenesis of the corpus callosum results from an arrest of growth which occurs between 12 and 18 weeks of gestation and usually involves the dorsal part or splenium, with the more anterior callosal segments being preserved. Indeed, callosal ontogenesis is currently believed to start in the 11th week at the level of the anterior portion of the body. From there development of the entire corpus callosum takes place in a bidirectional fashion, frontward to form the genu and the rostrum and backward to complete the body and the splenium[18]. Whether callosal partial agenesis represents a true malformation or is the consequence of a disruptive event is uncertain[6]. An association with interhemispheric arachnoid cyst, holoprosencephaly, asymmetric ventriculomegaly and migration disorders is reported[19,20].

Prenatal diagnosis of fetal callosal underdevelopment remains a difficult task with only few cases of partial agenesis reported in the literature[10,11,20,21]. In fetuses with

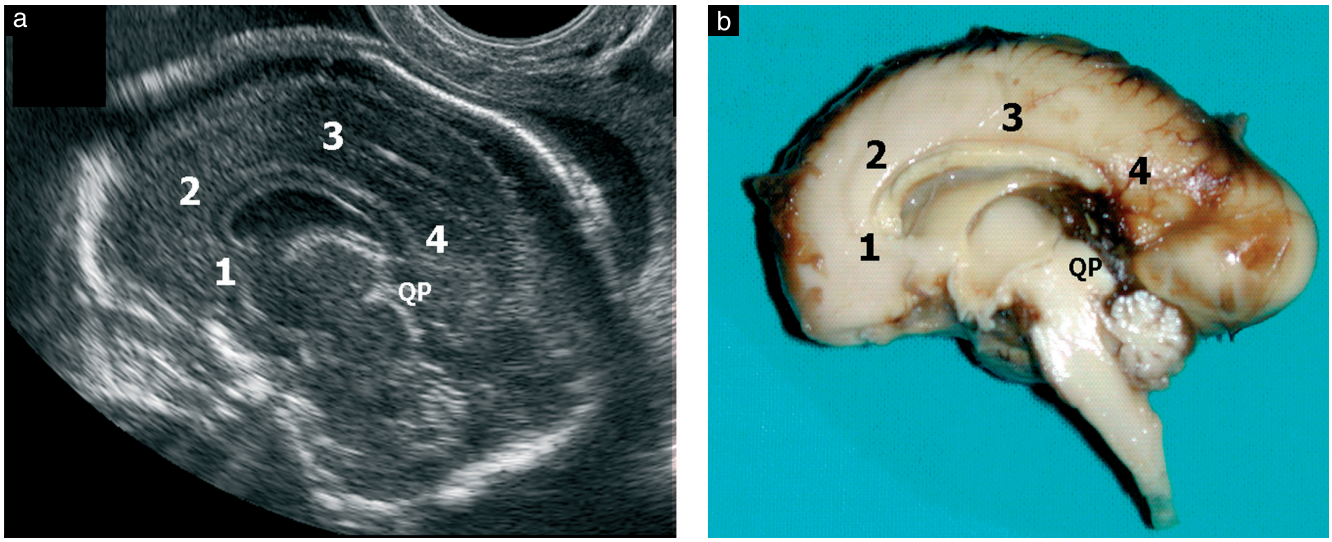

Figure 1 Brain of a 21-week fetus with normal corpus callosum at ultrasound (a) and pathology (b) examinations: the rostrum (1), genu (2), body (3) and splenium (4) are indicated. The corpus callosum appears of normal length, overlying posteriorly the quadrigeminal plate (QP).

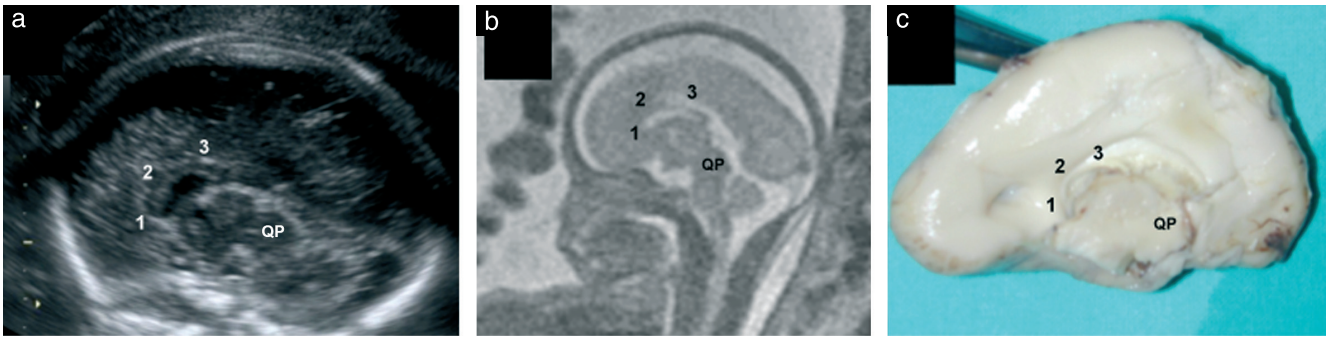

Figure 2 Brain of a 21-week fetus with partial agenesis of the corpus callosum at ultrasound (a), magnetic resonance imaging (b) and pathology (c) examinations: only the rostrum (1), genu (2) and body (3) are visible; the splenium is missing. The corpus callosum is short posteriorly and does not seem to overlay the quadrigeminal plate (QP).

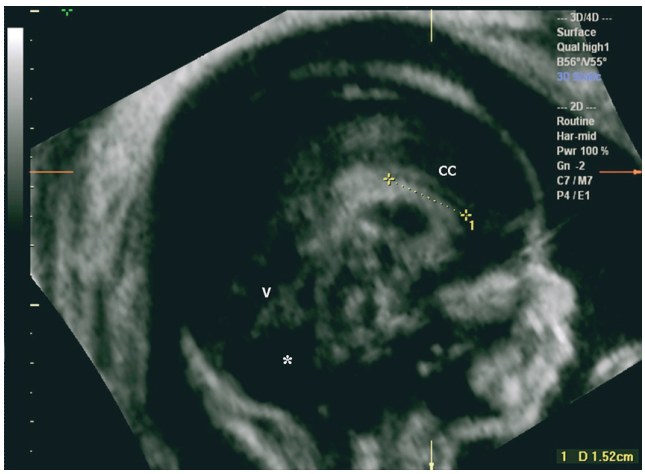

Figure 3 Reconstruction of the median plane from an ultrasound volume of the brain in a 21-week fetus with partial agenesis of the corpus callosum (CC) and Dandy–Walker complex. The CC appears short and thin, the cerebellar vermis (V) is hypoplastic and there is a wide communication between the 4th ventricle and the cisterna magna (*).

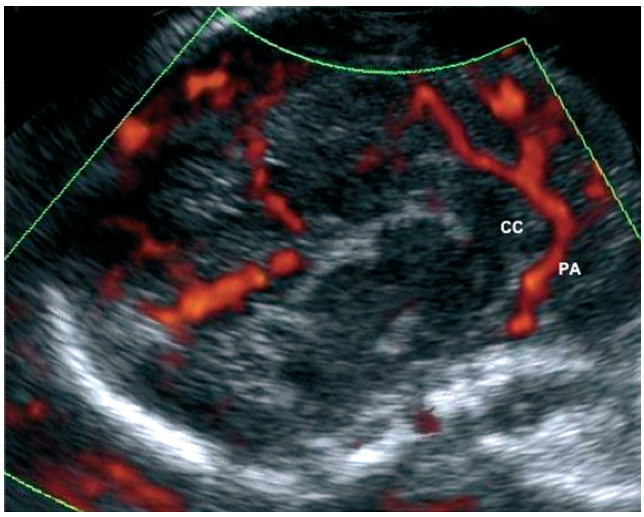

Figure 4 Median view of fetal brain at transvaginal power Doppler examination in a 21-week fetus with partial agenesis of the corpus callosum (CC): the pericallosal artery (PA) strictly follows the contour of the anterior part of the CC but takes an upward direction at the level of the missing splenium.

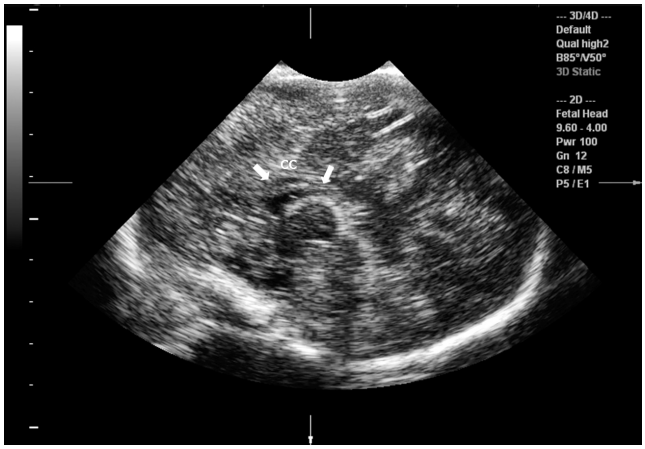

Figure 5 Reconstruction of the median plane from an ultrasound volume of the brain in a 21-week fetus with callosal hypoplasia. The corpus callosum (CC) appears thin but normal in length (arrows).

partial callosal agenesis a shorter corpus callosum may be demonstrated at ultrasound or MRI and eventually confirmed at pathology (Figures 2 and 3). In our series, antenatal diagnosis of partial agenesis was suspected at gray-scale ultrasound, but our confidence was increased by Doppler imaging, which additionally documented an abnormal course of the pericallosal arteries in all cases (Figure 4).

Callosal hypoplasia is a developmental disorder that may be induced by teratogens (radiation, alcohol) or compression (e.g. intracranial masses, obstructive hydrocephalus)[4,12]. Rather than a primary malformative abnormality callosal hypoplasia is more likely to depend upon an external factor affecting the number and size of callosal axons. This is apparently confirmed by our experience since callosal hypoplasia was often associated with additional brain anomalies. At prenatal ultrasound, callosal underdevelopment was suspected when callosal thickness in the median plane was below the normal range provided by normative charts. This was seen both at 2D and 3D ultrasound in our series (Figure 5). To date, only a few cases of callosal hypoplasia have been detected antenatally[12,22].

In cases of abnormal callosal findings at ultrasound, MRI was offered (from 2001) to confirm sonographic findings. MRI is considered by some to be the most accurate technique for investigating the fetal CNS and detecting antenatally subtle cerebral anomalies[23–25]. In fetuses with suspected callosal anomalies, it is worthy of recommendation in order to reinforce a difficult sonographic diagnosis and at the same time to exclude possible additional cerebral anomalies which may be overlooked at ultrasound but may affect the outcome considerably. As previously reported[26], in this study expert sonography and MRI performed equally well in the prenatal assessment of midline brain anomalies and in no case did the addition of MRI change the sonographic diagnosis. Furthermore, antenatal ultrasound findings regarding the corpus callosum were in all cases consistent with findings at postnatal neuroimaging or pathology.

There were often additional malformations at intra- or extracranial locations associated with callosal underdevelopment and, in our experience, some of these fetuses turned out to be affected by a chromosomal or genetic disorder. In view of this finding, whenever callosal underdevelopment is suspected, a careful survey of the entire fetal anatomy and prenatal karyotyping are warranted. Moreover, the risk of an underlying genetic syndrome that may be disclosed only after birth should always be mentioned when counseling the prospective parents. On the other hand, as suggested by our data, partial agenesis or hypoplasia of the corpus callosum may occur in isolation. In these cases, neurological outcome is reported by some to be similar to that in cases with absent corpus callosum[1,7,15], while according to others a worse outcome should be expected for cases with complete agenesis due to the greater disruption of neuronal function[6]. Volpe *et al.*[11] recently reported neurodevelopmental delay in two of eight cases of apparently isolated partial callosal agenesis. In our series the limited number of surviving infants with isolated underdevelopment of the corpus callosum does not allow us to draw any conclusions. Further studies are warranted to establish whether, in cases of apparently isolated callosal underdevelopment, expert sonography may help in detecting antenatally those fetuses that are likely to show an adverse outcome after birth. Moreover, particularly in these cases, prolonged and careful neurological follow-up of the surviving children would be desirable to fully understand the long-term impact of callosal dysgenesis on quality of life and to give reliable information to prospective parents.

In conclusion, our study confirms that a reliable diagnosis of partial callosal agenesis or callosal hypoplasia can be achieved antenatally by expert sonography. In all cases in this series prenatal diagnosis was confirmed either at pathology or postnatal evaluation. There is apparently an association with major intra- and extracranial anomalies, and possibly with chromosomal or genetic disorders. However, due the paucity of cases reported in literature, even in fetuses with apparently isolated findings the prognosis remains uncertain.

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