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Counseling in fetal medicine: agenesis of the corpus callosum

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ABSTRACT

In this Review, we aim to provide up-to-date and evidence-based answers to common questions regarding the diagnosis and prognosis of prenatally detected agenesis of the corpus callosum (ACC). A systematic literature search was performed to identify all reports of ACC and reference lists of articles were identified. ACC involves partial or complete absence of the main commissural pathway that connects the two cerebral hemispheres, and can be isolated (with no other abnormalities) or complex (coexisting with other abnormalities). It is a rare finding and the prevalence is difficult to estimate because of selection bias in reported series. The corpus callosum (CC) can be assessed on ultrasound by direct visualization, but indirect features, such as ventriculomegaly, absence of the cavum septi pellucidi or widening of interhemispheric fissure, are often the reason for detection in a screening population. Careful imaging in a center with a high level of expertise is required to make a full assessment and to exclude coexisting abnormalities, which occur in about 46% of fetuses. When available, magnetic resonance imaging appears to be an important adjunct as it allows direct visualization. It can reduce false-positive rates on ultrasound and can confirm ACC, it can assess whether this is complete or partial and it can help in detecting coexisting brain abnormalities not seen on ultrasound. The overall rate of chromosomal abnormality in fetuses with ACC is 18%, but this high rate includes both isolated and complex ACC; more recent studies suggest that chromosomal abnormalities are rare in isolated cases. Nevertheless, postnatal follow-up studies suggest that about 15% of cases thought to be isolated prenatally were found to have associated abnormalities after birth. Neurodevelopmental outcome in isolated ACC was recently reported in a systematic review and suggested normal outcome in about 65–75% of cases. Findings need to be considered in light of the several limitations of existing studies, in terms of study design, selection bias, varying definitions and imaging protocols, ascertainment bias and lack of control groups. These uncertainties mean that antenatal counseling is difficult and further large prospective studies are needed. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Agenesis of the corpus callosum (ACC) is a rare condition in which the main commissural pathway that connects the two cerebral hemispheres is partially or completely absent. It can be detected on antenatal ultrasound, but poses a significant diagnostic challenge as the outcome is variable[1], depending on whether there are coexisting abnormalities and on the underlying cause; however, even in isolated ACC, outcomes vary. In this review of the available literature, we aim to answer some common questions regarding ACC encountered in daily practice.

METHODS

We assembled a list of common questions encountered in our practice from fetal medicine consultants working at the fetal medicine unit at St George's Hospital, a tertiary-level unit. A systematic search strategy was then employed in order to identify all articles giving relevant information. A PubMed search was conducted on 5 May 2011 and updated on 31 July 2012. Over 3600 titles and abstracts were reviewed. The search strategy, keywords used and results are found in Appendix S1 and the studies[1–65] used in this Review are summarized in Appendices S2–S4.

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CLINICAL QUESTIONS

What is the corpus callosum?

The corpus callosum (CC) is the main commissural pathway in the brain and has an important role in the integration of information between the two hemispheres. It has four segments: the rostrum, genu, body and splenium; the narrowing between the body and splenium is called the isthmus (Figure 1).

The formation of the CC starts with the development of the genu; the body, the isthmus and the splenium develop at a later stage[2]. The development of the CC is thought to progress craniocaudally, with the exception of the most anterior part, the rostrum, that develops later, although some studies suggest that the development of the CC starts with the formation of the anterior body and progresses bidirectionally[29–34].

By 18–20 weeks of gestation, the CC assumes its final shape, although some thickening continues[3,35]; therefore, imaging of this structure before 20 weeks may not be optimal. This developmental sequence is thought to be important as it may point to the etiology: if partial ACC involves the anterior portion, it is usually due to a disruptive event (such as a vascular event or infectious cause)[4,36]. Conversely, if the posterior portion is absent, it may suggest an arrest in development[4].

What are the possible abnormalities of the corpus callosum?

There is wide variation in the terminology used to describe CC abnormalities, including: hypoplasia (thinning of the CC), hyperplasia (thickening of the CC) and agenesis (absence of the CC). When agenesis occurs, this can be complete (absence of all components) or partial (presence of a short remnant). Dysgenesis and hypogenesis (incomplete development) also refer to partial ACC[2,5,37,38]. Such differences in terminology should be considered when assessing reports of outcomes in this condition: although in many papers abnormalities of the CC are grouped, hypoplasia, complete agenesis and partial agenesis may be different clinical entities. Hypoplasia is rarely diagnosed antenatally, and most of the available series focus upon partial or complete agenesis.

Furthermore, major malformations of the forebrain can prevent the formation of the CC, such as encephaloceles and holoprosencephaly; in these situations the outcome is of course dictated not by the ACC itself but by the primary abnormality.

Terminology used in this paper

- Partial agenesis: partial absence of the CC
- Complete agenesis: total absence of the CC

Each of these may be

- Isolated: ACC with no other abnormalities
- Complex: ACC with other abnormalities

How common is agenesis of the corpus callosum?

The incidence is difficult to estimate because of selection bias in reported series. Large studies in healthy individuals using magnetic resonance imaging (MRI) showed no cases of ACC[39–42]. Similarly, two postmortem series involving 59 000 autopsies found ACC in only three cases[43,44]. However, it is important to note that assessment in healthy adults, study volunteers or routine autopsies is not unselected as these populations may be less likely to suffer from ACC. The best available data probably come from the California Birth Defect Monitoring Program and suggest a prevalence of about 1.4 per 10 000 live births for ACC and 0.4 per 10 000 live births for hypoplasia of the CC[45]. These figures may, however, be an underestimate of the real incidence, as it is likely that a proportion of asymptomatic individuals with ACC escaped detection in this study. These data suggest that anomalies of the CC may be quite frequent congenital anomalies of the central nervous system, with an overall incidence similar to that of neural tube defects. A higher prevalence of ACC in males has been reported by some but not other studies[6,45–47].

How can we reliably image the corpus callosum on ultrasound?

Normal ultrasound appearance of the corpus callosum

In mid-sagittal views of the fetal brain (two-dimensional (2D) ultrasound) the CC appears as a thin anechoic space, lined superiorly and inferiorly by two echogenic lines (Figure 1)[5]. Sonographic demonstration of the CC requires an adequate angle of insonation; mid-sagittal and midcoronal scans of the fetal brain are the best planes with which to visualize the CC and can be obtained with standard transabdominal ultrasound if the fetus is breech or with transvaginal ultrasound if the fetus is in vertex presentation[5,48,49]. Multiplanar sonography and transvaginal ultrasound may be useful in establishing the presence of the CC[50,51]. The pericallosal artery, which develops in close association with the CC, can act as a useful marker on 2D ultrasound imaging (Figure 1); this may be particularly useful when encountering resolution-related difficulties due to, for example, maternal obesity or fetal position. Offline analysis of three-dimensional (3D) volumes may also allow visualization, but is dependent on the plane of volume acquisition. 4D volume contrast imaging in the C-plane (4D VCI-C) is also effective in real-time reconstruction of mid-sagittal planes from axial views[52]. Comparison of 2D with 3D imaging and 4D VCI-C suggests that the quality of 2D ultrasound is superior, and that 3D ultrasound, while easy to perform, does not overcome all the limitations of 2D imaging[52].

Agenesis of the corpus callosum: direct visualization

The diagnosis of ACC is based upon non-visualization of the CC. If it is underdeveloped, measurement of its

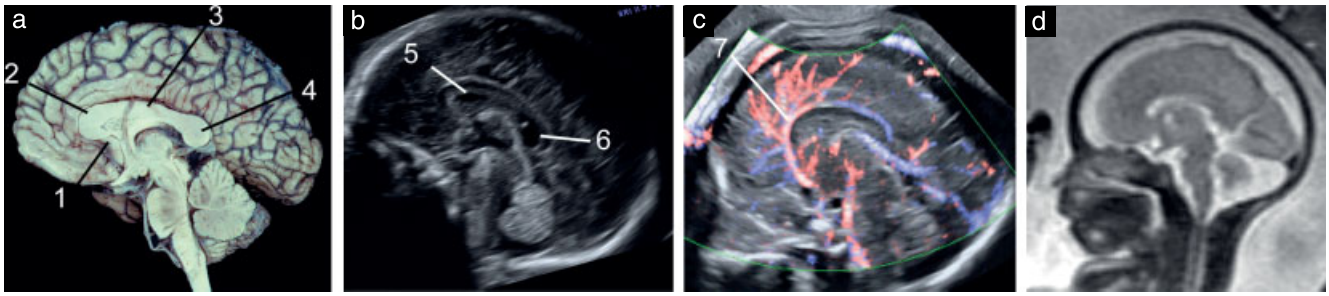

Figure 1 Normal appearance of the corpus callosum in a mid-sagittal view of the brain: (a) anatomical specimen from an adult brain; (b, c) fetal sonograms; (d) fetal magnetic resonance image. Labeled are: 1, rostrum; 2, genu; 3, body; 4, splenium; 5, cavum septi pellucidi; 6, cavum vergae; 7, pericallosal artery.

Table 1 Some key points on indirect features of agenesis of the corpus callosum (ACC)

Absence of the cavum septi pellucidi (CSP)
- Not specific to ACC; also associated with holoprosencephaly, hydrocephalus, septo-optic dysplasia, schizencephaly, encephalocele, porencephaly and hydranencephaly[53,54] (Figures 2 and 3)
- In partial ACC the CSP is usually present[2] (Figures 2 and 3)
Abnormalities of the ventricles
- Colpocephaly (dilatation of the atria and occipital horns of the lateral ventricles on the standard axial view at the transventricular level); this is the result of the absence of the posterior portion of the corpus callosum (CC), which allows expansion of the occipital horns. It is usually not associated with progressive ventriculomegaly[5,55] (Figure 3)
- Lateral displacement of the bodies of the lateral ventricles on coronal views due to a paired aberrant bundle of fibers (bundle of Probst) that fail to cross the hemispheres and run parallel to the midline. These paired structures bulge the medial borders of the frontal horns, which assume the shape of a bull's horn[5] (Figures 2 and 3)
- Upward displacement of the third ventricle, which reaches the level of the lateral ventricles (Figures 2 and 3)
Abnormal course of the pericallosal artery
- Complete ACC: the semicircular loop of the pericallosal artery is lost and the branches of the anterior cerebral artery ascend linearly[5]
- Partial ACC: the pericallosal artery follows the anterior part of the CC but then loses its normal course where the CC disappears posteriorly; at this level the artery takes an upward posterior oblique direction[2,7]
Widening of the interhemispheric fissure
- Absence of the CC frequently results in increased separation of the hemispheres, with a prominent interhemispheric fissure. In this condition sonography will reveal three parallel echogenic lines in the upper cranium, the middle one representing the falx cerebri and the lateral ones representing the medial borders of the separated hemispheres[5] (Figures 2 and 3)
Radial disposition of the sulci on the internal aspects of the hemispheres
- The absence of the CC results in abnormal induction of the medial cerebral convolutions, determining a radiate arrangement of cerebral sulci around the roof of the third ventricle[5] (Figure 4)

length and thickness is suggested; normative charts for comparison are available[35,50]. However, there are no data indicating the best threshold with which to diagnose partial agenesis or abnormal thickness. The available nomograms report the 90% prediction interval[35,50], and it would not be appropriate to use the threshold of the 5th centile to diagnose a rare condition. In practice, it is easy to recognize abnormal size of the CC only when there is a gross alteration. This means that cases with slight deviations from normal values, particularly in early gestation, represent a diagnostic dilemma.

Agenesis of the corpus callosum: indirect features

In practice it can be difficult to identify with certainty the presence or absence of the CC. However, ACC causes indirect brain rearrangements and these are often the first clues to the diagnosis (Table 1). These indirect signs are inconsistent and not always encountered in fetuses with partial agenesis of the CC[2,7]. Ghi *et al.*[7] showed that absence of the cavum septi pellucidi or ventriculomegaly was detected in eight out of 14 cases of partial agenesis of the CC; other signs of ACC were not demonstrated, which may reflect a minor disruption of the midline fibers.

How good is antenatal ultrasound in the detection of agenesis of the corpus callosum?

Prenatal sonographic diagnosis of agenesis of the CC is difficult. In expert hands, when a neurosonographic examination is performed, complete ACC may be diagnosed in the majority of cases at midgestation[49]. Nevertheless, in the standard examination of low-risk fetuses, visualization of the CC is not required and the condition may be suspected only in the presence of indirect findings, including ventriculomegaly or failure to visualize the cavum septi pellucidi[53–56]. Detection may also be gestational-age dependent, and in one series the diagnosis could never be made in early gestation[8].

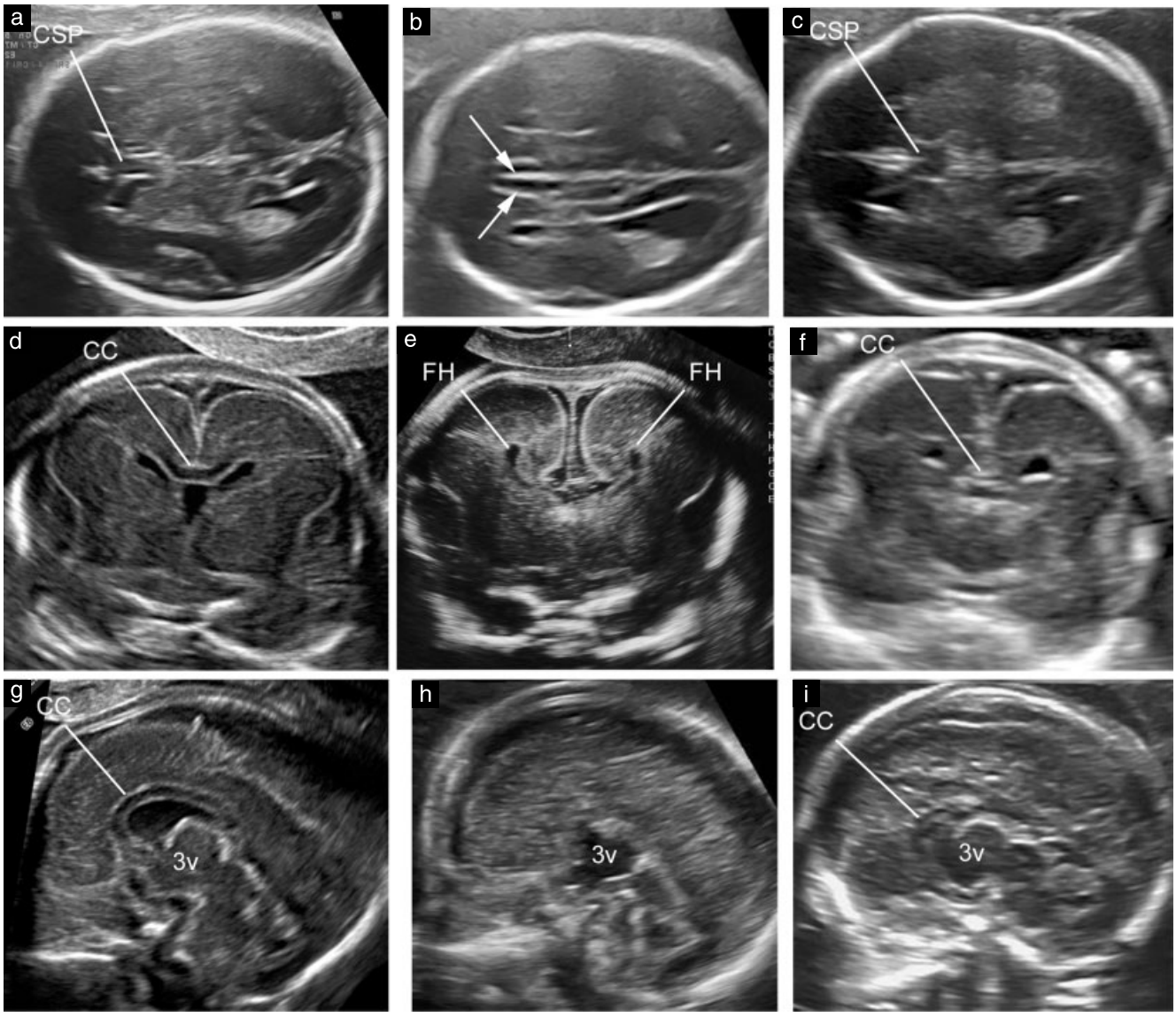

Figure 2 Sonography of a normal fetal brain (a,d,g) and fetal brains showing complete (b,e,h) and partial (c,f,i) callosal agenesis in axial (a–c), coronal (d–f) and mid-sagittal (g,h,i) views of the head in the second trimester of gestation. In complete agenesis, the anatomical complex formed by corpus callosum (CC) and cavum septi pellucidi (CSP) is completely absent, the interhemispheric fissure is enlarged (arrows), and the frontal horns (FH) are more widely separated than normal. In partial agenesis, the findings are more subtle, and the CC and CSP are present but shortened. 3v, third ventricle.

Distinguishing isolated from complex cases

ACC has been associated with cranial and extracranial anomalies, and there is an association with chromosomal and genetic abnormalities. Some of these associated conditions are subtle and difficult to recognize antenatally, and careful imaging in a center with a high level of expertise is required. In our review we found a prevalence of associated brain abnormalities of 45.8% (Table 2, Appendix S2). It is important to note that this rate is likely to be higher than the true figure due to bias: truly isolated cases may escape detection, while those with associated abnormalities are detected, referred to specialist centers and reported in the literature. The most frequently reported brain abnormalities associated with ACC are those of the posterior fossa, interhemispheric cysts and neuronal migration disorders.

Should magnetic resonance imaging be part of the assessment of suspected agenesis of the corpus callosum?

MRI allows direct visualization of the CC. This is important, as the diagnosis of ACC by ultrasound has been associated with a false-positive rate ranging from 0% to 20%[2,5,9,10]. In contrast, MRI can confirm ACC, assess whether this is complete or partial and may also help in detecting coexisting brain abnormalities not seen on ultrasound, such as anomalies of gyration and heterotopia[11,12,57,58]. In a recent systematic review, prenatal MRI was associated with detection of

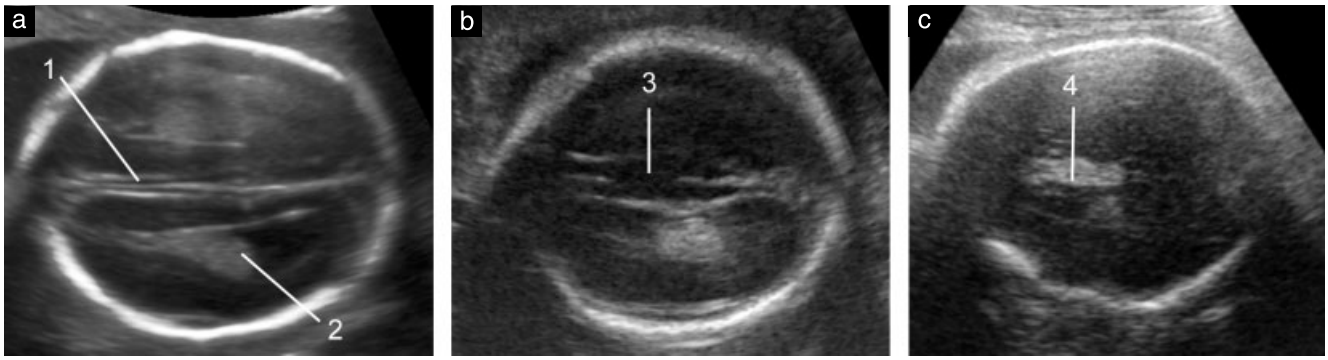

Figure 3 (a–c) Summary of sonographic findings that are associated with agenesis of the corpus callosum in the axial plane: 1) the cavum septi pellucidi (CSP) is not demonstrated and its position is occupied by three lines that are due to the widened interhemispheric fissure, centrally partitioned by the falx cerebri; 2) the frontal horns of the lateral ventricles are further away than normal from the midline (laterally displaced) and the atria of the lateral ventricles slightly enlarged; this results in a 'tear-shaped' appearance of the lateral ventricles; 3) an interhemispheric cyst is seen; 4) an echogenic structure is seen in the position normally occupied by the CSP; this is a lipoma, which is frequently associated with partial or complete callosal agenesis but is usually visible only in late gestation.

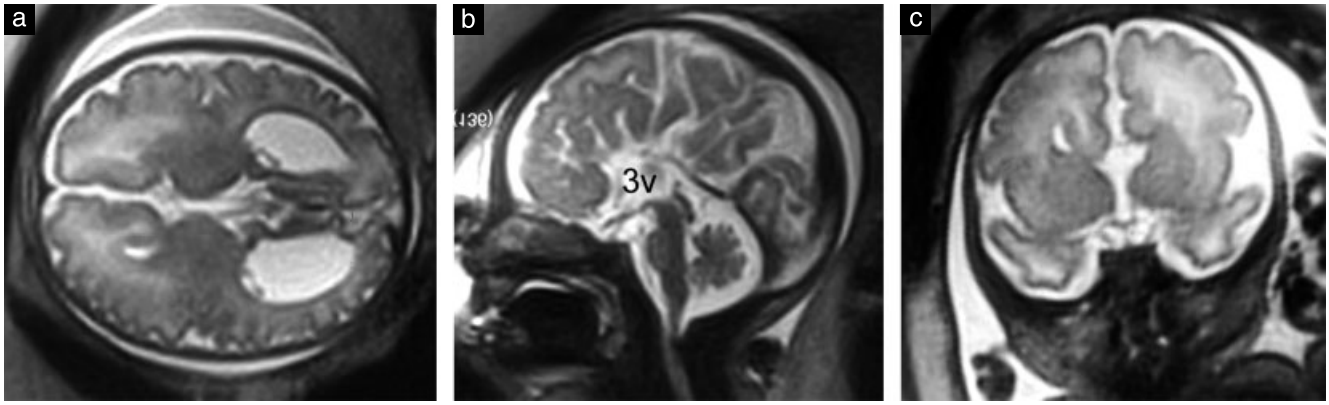

Figure 4 Magnetic resonance imaging (MRI) of agenesis of the corpus callosum in a third-trimester fetus: (a) axial, (b) mid-sagittal and (c) coronal views. Apart from demonstrating the absence of the corpus callosum, MRI has the advantage of clearly showing the normality of the convolutional pattern, a finding that has a major impact on prognosis. Notice the radial arrangement of the gyri around the roof of the third ventricle (3v).

additional abnormalities in 22.5% of cases compared with ultrasonography[1].

The association of ACC with other cerebral anomalies increases the likelihood of a later neurological impairment; therefore, MRI should be considered a part of ACC assessment, particularly in fetuses with apparently isolated ACC.

Should prenatal karyotyping be offered in agenesis of the corpus callosum?

ACC has been associated with several chromosomal rearrangements, but it is difficult to be certain regarding the incidence of chromosomal abnormalities in ACC because studies are not consistent in their reporting of chromosomal analysis[13]. We found the overall rate of chromosomal abnormality to be 17.8% (Table 2, Appendix S3), but it is important to note that this high rate includes both isolated and complex ACC. A recent study suggests that this high risk of chromosomal abnormalities is confined to complex cases[14]. Chromosomal microdeletions may be associated with ACC and therefore chromosomal analysis using comparative genomic hybridization should be considered.

Which genetic syndromes are associated with agenesis of the corpus callosum?

ACC has been associated with several syndromes with autosomal dominant, autosomal recessive or X-linked mode of inheritance[3,59]. An Online Mendelian Inheritance in Man (OMIM) search for 'Agenesis of the corpus callosum' resulted in 238 entries. The more common genetic causes of callosal agenesis are:

Aicardi syndrome: found almost exclusively in girls as it is inherited as an X-linked dominant trait; it is characterized by the presence of ACC associated with chorioretinal abnormalities, infantile seizures and mental retardation[60];

Andermann syndrome: a rare autosomal recessive disorder characterized by ACC, progressive motor-sensory neuropathy and mental retardation[61].

Table 2 Papers reporting on the incidence of chromosomal abnormalities and coexisting brain abnormalities in fetuses with agenesis of the corpus callosum (ACC)

Reference	*Year*	*Type of ACC*	*Cases with chromosomal abnormality* (n *(%))*	*Cases with other brain abnormality* (n *(%))*
Serur[13]	1988	Both	2/33 (6.1)	—
Bertino[23]	1988	Both	—	3/7 (42.9)
Blum[22]	1990	Both	—	8/16 (50)
Pilu[5*]	1993	Both	6/29 (20.7)	10/35 (28.6)
Vergani[4]	1994	Both	1/14 (7.1)	5/14 (35.7)
Bennett[8]†	1996	Both	2/10 (20)	3/14 (21.4)
D'Ercole[11]	1998	Both	0/14 (0)	9/14 (64.3)
Sonigo[12]	1998	Both§	—	30/50 (60)
Marszal[26]	2000	NS	2/7 (28.6)	—
Dos Santos[25]	2002	Complete	3/17 (17.6)	—
Shevell[6]	2002	Both	3/24 (12.5)	—
Glenn[9]	2005	Both	—	8/8 (100)
Bedeschi[15]	2006	Both	7/62 (11.3)	—
Volpe[2]	2006	Partial	3/18 (16.7)	8/19 (42.1)
Pisani[16]	2006	Complete	0/9 (0)	—
Fratelli[10]	2007	Complete	33/117 (28.2)	30/117 (25.6)
Chadie[17]	2008	Both	0/13 (0)	—
Schell-Apacik[3]	2008	Both	8/41 (19.5)	—
Tang[20]	2009	Complete	—	27/29 (93.1)
Cignini[24]	2010	Complete	1/17 (5.9)	—
Ghi[7]	2010	Partial	—	5/14 (35.7)
Li[14]‡	2012	Complete	12/41 (29.3)	27/41 (65.9)
Total			83/466 (17.8)	173/378 (45.8)

Denominators in some studies may differ because karyotype was not reported in all cases. *Includes the paper by Sandri *et al.*[21]. †Excludes one case of holoprosencephaly. ‡Only includes cases of complete ACC. §Not clearly specified whether ACC or other callosal abnormalities. Both, both partial and complete ACC; NS, not stated.

Given the uncertain prevalence of ACC, it is very difficult to establish the frequency of underlying genetic syndromes. Bedeschi *et al.*[15] studied 63 cases of ACC with a neuropsychiatric disorder (mental retardation of varying severity, learning disabilities or epilepsy) and found that 33% of the cases had a recognizable syndrome. Schell–Apacik studied 41 patients with ACC and found that 12% had a genetic syndrome[3].

Apart from genetic syndromes, ACC can be caused by non-syndromic conditions such as fetal alcohol syndrome and metabolic disorders[62].

Should screening for congenital infection be performed?

Although ACC has been reported in association with cytomegalovirus, toxoplasmosis, rubella and influenza virus, other associated abnormalities usually coexist; the value of screening for these infections in isolated ACC is uncertain[16,17,63,64].

Should serial antenatal examinations be arranged?

The prognosis in ACC is dependent on the coexistence of other abnormalities; these may include abnormalities of cortical development, which can only be assessed with advancing gestation. Therefore, additional detailed fetal ultrasound examination (s) should be considered, in order to search for cerebral and extracerebral abnormalities that may not be evident during the second-trimester examination. There is no agreement in the literature regarding the timing and frequency of such follow-up in fetuses with ACC.

What is the risk that the agenesis of the corpus callosum is not truly isolated?

Structural abnormalities not detected prenatally may be apparent only on postnatal imaging or clinical examination. The ability of fetal imaging to correctly diagnose isolated ACC will vary depending upon a number of factors, the most important one probably being the time in gestation, as it is unlikely that some anomalies, such as cortical malformations, will be detected in the second trimester; other variables include: the clarity of ultrasound imaging achieved (which may be limited, for example, by maternal habitus) and expertise of the operators involved; the imaging protocol used; and the use of MRI. Furthermore, the rigor, timing and length of postnatal follow-up will of course have a significant influence on the final diagnosis. Thus, a precise estimate of the discrepancy between prenatal diagnosis and postnatal assessment of ACC may be subject to some bias depending on the quality of the studies.

Overall, our review suggests that 15.1% of cases thought to be isolated prenatally were found to have associated abnormalities after birth; this proportion needs to be interpreted with some caution given the limitations outlined above, nevertheless, it highlights

the importance of postnatal assessment and follow-up (Appendix S4).

What is the neurological outcome of children with a prenatal diagnosis of isolated agenesis of the corpus callosum?

A recent systematic review[1] assessed the rate of neurodevelopmental outcome in 132 fetuses (16 studies) with isolated ACC. The authors reported neurodevelopmental outcome as: normal; borderline or moderate disability; or severe disability. In complete ACC, the respective figures were 74.3%, 14.3% and 11.4%, while for isolated partial ACC, they were 65.5%, 6.9% and 27.6%. When taking into account only those studies using MRI and standardized tools of neurodevelopmental assessment, in complete ACC, the rates were 83.7%, 8.2% and 8.2% for normal, borderline/moderate and severe disability, respectively. The corresponding rates for partial ACC were not reported due to the small number of cases. They found no statistically significant difference in outcome between fetuses with isolated complete ACC and those with isolated partial ACC[1].

The authors of the review highlighted many limitations in existing studies, including limited and inconsistent data that prevented subgroup analyses, for example between partial and complete absence of the CC. Therefore, providing a precise estimate of the risk of neurodevelopmental delay is difficult. In our view, one important limitation of the available studies is the time of follow-up: in most cases, assessment was made in the preschool period. This may represent an important shortcoming, as in one series a progressive decline of intellect was noted, with a considerable number of infants demonstrating learning difficulties in school[18,19].

What are the limitations of the available studies?

- *Study design*. Most studies report a small number of cases collected retrospectively.
- *Population selection*. Most studies report on a referred population. However, cases of ACC with few indirect signs are less likely to be detected during screening and will not be referred. This means that studies are likely to include more severe cases, and this could influence the reported risk of poor neurodevelopmental outcome.
- *Disease definition*. Complete and partial, and complex and isolated cases, are often considered together.
- *Imaging protocol*. Antenatal assessment of ACC differs between studies and not all include MRI evaluation.
- *Ascertainment bias*. There are high rates of pregnancy termination in pregnancies with a fetus affected by ACC and this may influence outcome, with more severe cases likely to undergo termination. In addition, many studies report high proportions of cases lost to follow-up.
- *Outcome assessment and reporting*. Subjective tests are often used to assess neurological development and there is a lack of distinction in the severity of neurodevelopmental delay.
- *Length of follow-up*. Many studies report follow-up soon after birth, and such assessment may not be sufficiently sensitive to detect abnormal neurological function.
- *Lack of control groups*. This prevents comparison of outcomes with those of the normal population.

CONCLUSION

Although the precise incidence is unknown, ACC appears to be a rare condition. It may be suspected at the time of the routine anomaly scan due to the presence of indirect features, or diagnosed on direct visualization. However, in isolation it may remain undetected. The finding should trigger detailed assessment to establish whether it is isolated, or if there are associated ultrasound abnormalities. Careful evaluation of fetal anatomy should be carried out in an expert setting and this should include multiplanar neurosonography, for which transvaginal imaging may be required. When available, fetal MRI is indicated, allowing confirmation of the finding and assessment of coexisting brain abnormalities. In part due to the rarity of the condition, there remain many gaps in our knowledge: it is difficult to establish the probability for chromosomal abnormalities, but it appears that, in cases with no coexisting structural anomalies, chromosomal abnormalities are uncommon. Similarly, the risk of there being an underlying congenital infection appears low if there are no associated features. The rate of neurodevelopmental delay in infants with a prenatal diagnosis of isolated ACC is about 25–30%, and this appears to be similar in complete and partial ACC. However, it must be recognized that there are many limitations in the studies that have reported on this condition, and such inconsistent data mean that it is difficult to provide a precise estimate of the risk of neurodevelopmental delay. Given this, both antenatal and postnatal follow-up should be considered when this diagnosis is made.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy used for the literature review in this article

Appendix S2 Papers reporting on the incidence of coexisting brain abnormalities in agenesis of the corpus callosum diagnosed antenatally

Appendix S3 Papers reporting on the incidence of chromosomal abnormalities in fetuses with agenesis of the corpus callosum

Appendix S4 Papers reporting on the rate of associated abnormalities detected postnatally in fetuses diagnosed prenatally as having isolated agenesis of the corpus callosum

