Fetal Diagnosis and Therapy

Research Article

Fetal Diagn Ther 2021;48:217–226
DOI: 10.1159/000512953

Received: June 20, 2020
Accepted: November 8, 2020
Published online: March 8, 2021

Prenatal Imaging Features and Postnatal Outcome of Short Corpus Callosum: A Series of 42 Cases

Caroline Bartholmot[a, b] Sara Cabet[a, c] Mona Massoud[a] Jérôme Massardier[a] Axel Fichez[d] Vincent Des Portes[e] Laurent Guibaud[a, c]

[a]Centre Pluridisciplinaire de Diagnostic Prénatal, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon 1, Lyon-Bron, France; [b]Centre Pluridisciplinaire de Diagnostic Prénatal, Montpellier, France; [c]Imagerie pédiatrique et fœtale, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon 1, Lyon-Bron, France; [d]Centre Pluridisciplinaire de Diagnostic Prénatal, Hôpital de la Croix Rousse, Lyon, France; [e]Service de Neuropédiatrie, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon 1, Lyon-Bron, France

Keywords
Brain · Corpus callosum · Prenatal diagnosis

Abstract
Objectives: Our goal was to provide a better understanding of isolated short corpus callosum (SCC) regarding prenatal diagnosis and postnatal outcome. ***Methods:*** We retrospectively reviewed prenatal and postnatal imaging, clinical, and biological data from 42 cases with isolated SCC. ***Results:*** Prenatal imaging showed SCC in all cases (n = 42). SCC was limited to rostrum and/or genu and/or splenium in 21 cases, involved body in 16 cases, and was more extensive in 5 cases. Indirect imaging features included typical buffalo horn ventricles (n = 14), septal dysmorphism (n = 14), parallel lateral ventricles (n = 12), and ventriculomegaly (n = 4), as well as atypical features in 5 cases. SCC was associated with interhemispheric cysts and pericallosal lipomas in 3 and 6 cases, respectively. Aneuploidy was found in 2 cases. Normal psychomotor development, mild developmental disorders, and global developmental delay were found in 70, 15, and 15% of our cases, respectively. ***Conclusions:*** SCC should be investigated to look for pericallosal lipoma and typical versus atypical indirect features of corpus callosum agenesis (CCA). Prenatal counselling should be guided by imaging as well as clinical and genetic context. Outcome of patients with SCC was similar to the one presenting with complete CCA.

Introduction

The corpus callosum (CC) is the main cerebral commissure, which begins to form during the 12th week of gestation to become complete around the 20th week of gestation [1–4]. Biometrically, the growth of the CC is linear throughout in utero development [5–8].

Callosal anomalies include complete agenesis of the CC (CCA) as well as other conditions, especially short CC (SCC) which we reported under the term of "callosal dysgenesis" (Fig. 1, see online suppl. Fig. 1; see www.karger.com/doi/10.1159/000512953 for all online suppl. material). SCC may be either "isolated" or associated with other cerebral or extra-encephalic anomalies. Our goal

karger@karger.com
www.karger.com/fdt

Laurent Guibaud
Imagerie pédiatrique et foetale, Hôpital Femme Mère Enfant
Université Claude Bernard Lyon I
59, Boulevard Pinel, FR–69677 Lyon-Bron (France)
laurent.guibaud@chu-lyon.fr

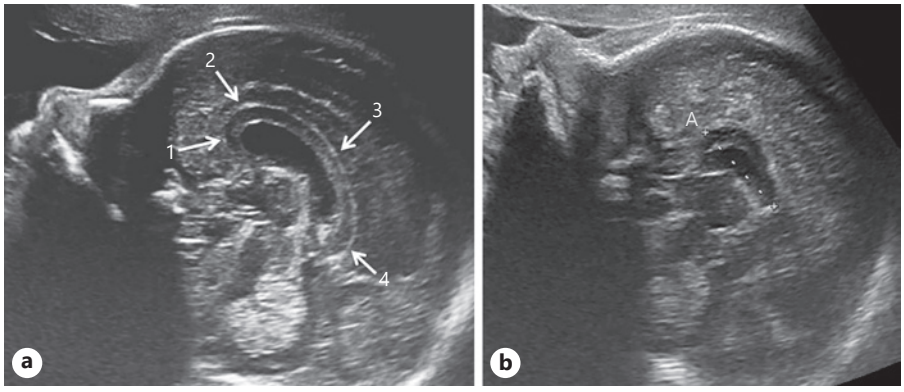

Fig. 1. Normal and SCC on midsagittal sonographic plane. **a** Normal corpus callosum at 27 WG showing the rostrum (1), genu (2), body (3), and splenium (4). **b** SCC, measuring 20–21 mm in length at 25 WG (<1st percentile) (Case 6). Note that echogenicity of both the nasal bone anteriorly and the vermis posteriorly, as well as fourth ventricle, especially the fastigium, are clearly visible and represent important anatomical landmarks to assess the precision of the midsagittal plane. SCC, short corpus callosum.

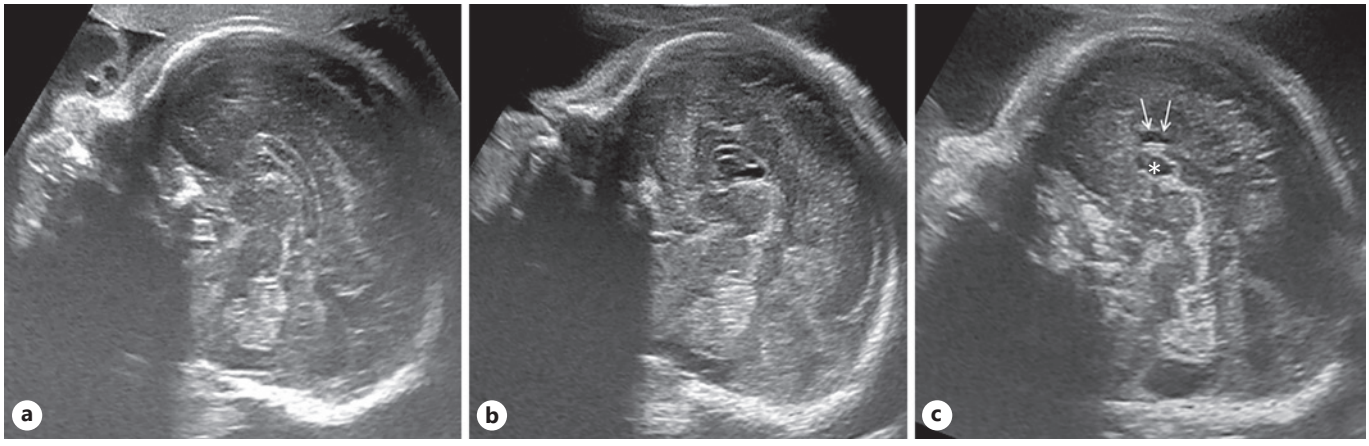

Fig. 2. Classification of callosal dysgenesis on a strict midsagittal sonographic plane. **a** Group A: dysgenesis involving one or both extremities of the corpus callosum. In this case, the rostum is not identified and the body is underdeveloped (Case 28). **b** Group B: partial agenesis or dysgenesis involving at least one part of the callosal body. In this case, the rostrum and splenium, as well as the posterior part, are not identified and the corpus callosum is limited to the anterior part of the body and an underdeveloped genu (Case 20). **c** Group C: corpus callosum limited to a callosal bud. In this case, the corpus callosum is limited to the bud at the junction between the genu and body (arrows) with a very tiny cavum septum pellucidum (*) (Case 16).

was to provide a better understanding of "isolated" SCC, including the postnatal outcome, and to propose a systematic prenatal approach of such conditions based on retrospective analysis of the prenatal data from our cohort of 42 foetuses.

Methods

We retrospectively reviewed the data from 42 consecutive cases with isolated SCC from our Foetal Medical Centre over a 7-year period (2010–2016). SCC was defined as isolated based on the absence of any other cerebral or extra-encephalic malformation (excluding indirect features of CCA). A SCC was defined by a reduced antero-posterior diameter, less than or equal to the first percentile, using the reference curves from Cignini et al. [9] (ultrasound examination) and Tilea et al. [10] (MRI).

Gestational age was determined on the basis of first-trimester scan (CCL). All patients were referred due to foetal brain anomalies after the second or third-trimester ultrasound screening (22 WG or 32 WG, respectively). Prenatal diagnostic imaging included, in all cases, strict midsagittal transabdominal sonographic and foetal MRIs for precise anatomical analysis, which allowed us to classify dysgenesis into 3 groups (Fig. 2):

- Group A: dysgenesis involving one or both extremities of the CC;
- Group B: partial agenesis or dysgenesis involving at least one part of the callosal body;
- Group C: CC limited to an anterior bud.

Imaging analysis includes anatomical analysis of both corpus callosum (length, missing parts, and thickness) and pericallosal area (abnormal echogenicity and cyst), as well as presence of typical/atypical indirect features of callosal dysgenesis. Note that callosal thickness was subjectively assessed.

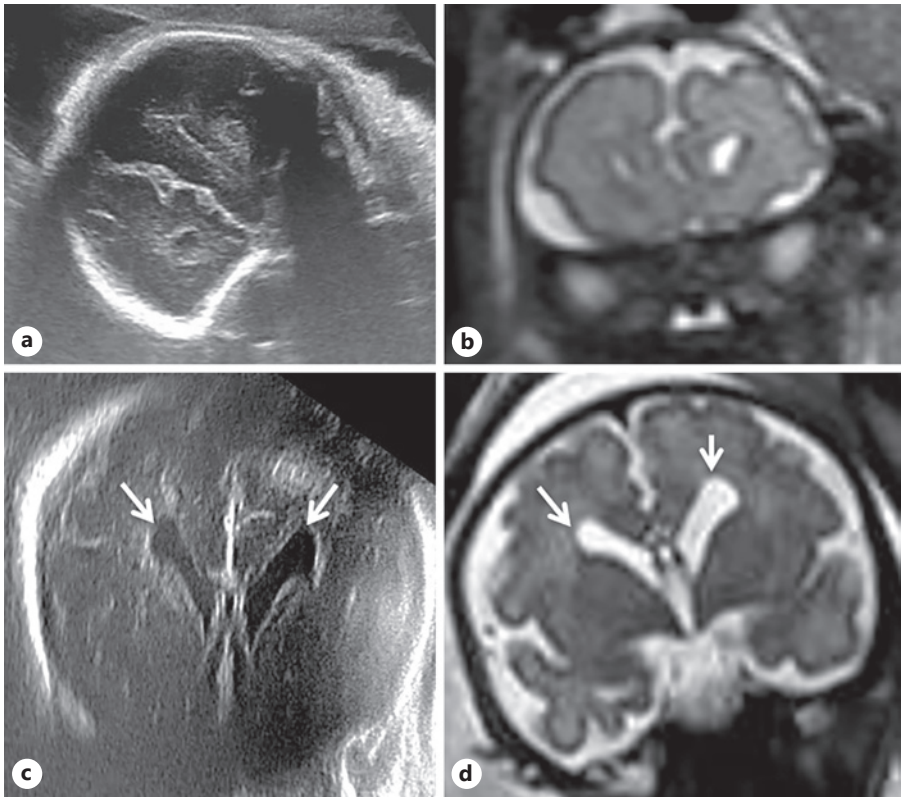

Fig. 3. Atypical indirect features on prenatal imaging. **a**, **b** DIHF on coronal sonographic and T2-weighted foetal MRIs (Case 1). **c**, **d** Atypical ventricular dysmorphism with "drop-shaped" frontal horns on coronal sonographic and T2-weighted foetal MRI (arrows) (Case 1). DIHF, distortion of the interhemispheric fissure.

Prenatal CGH Array Was Systematically Proposed

Characteristics of the cases are summarized in online suppl. Table 1. For each patient, we recorded the following data: age at diagnosis by US, referral reason, type of callosal dysgenesis, typical and atypical indirect signs of CCA, thick or thin CC, pericallosal lipoma, interhemispheric cyst, genetic data, outcome, term of delivery, gender, family past, postnatal MRI, developmental assessment, and age at the assessment. Postnatally, all children benefited from psychomotor evaluation and brain MRI.

Neurodevelopment clinical assessment was conducted with a paediatric neurologist at 1, 6, 12, and 24 months, then once a year until the age of 3 and at 5 years. Standardized Wechsler Intelligence Scales (WPPSI) was performed at 3 and 5 years. WPPSI-III or WPPSI-IV tests were used at 3 and 5 years, respectively. Intellectual Quotient (IQ) tests were performed by the same neuropsychologist, and performance related to school curriculum, learning disabilities, and participation in a rehabilitation program was also recorded (online suppl. Table 2).

The duration of follow-up was variable, depending on age of the last follow-up visit. Based on the results of these cognitive and motor ability tests, children were divided into 3 groups:

- Group 1: normal psychomotor development: no cognitive, behavioural or motor impairments.
- Group 2: developmental disorders without intellectual deficit (mild anomalies): specific cognitive, motor, or oral language disorders.
- Group 3: global developmental delay: severe cognitive disorders or autism spectrum disorders.

This article describes a cohort of anonymized patients who were clinically managed and who were not subjected to research investigations for the purpose of this study, and ethical approval was, therefore, not sought.

Results

All data of the 42 foetuses diagnosed with isolated SCC are summarized in online suppl. Tables 1 and 2. The mean term at diagnosis was 30 WG (22–35 WG). Twenty-two cases were diagnosed after the 2nd-trimester ultrasound (<30 WG), and 20 cases were diagnosed after the 3rd-trimester ultrasound (>30 WG). Prenatal imaging showed a SCC in all cases ($n = 42$), associated with abnormal focal thickness in 16 cases (thin, $n = 13$; thick, $n = 3$). Callosal dysgenesis was limited due to a missing part involving the rostrum and/or genu and/or splenium in 21 cases (Group A), involving part of the body in 16 cases (Group B) and was more extensive in 5 cases in which only a callosal bud was identified (almost complete agenesis) (Group C).

Indirect imaging features included typical buffalo horn ventricles ($n = 14$), septal dysmorphism ($n = 14$),

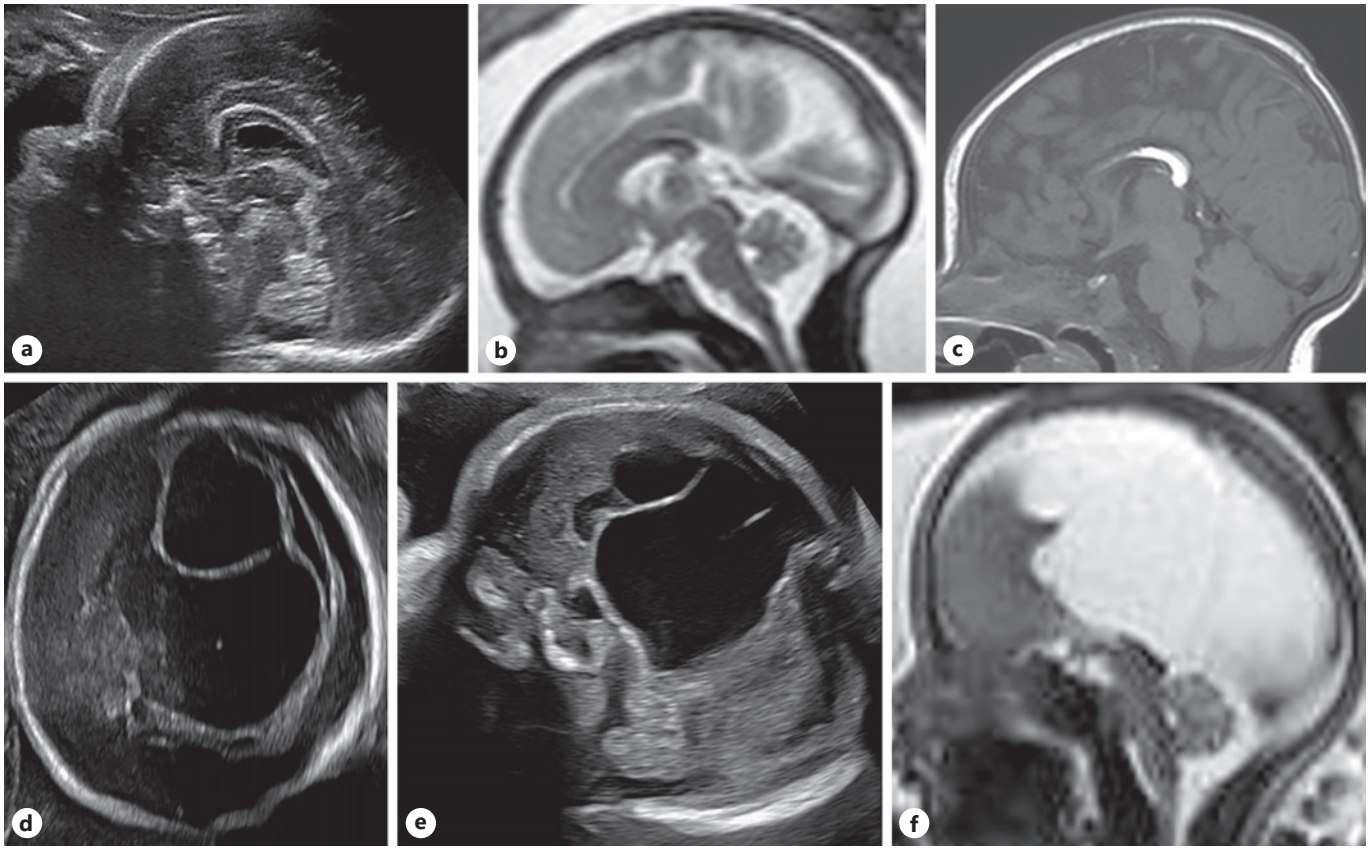

Fig. 4. Dysgenesis of the corpus callosum with pericallosal lesions. **a–c** Pericallosal lipomas appearing as a discrete echogenic pericurvilinear line above the corpus callosum on a midsagittal sonographic image (**a**), corresponding to callosal hypointensity on prenatal T2-weighted MRI (**b**), due to fat/water chemical shift artefact and displaying a curvilinear hyperintensity on postnatal T1-weighted MRI (**c**) (Case 6). **d–f** Interhemispheric cysts on axial and sagittal sonographic and T2-weighted MRI appearing as well-defined round anechogenic septated structures located between the 2 hemispheres (Case 11).

parallel lateral ventricles (n = 12), and ventriculomegaly (n = 4) (online suppl. Fig. 2). Atypical indirect features, including ventricular dysmorphism with "drop-shaped" frontal horns and distortion of the interhemispheric fissure (DIHF), were present in 2 and 3 cases, respectively (Fig. 3).

The distribution of indirect signs according to groups was the following:

- Group A (n = 21): 1 sign in 5 cases, 2 signs in 3 cases, 3 signs in 3 cases, and none in 10 cases;
- Group B (n = 16): 1 sign in 4 cases, 2 signs in 4 cases, 3 signs in 1 case, and none in 7 cases;
- Group C (n = 5): 1 sign in 1 case, 2 signs in 1 case, 3 signs in 2 cases, and none in 1 case.

SCC was associated with interhemispheric cysts and pericallosal lipomas in 3 (Cases 5/11/29) and 6 (Cases 6/17/22/31/34/38) cases, respectively, including 1 case of pericallosal lipoma diagnosed only postnatally (Case 34) (Fig. 4).

Amniocentesis was performed in 33 cases (78.5%) allowing CGH array analysis that showed a large chromosomal rearrangement in 2 cases: partial 3p deletion and partial 20qter trisomy, respectively. Our series included 2 familial cases (Cases 8/37) and 1 case related to foetal alcohol syndrome (FAS) (Case 24).

There were 6 terminations of pregnancy and 36 live births. Postnatal brain MRI was performed in 31 children (86%) at a mean of 1.8 months (from Day 2 to 31 months). Regarding the splenium, MR performed in the early postnatal period demonstrated in 4 cases a splenium that was too thin to be clearly delineated (MRI performed at a mean age of 1.8 months) which was normal on a later MRI examination after completion of callosal modelling (Cases 2/15/20/23).

Follow-up data were available for all 36 born babies, except one who was lost to follow-up, over an average of 47 months (from 8 to 90 months). Clinical evaluation was carried out during the first month of life for all the newborns, then at 6 months and once a year until the age of 3 for 26 children (72%) and at 5 years of age for 11 children (30%). Among our 35 patients, 14 were under 3 years of life and therefore were not evaluated using a standardized cognitive assessment scale. Our 35 patients were classified into 3 groups according to their cognitive abilities.

Regardless of the age at the end of follow-up, 25 children (70%) presented with normal psychomotor development (Group 1), 5 children (15%) with mild developmental disorders (Group 2), and 5 children (15%) with global developmental delay (Group 3). Neurodevelopmental outcome was favourable overall in 85% (Groups 1 and 2).

Among the 5 children in Group 2, one had hemiparesis following surgery on the interhemispheric cyst (Case 5). Two had predominantly language delay (Cases 17/30), including the one with partial 3p deletion – Case 30). One had mild both postural and language delay (Case 32) and the last child presented both postural delay (walk acquired at 27 months) and minor motor disorder (Case 25).

Among the 5 children in Group 3, one had autism (Case 3). Another child had an overall postural delay with major hypotonia despite a very short follow-up of 8 months (Case 14). One with partial 20qter trisomy had language delay associated with intellectual disability (Case 20). One child had global psychomotor delay associated with axial hypotonia and peripheral hypertonia as well as strabismus (Case 27). Finally, the last child, born from a diamniotic monochorionic twin pregnancy, had postural, language, and autism spectrum disorders. Interestingly, his co-twin presented the same handicap despite a normal corpus callosum (Case 39). Both twins had normal genetic tests.

Discussion

This retrospective study of 42 prenatal cases of SCC leads us to propose a systematic approach based on both callosal analysis (length, thickness, and different anatomical parts) and identification of pericallosal lesions as well as "classic" versus "atypical" indirect features suggestive of callosal dysgenesis, within a precise clinical and genetic context, which should be of help for prenatal counselling, especially regarding postnatal outcome.

Anatomical Analysis of the Short Corpus Callosum

Guidelines for routine sonographic analysis of foetal brain refer to examination conducted using axial planes and do not include midsagittal images, which are required for analysis of the length and thickness of the CC and identification of its different anatomical parts [11]. However, "short CC" has currently become an increasing indication for prenatal counselling because measurement of the callosal length on midsagittal plane is increasingly performed in routine practice [12]. On a technical point of view, a precise strict midsagittal image is mandatory to diagnose "short CC" and avoid any false image induced by off-midsagittal plane (online suppl. Fig. 3) [13–16]. On foetal MRI, one should be aware that the inferior sagittal sinus and internal cerebral veins located close to the posterior part of the CC should not be misinterpreted as a callosal structure. In this manuscript, we defined SCC as an antero-posterior diameter, less than or equal to the first percentile, using the reference curves from Cignini et al. [9] (ultrasound examination) and Tilea et al. [10] (MRI). We should underline that the choice of these references remains debatable since variations between references clearly exist but discussion about such variation was beyond the scope of this manuscript. One should note that the interest of measuring a ratio between the CC length and the internal cranial occipitofrontal dimension in midsagittal plane was recently underlined when facing a SCC [17]. Indeed, this ratio (internal cranial occipitofrontal dimension/CC length) practically does not change throughout a normal pregnancy and is significantly higher in pregnancies with SCC. For the authors, the mean advantage of measuring this ratio is that it offers a rapid evaluation of the CC without the need to refer to biometry tables [17].

If a SCC is suspected, one should carefully analyse its different anatomical parts (Fig. 1) [14]. We should underline that ultrasound provides a more precise analysis of the CC anatomy regarding spatial resolution compared to MRI. Indeed, the genu and rostrum, which are very close laterally to the adjacent frontal lobes, are more difficult to analyse on MRI compared to ultrasound [18–21].

However, one should be aware that, according to the sonographic approach, analysis of callosal anatomy is more straightforward for both the genu and rostrum anteriorly and splenium posteriorly [22, 23]. Overall, in our experience, we are more confident for CC length and anatomical analysis on sonographic analysis than on MR analysis. These technical considerations account for why some cases of partial callosal agenesis in Group A, with only part of the genu and/or rostrum absent, were better visualized by ultrasound rather than MRI.

Concerning the splenium, its late prenatal and postnatal modelling reflects the fact that the splenium in the prenatal or early postnatal period can sometimes be difficult to detect due to its physiological thinness [24]. Indeed, even in the early postnatal period, MRI demonstrated, in 4 cases of our series, a splenium that was too thin to be clearly delineated (MRI performed at a mean age of 1.8 months) which was normal on later MRI examination after completion of callosal modelling. This, therefore, weakens the correlation between prenatal and long-term postnatal imaging. It is thus important to underline that a thin splenium on prenatal or early postnatal imaging can be normal on long-term imaging after completion of its modelling [18].

When dealing with callosal dysgenesis, one should note whether CC is of normal thickness, abnormally thin (which defines hypoplastic CC), or too thick (defined as >5 mm). In routine practice, assessment of the thickness of the CC is more often subjective even though reference tables exist [8, 25]. Regarding thin and thick CC, one should be aware of 2 important points: (1) any abnormal thinness of the CC should be correlated to head circumference because (2) in cases with associated microcephaly or extended clastic lesion, the thinness of the commissures reflects only axonal volume reduction [26]. On the other hand, thick CC can be a transitional feature, identified during the second trimester with normalization of callosal thickness in the second half of pregnancy, related to physiological axonal pruning [2, 27]. Increased thickness of the CC may be associated with normal callosal length or with a SCC (online suppl. Fig. 4) [28, 29]. This anomaly can be global or focal as in our series in 3 cases and 1 case, respectively. Thick CC has been well illustrated and was commented on by Malinger et al. [25], especially in association with megalencephaly which was not encountered in our series.

Pericallosal Structures

A SCC may reflect dysgenesis secondary to a pre-existing lesion on the midline, essentially related to lipoma or interhemispheric cyst, as encountered in our series in 6 and 3 cases, respectively, which constitutes obstacle to the passage of the commissural fibres comprising the CC (Fig. 4) [3]. Although interhemispheric cysts are often easily diagnosed, especially in cases of large ones which may conceal callosal dysgenesis [30, 31], pericallosal lipoma can be easily overlooked in the second trimester, especially in cases of curvilinear lipoma, as illustrated in one case of our series in which the SCC was diagnosed postnatally, related to a pericallosal lipoma (Fig. 4). As stated initially by Atallah et al. [32] and confirmed by Shinar et al. [33], callosal dysgenesis, especially SCC, should always raise a suspicion of underlying pericallosal lipoma, as encountered in 6 cases of our series. Atallah et al. [32] underlined that pericallosal lipoma gives rise to curvilinear echogenicity located at the site of the pericallosal sulcus, which can be easily overlooked, and is more easily depicted in the third trimester. This is particularly important in countries in which termination of pregnancy is not allowed after 22 or 24 weeks, at a time when callosal dysgenesis can appear "isolated." This point is crucial and should be stressed in terms of prenatal counselling since curvilinear lipomas are most often associated with normal psychomotor development [32, 34].

"Classic" versus "Atypical" Indirect Features of Corpus Callosum Agenesis

The cavum septum pellucidum, which is absent in cases of CCA, can be present in cases of partial agenesis, which represents the main cause of SCC. In such cases, other indirect findings, if present, can be helpful to reveal underlying callosal dysgenesis. However, in our series, ventricular dysmorphism suggestive of CC dysgenesis was found in 14 cases (33%) and colpocephaly in 4 cases (9.5%) [35]. Thus, as reported by Shen et al. [36] and Karl et al. [37], attention should be paid to septal cavity dysmorphia, and more specifically to the inversion of transverse and antero-posterior diameter ratio, which was found in 14 cases (33%). Although intuitively, the more subtle the dysgenesis of the CC and the more subtle the indirect findings, we did not find a significant difference in the occurrence of indirect signs between Groups A, B, and C, most likely related to a lack of study power (non-significant higher frequency of indirect signs in Group C).

Two "atypical" indirect features were identified that merit further comment (Fig. 3). In 3 cases, an anterior part of the DIHF was found. Vinurel et al. [38] have shown that such a DIHF should be considered as an anatomical variant, leading to a search for an anomaly in brain organization, in particular of the median line, and cannot be considered as an associated malformation. This DIHF should, therefore, be considered similarly to anomalies of the septal cavity, as an indirect sign of an anomaly of the median line without prognostic incidence per se.

On the other hand, we encountered atypical ventricular dysmorphism with drop-shaped frontal horns on coronal plane in 2 of our cases, including one familial form of SCC. In our experience, such frontal horn dysmorphia should be considered as an element of orientation towards syndromic callosal dysgenesis [12, 39, 40].

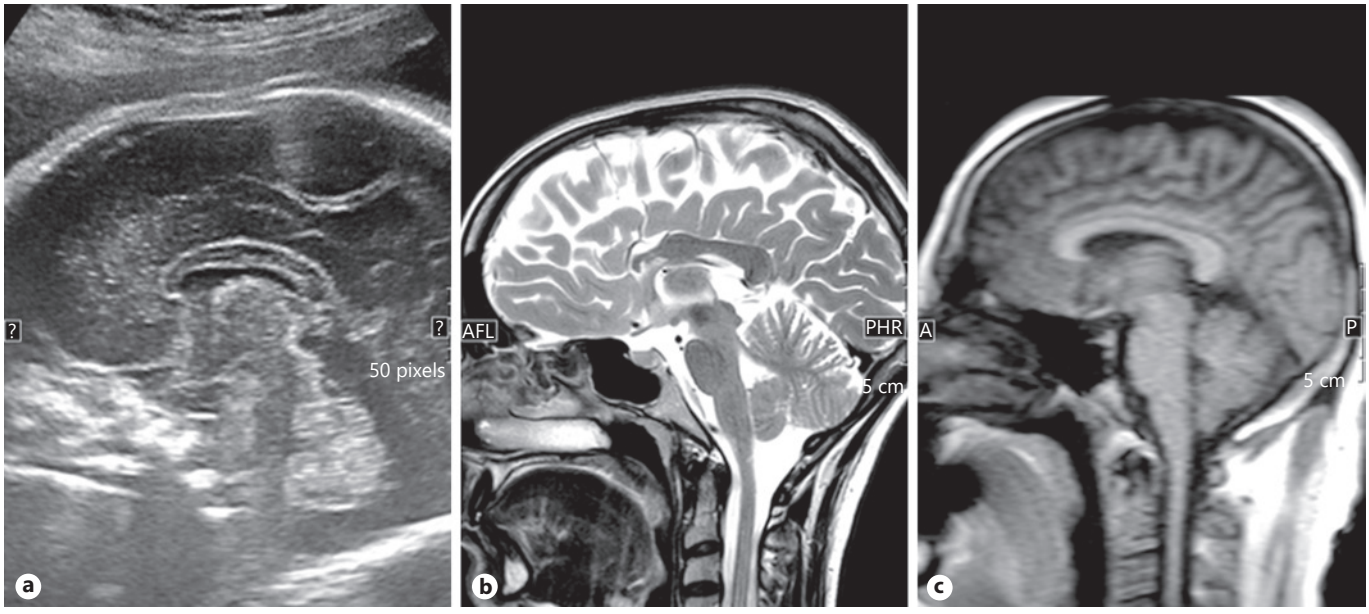

Fig. 5. Foetus with a SCC and parental MRIs to investigate evidence of a familial callosal disorder. **a** Midsagittal sonographic image of a foetus at 32 WG showing a SCC of 29 mm in length, with an absence of the rostrum as well as underdevelopment of the genu with a thick mid-part of the callosal body. **b**, **c** Maternal T2-weighted midsagittal MRI (**b**) demonstrating similar anatomical features to her foetus, including absence of the rostrum as well as underdevelopment of the genu with a thick mid-part of the callosal body, whereas paternal T1-weighted gradient-echo midsagittal MRI (**c**) showing normal corpus callosum. Note that although the mother had schooling difficulties, she had a normal social and professional life without any intellectual deficit (recent case, not included in our series). SCC, short corpus callosum.

Clinical and Genetic Context

Regarding the context, consanguinity, toxic substances consumption (alcohol, anti-vitamin K, etc.), or severe maternal epilepsy should be checked as risk factors [2]. Indeed, callosal anomalies are common in FAS with an incidence of 6.8%, with particular involvement of the anterior and/or posterior parts of the CC [41–43]. One case of our Group A with SCC, demonstrating no genu or rostrum and a lack of splenium modelling, was related to FAS, despite an absence of any other classic suggestive findings, such as facial dysmorphism or decrease in cephalic biometry (online suppl. Fig. 5). Interestingly, it has been reported that the posterior part of the CC is particularly vulnerable to alcohol effects [42]. Notably, for this child, the oldest in our series, psychomotor development (Group 1), and schooling were normal.

In addition to precise medical anamnesis, any case of callosal dysgenesis requires genetic counselling to investigate a syndromic entity, especially in cases of consanguinity or indirect atypical features (drop-shaped frontal horns), as previously mentioned. Indeed, callosal anomalies, even isolated, have been reported in association with chromosomal, genetic, or metabolic anomalies [44–55]. In our series, cytogenetic investigations, based on CGH array, were performed in 33 patients with a completion rate of 78.5% and were normal for the 2 familial forms. CGH array anomalies were found in 2 of our patients corresponding to partial 3p deletion and partial 20qter trisomy, respectively. In both cases, the chromosomal rearrangement involved several genes, but none of them are known to be involved in the formation of the CC.

One should note that whole-exome sequencing is currently proposed in most foetal medicine centres to look for any pathogenic exonic variants, which encompass more than 30–45% of syndromic entities involving the corpus callosum [2, 56–58]. However, at the time of our study, whole-exome sequencing was not available. Finally, to support dominant genetic callosal disorders, a midsagittal MRI of the CC of both parents should also be performed to look for any parental dysgenesis, which would help to guide prenatal counselling, as illustrated in Figure 5.

Prenatal Counselling for Postnatal Prognosis

Prenatal counselling for isolated callosal abnormalities remains debatable. As a result, the parental decision to

continue or terminate pregnancy differs, not only based on the couples themselves but also on the available medical information, which remains heterogeneous amongst foetal medical centres [56, 59].

In our series, postnatal clinical assessment included, for each child, both parental evaluation of the child's behaviour and neuropediatric assessment. However, as a limitation of our series, a standardized cognitive assessment scale was not used for all children since 14 children were under 3 years of age at the last follow-up visit. Psychomotor assessment was satisfactory (Group 1) in 25 children (70%), with only slight developmental issues but no intellectual disability (Group 2) in 5 children (15%), and neurodevelopmental delay (Group 3) in 5 (15%).

The postnatal follow-up of our cohort showed a rather good prognosis in children with isolated callosal dysgenesis (70% favourable progression), which is consistent with existing studies [56, 60–63]. Volpe et al. [64] reported similar outcome between isolated partial callosal agenesis and isolated CCA, with 75% favourable results for the latter. However, it should be noted that the majority of children were evaluated within a pre-school age, which may, therefore, have led to overestimation of a favourable outcome. Indeed, one should note that neuropsychiatric symptoms, such as communication or social interaction deficits, or hyperactivity, may appear later in childhood, as encountered in patients with CCA, which is difficult to predict in cases of isolated callosal dysgenesis [56, 65–68]. Extended postnatal follow-up (beyond 5 years) is required to complete data on neurodevelopmental status, particularly on interactions and school admissions, in order to provide more accurate information to families [64, 69, 70].

Finally, SCC should be accurately investigated by neurosonography and foetal MRI to describe, as precisely as possible, length, thickness, and missing anatomical parts. Any feature suggestive of callosal dysgenesis related to pericallosal lipoma should be scrutinized, as well as classic or atypical indirect features of CCA. All these elements, in association with the clinical and genetic context, are important in guiding prenatal counselling. In our series, the proportion of patients with favourable outcome was the same for those with either callosal dysgenesis or CCA.

Statement of Ethics

This article describes a cohort of anonymized patients who were clinically managed and who were not subjected to research investigations for the purpose of this study, and ethical approval was, therefore, not sought.

Conflict of Interest Statement

All the authors have no conflict of interest to disclose.

Funding Sources

The authors did not receive any funding.

References

1 Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci. 2007;8(4):287–99.
2 Paul LK. Developmental malformation of the corpus callosum: a review of typical callosal development and examples of developmental disorders with callosal involvement. J Neurodev Disord. 2011;3(1):3–27.
3 Bénézit A, Hertz-Pannier L, Dehaene-Lambertz G, Monzalvo K, Germanaud D, Duclap D, et al. Organising white matter in a brain without corpus callosum fibres. Cortex. 2015;63:155–71.
4 Raybaud C. The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. Neuroradiology. 2010;52(6):447–77.
5 Rash BG, Richards LJ. A role for cingulate pioneering axons in the development of the corpus callosum. J Comp Neurol. 2001;434(2):147–57.
6 Innocenti GM, Clarke S. Multiple sets of visual cortical neurons projecting transitorily through the corpus callosum. Neurosci Lett. 1983;41(1–2):27–32.
7 Rakic P, Yakovlev PI. Development of the corpus callosum and cavum septi in man. J Comp Neurol. 1968;132(1):45–72.
8 Achiron R, Achiron A. Development of the human fetal corpus callosum: a high-resolution, cross-sectional sonographic study. Ultrasound Obstet Gynecol. 2001;18(4):343–7.
9 Cignini P, Padula F, Giorlandino M, Brutti P, Alfò M, Giannarelli D, et al. Reference charts for fetal corpus callosum length: a prospective cross-sectional study of 2950 fetuses. J Ultrasound Med. 2014;33(6):1065–78.
10 Tilea B, Alberti C, Adamsbaum C, Armoogum P, Oury JF, Cabrol D, et al. Cerebral biometry in fetal magnetic resonance imaging: new reference data. Ultrasound Obstet Gynecol. 2009;33(2):173–81.
11 Guidelines ISUOG. Sonographic examination of the fetal central nervous system: guidelines for performing the "basic examination" and the "fetal neurosonogram". Ultrasound Obstet Gynecol. 2007;29:109–16.
12 Rüland AM, Berg C, Gembruch U, Geipel A. Prenatal diagnosis of anomalies of the corpus callosum over a 13-year period. Ultraschall Med. 2016;37(6):598–603.
13 Cagneaux M, Guibaud L. From cavum septi pellucidi to anterior complex: how to improve detection of midline cerebral abnormalities. Ultrasound Obstet Gynecol. 2013;42:484–6.
14 Youssef A, Ghi T, Pilu G. How to image the fetal corpus callosum. Ultrasound Obstet Gynecol. 2013;42(6):718–20.

15 Guibaud L, Lacalm A. Etiological diagnostic tools to elucidate "isolated" ventriculomegaly. Ultrasound Obstet Gynecol. 2015;46(1):1–11.
16 D'Ercole C, Girard N, Cravello L, Boubli L, Potier A, Raybaud C, et al. Prenatal diagnosis of fetal corpus callosum agenesis by ultrasonography and magnetic resonance imaging. Prenat Diagn. 1998;18:247–53.
17 Tepper R, Leibovitz Z, Garel C, Sukenik-Halevy R. A new method for evaluating short fetal corpus callosum. Prenat Diagn. 2019;39(13):1283–90.
18 Garel C, Cont I, Alberti C, Josserand E, Moutard ML, Ducou le Pointe H. Biometry of the corpus callosum in children: MR imaging reference data. AJNR Am J Neuroradiol. 2011;32(8):1436–43.
19 Blondiaux E, Garel C. Fetal cerebral imaging: ultrasound vs. MRI: an update. Acta radiol. 2013;54(9):1046–54.
20 Dhouib A, Blondiaux E, Moutard ML, Billette de Villemeur T, Chalard F, Jouannic JM, et al. Correlation between pre- and postnatal cerebral magnetic resonance imaging. Ultrasound Obstet Gynecol. 2011;38(2):170–8.
21 Manganaro L, Bernardo S, De Vito C, Antonelli A, Marchionni E, Vinci V, et al. Role of fetal MRI in the evaluation of isolated and non-isolated corpus callosum dysgenesis: results of a cross-sectional study. Prenat Diagn. 2017 Mar 1;37(3):244–52.
22 Garel C, Moutard ML. Main congenital cerebral anomalies: how prenatal imaging aids counseling. Fetal Diagn Ther. 2014;35(4):229–39.
23 Guibaud L. Contribution of fetal cerebral MRI for diagnosis of structural anomalies. Prenat Diagn. 2009;29(4):420.
24 Barkovich AJ, Kjos BO. Normal postnatal development of the corpus callosum as demonstrated by MR imaging. AJNR Am J Neuroradiol. 1988;9(3):487–91.
25 Lerman-Sagie T, Ben-Sira L, Achiron R, Schreiber L, Hermann G, Lev D, et al. Thick fetal corpus callosum: an ominous sign? Ultrasound Obstet Gynecol. 2009;34(1):55–61.
26 Guibaud L, Lacalm A. Diagnostic imaging tools to elucidate decreased cephalic biometry and fetal microcephaly: a systematic analysis of the central nervous system. Ultrasound Obstet Gynecol. 2016;48(1):16–25.
27 Innocenti GM, Price DJ. Exuberance in the development of cortical networks. Nat Rev Neurosci. 2005;6(12):955–65.
28 Göçmen R. Oğuz KK. Mega corpus callosum and caudate nuclei with bilateral hippocampal malformation. Diagnostic Interv Radiol. 2008;14:69–71.
29 Nasrallah HA, Andreasen NC, Coffman JA, Olson SC, Dunn VD, Ehrhardt JC, et al. A controlled magnetic resonance imaging study of corpus callosum thickness in schizophrenia. Biol Psychiatry. 1986;21(3):274–82.
30 Fuchs F, Moutard ML, Blin G, Sonigo P, Mandelbrot L. Prenatal and postnatal follow-up of a fetal interhemispheric arachnoid cyst with partial corpus callosum agenesis, asymmetric ventriculomegaly and localized polymicrogyria: case report. Fetal Diagn Ther. 2009;24:385–8.
31 Cagneaux M, Lacalm A, Huissoud C, Allias F, Ville D, Massardier J, et al. Agenesis of the corpus callosum with interhemispheric cyst, associated with aberrant cortical sulci and without underlying cortical dysplasia. Ultrasound Obstet Gynecol. 2013;42(5):603–5.
32 Atallah A, Lacalm A, Massoud M, Massardier J, Gaucherand P, Guibaud L. Prenatal diagnosis of pericallosal curvilinear lipoma: specific imaging pattern and diagnostic pitfalls. Ultrasound Obstet Gynecol. 2018;51(2):269–73.
33 Shinar S, Har-Toov J, Lerman-Sagie T, Malinger G. Thick corpus callosum in the second trimester can be transient and is of uncertain significance. Ultrasound Obstet Gynecol. 2016;48(4):452–7.
34 Ickowitz V, Eurin D, Rypens F, Sonigo P, Simon I, David P, et al. Prenatal diagnosis and postnatal follow-up of pericallosal lipoma: report of seven new cases. AJNR Am J Neuroradiol. 2001;22(4):767–72.
35 Mordefroid M, Grabar S, André Ch, Merzoug V, Moutard M, Adamsbaum C. [Partial corpus callosum agenesis]. J Radiol. 2004;85(11):1915–26.
36 Shen O, Gelot AB, Moutard ML, Jouannic JM, Sela HY, Garel C. Abnormal shape of the cavum septi pellucidi: an indirect sign of partial agenesis of the corpus callosum. Ultrasound Obstet Gynecol. 2015;46(5):595–9.
37 Karl K, Esser T, Heling KS, Chaoui R. Cavum septi pellucidi (CSP) ratio: a marker for partial agenesis of the fetal corpus callosum. Ultrasound Obstet Gynecol. 2017;50:336–41.
38 Vinurel N, Van Nieuwenhuyse A, Cagneaux M, Garel C, Quarello E, Brasseur M, et al. Distortion of the anterior part of the interhemispheric fissure: significance and implications for prenatal diagnosis. Ultrasound Obstet Gynecol. 2014;43(3):346–52.
39 Karl K, Kainer F, Heling KS, Chaoui R. Fetal neurosonography: extended examination of the CNS in the fetus. Ultraschall Med. 2011;32(4):342–61.
40 Paladini D, Pastore G, Cavallaro A, Massaro M, Nappi C. Agenesis of the fetal corpus callosum: sonographic signs change with advancing gestational age. Ultrasound Obstet Gynecol. 2013;42(6):687–90.
41 Roebuck TM, Mattson SN, Riley EP. A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res. 1998;22(2):339–44.
42 Roebuck-Spencer TM, Mattson SN, Marion SD, Brown WS, Riley EP. Bimanual coordination in alcohol-exposed children: role of the corpus callosum. J Int Neuropsychol Soc. 2004;10(4):536–48.
43 Sowell ER, Mattson SN, Thompson PM, Jernigan TL, Riley EP, Toga AW. Mapping callosal morphology and cognitive correlates: effects of heavy prenatal alcohol exposure. Neurology. 2001;57(2):235–44.
44 Alby C, Malan V, Boutaud L, Marangoni MA, Bessières B, Bonniere M, et al. Clinical, genetic and neuropathological findings in a series of 138 fetuses with a corpus callosum malformation. Birth Defects Res Part A Clin Mol Teratol. 2016;106(1):36–46.
45 Alby-Averseng C. Etude clinique et génétique des anomalies du corps calleux chez le foetus. Médecine humaine et pathologie. Paris: Université Sorbonne Paris Cité; 2015.
46 Mignot C, Moutard ML, Rastetter A, Boutaud L, Heide S, Billette T, et al. ARID1B mutations are the major genetic cause of corpus callosum anomalies in patients with intellectual disability. Brain. 2016;139(11):e64.
47 Heide S, Keren B, Billette de Villemeur T, Chantot-Bastaraud S, Depienne C, Nava C, et al. Copy number variations found in patients with a corpus callosum abnormality and intellectual disability. J Pediatr. 2017;185:160–6.e1.
48 Spaggiari E, Baumann C, Alison M, Oury JF, Belarbi N, Dupont C, et al. Mowat-wilson syndrome in a fetus with antenatal diagnosis of short corpus callosum: advocacy for standard autopsy. Eur J Med Genet. 2013;56(6):297–300.
49 Marsh APL, Edwards TJ, Galea C, Cooper HM, Engle EC, Jamuar SS, et al. DCC mutation update: congenital mirror movements, isolated agenesis of the corpus callosum, and developmental split brain syndrome. Hum Mutat. 2018;39(1):23–39.
50 Depienne C, Nava C, Keren B, Heide S, Rastetter A, Passemard S, et al. Genetic and phenotypic dissection of 1q43q44 microdeletion syndrome and neurodevelopmental phenotypes associated with mutations in ZBTB18 and HNRNPU. Hum Genet. 2017;136(4):463–79.
51 Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. Brain. 2014;137(Pt 6):1579–613.
52 Huang J, Wah IY, Pooh RK, Choy KW. Molecular genetics in fetal neurology. Semin Fetal Neonatal Med. 2012;17(6):341–6.
53 Masurel-paulet A, Callier P, Thauvin-robinet C, et al. Multiple cysts of the corpus callosum and psychomotor delay in a patient with a 3.1 Mb by array-CGH. Am J Med Genet A. 2009;149A:1504–10.
54 Jiang Y, Qian YQ, Yang MM, Zhan QT, Chen Y, Xi FF, et al. Whole-exome sequencing revealed mutations of MED12 and EFNB1 in fetal agenesis of the corpus callosum. Front Genet. 2019 Nov 25;10:1201.

55 Marsh AP, Heron D, Edwards TJ, Quartier A, Galea C, Nava C, et al. Mutations in DCC cause isolated agenesis of the corpus callosum with incomplete penetrance. Nat Genet. 2017 Mar 30;49(4):511–4.
56 Moutard ML, Kieffer V, Feingold J, Lewin F, Baron JM, Adamsbaum C, et al. Isolated corpus callosum agenesis: a ten-year follow-up after prenatal diagnosis (How are the children without corpus callosum at 10 years of age?) Prenat Diagn. 2012 Mar;32(3):277–83.
57 Isapof A, Kieffer V, Sacco S, Billette de Villemeur T, Gelot A, Garel C, et al. Impact du dépistage anténatal des agénésies du corps calleux sur le devenir des grossesses. Etude de 155 dossiers de 2000 à 2006. Arch Pediatr. 2010;17:226–32.
58 Heide S, Spentchian M, Valence S, Buratti J, Mach C, Lejeune E, et al. Prenatal exome sequencing in 65 fetuses with abnormality of the corpus callosum: contribution to further diagnostic delineation. Genet Med. 2020 Jun 22; 22:1887–91.
59 Santo S, D'Antonio F, Homfray T, Rich P, Pilu G, Bhide A, et al. Counseling in fetal medicine: agenesis of the corpus callosum. Ultrasound Obstet Gynecol. 2012;40(5):513–21.
60 Moutard ML, Lewin F, Baron JM, Kieffer V, Descamps P. [Prognosis of isolated agenesis of the corpus callosum]. Neurochirurgie. 1998;44(1 Suppl):96–8.
61 Moutard ML, Kieffer V, Feingold J, Kieffer F, Lewin F, Adamsbaum C, et al. Agenesis of corpus callosum: prenatal diagnosis and prognosis. Childs Nerv Syst. 2003;19:471–6.
62 Moutard ML, Kieffer V, Feingold J, Kieffer F, Lewin F, Adamsbaum C, et al. Agenesis of corpus callosum: prenatal diagnosis and prognosis. Childs Nerv Syst. 2003 Aug 1; 19(7–8):471–6.
63 Romaniello R, Marelli S, Giorda R, Bedeschi MF, Bonaglia MC, Arrigoni F, et al. Clinical characterization, genetics, and long-term follow-up of a large cohort of patients with agenesis of the corpus callosum. J Child Neurol. 2017 Jan 1;32(1):60–71.
64 Volpe P, Paladini D, Resta M, Stanziano A, Salvatore M, Quarantelli M, et al. Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus. Ultrasound Obstet Gynecol. 2006;27(5):509–16.
65 Francesco P, Maria-Edgarda B, Giovanni P, Dandolo G, Giulio B. Prenatal diagnosis of agenesis of corpus callosum: what is the neurodevelopmental outcome? Pediatr Int. 2006; 48(3):298–304.
66 Sotiriadis A, Makrydimas G. Neurodevelopment after prenatal diagnosis of isolated agenesis of the corpus callosum: an integrative review. Am J Obstet Gynecol. 2012;206(4):337–5.
67 DAntonio F, Pagani G, Familiari A, Khalil A, Sagies T-L, Malinger G, et al. Outcomes associated with isolated agenesis of the corpus callosum: a meta-analysis. Pediatrics. 2016; 138(3):e20160445.
68 Mangione R, Fries N, Godard P, Capron C, Mirlesse V, Lacombe D, et al. Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum. Ultrasound Obstet Gynecol. 2011;37(3):290–5.
69 Murias K, Moir A, Myers KA, Liu I, Wei XC. Systematic review of MRI findings in children with developmental delay or cognitive impairment. Brain Dev. 2017;39(8):644–55.
70 Des Portes V, Rolland A, Velazquez-Dominguez J, Peyric E, Cordier MP, Gaucherand P, et al. Outcome of isolated agenesis of the corpus callosum: a population-based prospective study. Eur J Paediatr Neurol. 2018 Jan 1;22(1): 82–92.