The "cortical invagination sign": a midtrimester sonographic marker of unilateral cortical focal dysgyria in fetuses with complete agenesis of the corpus callosum

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BACKGROUND: Agenesis of the corpus callosum is associated with several malformations of cortical development. Recently, features of focal cortical dysgyria have been described in fetuses with agenesis of the corpus callosum.

OBJECTIVE: This study aimed to describe the "cortical invagination sign," a specific sonographic feature of focal cortical dysgyria, which is consistently seen at midtrimester axial brain ultrasound in fetuses with complete agenesis of the corpus callosum.

STUDY DESIGN: This was a retrospective analysis of prospectively collected data from 2018 to 2021, including patients referred to 5 fetal medicine centers in the second trimester of pregnancy (19 0/7 to 22 0/7 weeks of gestation) with suspected complete agenesis of the corpus callosum. All cases with the diagnosis of complete agenesis of the corpus callosum were submitted to an axial sonographic assessment of the fetal brain on the transventricular plane. In this scanning section, the mesial profile of both cerebral hemispheres at the level of the frontal-parietal cortex was investigated. In this area, the operator looked for an abnormal invagination of the cortical surface along the widened interhemispheric fissure, which was referred to as the "cortical invagination sign." All fetuses were submitted to dedicated antenatal magnetic resonance imaging to reassess the ultrasound findings. Cases with additional brain anomalies, which did not involve the cortex, were excluded. The final diagnosis was confirmed at postnatal brain magnetic resonance imaging or postmortem examination, for cases undergoing termination of pregnancy. The primary outcome of this study was to evaluate the presence and laterality of the "cortical invagination sign" in fetuses with complete agenesis of the corpus callosum at antenatal ultrasound and magnetic resonance imaging.

RESULTS: During the study period, 64 cases of complete agenesis of the corpus callosum were included; of those cases, 50 (78.1%) resulted in termination of pregnancy, and 14 (21.9%) resulted in a live birth. The "cortical invagination sign" was detected at ultrasound in 13 of 64 cases (20.3%) and at targeted brain magnetic resonance imaging in 2 additional cases (23.4%), all of which were electively terminated. Moreover, the "cortical invagination sign" was found to be exclusively unilateral and on the left cerebral hemisphere in all the cases. There was a predominant number, although nonsignificant, of male fetuses (80.0% of cases; P=.06) in the group of complete agenesis of the corpus callosum with the "cortical invagination sign."

CONCLUSION: The "cortical invagination sign" is a specific marker of focal cortical dysgyria, which seems to characterize at midtrimester of pregnancy in a large group of fetuses with complete agenesis of the corpus callosum. The etiology, pathophysiology, and prognostic significance of this finding remain to be elucidated.

Key words: agenesis of the corpus callosum, cortical dysgyria, malformations of cortical development, midtrimester ultrasound, neurosonography, prenatal diagnosis, nervous system malformation

Introduction

The corpus callosum is the telencephalic commissure with the largest corticocortical bundle of white matter connecting the right and left cerebral hemispheres in humans.[1] Agenesis of the corpus callosum (ACC), complete or partial, is one of the most common congenital malformations of the central nervous system with an approximate prevalence of 1 in 4000 live births.[2,3] Prenatal diagnosis of ACC is feasible and accurate from midtrimester onward using a combination of transabdominal ultrasound and transvaginal ultrasound.[4,5]

Complete ACC is associated with a large range of adverse neurodevelopmental outcomes; however, the main determinant of these outcomes is the presence or absence of additional cerebral or extracerebral malformations or genetic conditions.[6–10] One of the most frequent associated brain abnormalities observed in ACC is malformations of cortical development (MCD).[10–13] Antenatal brain magnetic resonance imaging (MRI) is the gold standard for the diagnosis of MCD, given its higher diagnostic accuracy than prenatal ultrasound.[14,15] Consequently, antenatal brain MRI is routinely performed in fetuses with prenatal diagnosis of ACC to confirm or exclude these malformations.[16,17] Most of the available works of literature have focused on the large spectrum of MCD associated with complete ACC. A recent study using MRI has described clinical phenotypes of

Cite this article as: Ramirez Zegarra R, Casati D, Volpe N, et al. The "cortical invagination sign": a midtrimester sonographic marker of unilateral cortical focal dysgyria in fetuses with complete agenesis of the corpus callosum. Am J Obstet Gynecol MFM 2023;5:101198.

2589-9333/$36.00

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http://dx.doi.org/10.1016/j.ajogmf.2023.101198

AJOG MFM at a Glance

Why was this study conducted?

Agenesis of the corpus callosum (ACC) is associated with features of focal cortical dysgyria and other malformations of cortical development. Sonographic data regarding the diagnosis of focal cortical dysgyria in fetuses with ACC are lacking.

Key findings

Approximately 20% of the fetuses with complete ACC presented a peculiar type of unilateral focal cortical dysgyria, that is, the "cortical invagination sign," which can be easily documented at axial midtrimester brain ultrasound or magnetic resonance imaging.

What does this add to what is known?

The "cortical invagination sign" is a peculiar type of focal cortical dysgyria, which seems to affect mainly the mesial profile of the left frontal-parietal cerebral lobe and has a higher incidence in male fetuses.

unilateral focal cortical abnormalities associated with complete ACC.[18] However, no study has reported such findings using ultrasound.

This study aimed to describe a new midtrimester sonographic sign, the "cortical invagination sign"—a specific sonographic feature of focal abnormal sulcation—which was noted at axial brain ultrasound in a large cohort of fetuses with a complete ACC.

Material and Methods

This was a retrospective analysis of prospective data collected at 5 fetal medicine centers (4 in Italy and 1 in France) from 2018 to 2021, on a cohort of fetuses with sonographically confirmed complete ACC in the second trimester of pregnancy (19 0/7 to 22 0/7 weeks of pregnancy) (Supplementary Table). Of note, some of the cases from the Vittore Buzzi Children's Hospital have been already published.[19] The only a priori exclusion criteria were: evidence of extracranial malformations. The study was approved by the local ethics committee of each participating unit (approval number: 676/2022/OSS/UNIPR).

According to the local protocol of all the collaborating centers, fetuses with suspected malformations were evaluated by fetal medicine experts with more than 10 years of experience in the field. All cases with the diagnosis of complete ACC were submitted to an axial sonographic assessment of the fetal brain on the transventricular plane. In this scanning section, the mesial profile of both cerebral hemispheres at the level of the frontal-parietal cortex was investigated. To have a better view of the proximal hemisphere of the fetuses, we took the following steps:

1. We waited for a short period for the fetus to turn 180° its orientation so that the proximal cerebral hemisphere became the distal one.
2. After the acquisition of the correct standard transventricular plane, the operator angled the transducer caudally up to 45°. This allowed the ultrasound beam to go through the temporal suture and to produce a clearer view proximal fetal brain reducing the near-field shadowing of the bony calvarium.

At the level of the frontal-parietal cortex, the operator looked for an abnormal invagination of its mesial surface along the widened interhemispheric fissure, which was referred to as the "cortical invagination sign" (Figure 1). In addition, multiplanar neurosonography was performed transvaginally in cephalic-presenting fetuses. According to local protocol, all pregnant women underwent genetic counseling and were offered amniocentesis with standard karyotype, chromosomal microarray, and, from 2021, clinical exome sequencing or cortical malformation gene panel. Subsequently, all included fetuses were submitted to a dedicated antenatal brain MRI to confirm the ultrasound findings (Figure 2). Here, the "cortical invagination sign" was assessed only qualitatively, in terms of its presence or absence, but it was not measured neither at ultrasound nor at MRI. Cases of complete ACC, which were found to have additional brain structural anomalies beyond the "cortical invagination sign," including other types of MCD, at expert neurosonogram, brain MRI, or follow-up, were excluded. The final diagnosis of complete ACC and the aspect of the mesial frontal-parietal cortex were verified at postnatal brain MRI or at postmortem examination, for cases undergoing termination of pregnancy (TOP).

For study purposes, the main clinical data were collected from the medical records of each patient. Maternal and fetal data included age, body mass index, gestational age (GA), and fetal sex. Imaging variables included the presence or absence of the "cortical invagination sign" and the laterality of this cortex abnormality. Data were recorded and stored in a Microsoft Excel–secured pseudonymized database (Microsoft, Redmond, WA), which was accessible only to the members of the research team of each participating unit.

The primary outcome of this study was to evaluate the prevalence and laterality of the "cortical invagination sign" in fetuses with complete ACC at antenatal ultrasound and MRI, which was later confirmed after birth.

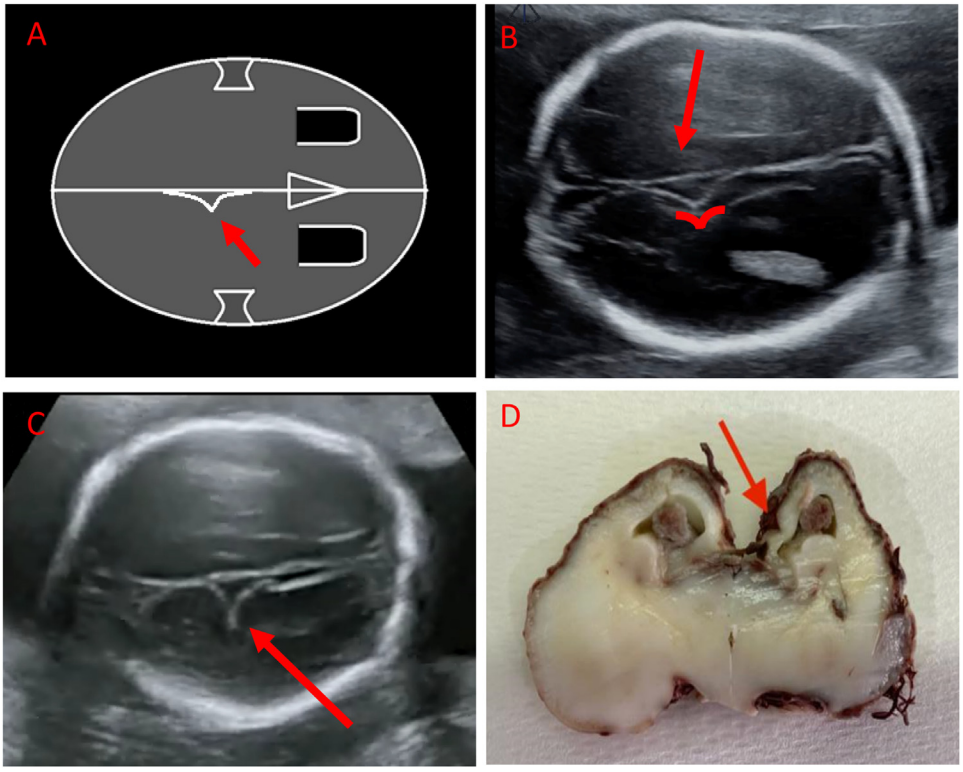
Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (version 22; IBM Inc, Armonk, NY). For univariate comparison between groups, we used the chi-square test for categorical and the Student *t* test for continuous variables, and the results were presented as number (percentage) or mean±standard deviation. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[20]

Results

From 2018 to 2021, 64 cases of fetuses with antenatal diagnosis of complete ACC were selected for the study (Figure 3). The main demographic

FIGURE 1
The "cortical invagination sign", a sign of unilateral focal cortical dysgyria



A, Schematic representation of the transventricular plane of the fetal brain. The *red arrow* points toward an abnormal invagination of the cortical surface along the interhemispheric fissure in the frontal-parietal lobe, which was defined as the "cortical invagination sign." **B and C,** A transventricular axial ultrasound image from 2 exemplificative cases with complete agenesis of corpus callosum and "cortical invagination sign," which is an abnormal invaginating sulcus located in the left frontal-parietal lobe along the interhemispheric fissure. The *arrows* point at the "cortical invagination sign." **D,** Coronal section of the fetal brain. Absence of the cavum septi pellucidi. Note the abnormal invagination of the cortical surface (*red arrow*), the "cortical invagination sign."

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maternal and fetal features of the study population are shown in the Table. Our maternal population had a mean age of 33.3±5.6 years and a mean body mass index at booking of 22.5±4.3 kg/m^2. The mean GA at the time of the ultrasound scan was 21 1/7±1 0/7 weeks of gestation. Moreover, 38 fetuses (59.4%) were male, and 26 fetuses (40.6%) were female. Of note, 50 pregnancies (78.1%) were terminated, and 14 pregnancies (21.9%) resulted in a live birth. Karyotype was performed in 51 of 64 patients (79.7%), chromosome microarray was performed in 50 of 64 cases (78.2%), and clinical exome sequencing was performed in 3 of 64 cases (4.7%). No case of genetic or chromosomal anomaly was documented in our population.

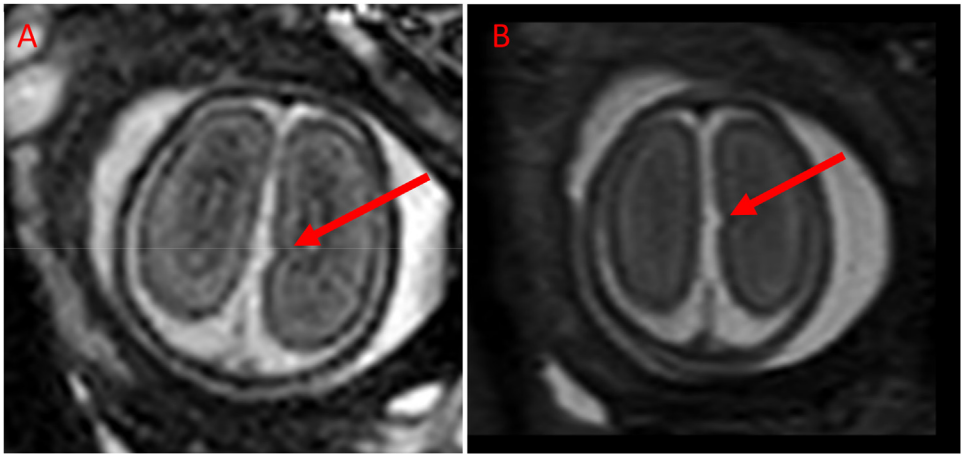
The "cortical invagination sign" was found in 13 of 64 cases (20.3%) at midtrimester ultrasound scan and in 2 additional cases (23.4%) at subsequent targeted MRI performed before 23 weeks of gestation. Moreover, the "cortical invagination sign" was confined to the left hemisphere in all cases (13/13 fetuses at ultrasound and 15/15 fetuses at antenatal MRI). All our cases affected with the "cortical invagination sign" resulted in TOP. No maternal or pregnancy factor seemed significantly associated with the presence of the "cortical invagination sign." There was a predominant number of male fetuses (12/15 male fetuses [80.0%] vs 3/15 female fetuses[20.0%]) in the group of complete ACC with the "cortical invagination sign"; however, this difference did not reach statistical significance (P=.06) (Table). In all cases than resulted in TOP, complete ACC was confirmed at postmortem. Moreover, in those cases with the "cortical invagination sign" at antenatal imaging, a unilateral indentation of the mesial cortex surface was confirmed at macroscopic examination (Figure 1, D), although histology documented an irregular piling of the cortical neurons (Figure 4).

Comment

Principal findings

Here, we demonstrated that approximately 20% of fetuses with complete ACC present a peculiar type of unilateral focal cortical dysgyria—that is, the

FIGURE 2
Magnetic resonance imaging of the "cortical invagination sign"



A. Exemplificative axial T2-weigthed section of a male fetuses with complete agenesis of the corpus callosum and the "cortical invagination sign" at 21 weeks of gestation. **B.** Exemplificative axial T2-weigthed section of another male fetuses with complete agenesis of the corpus callosum and the "cortical invagination sign" at 20 weeks of gestation.

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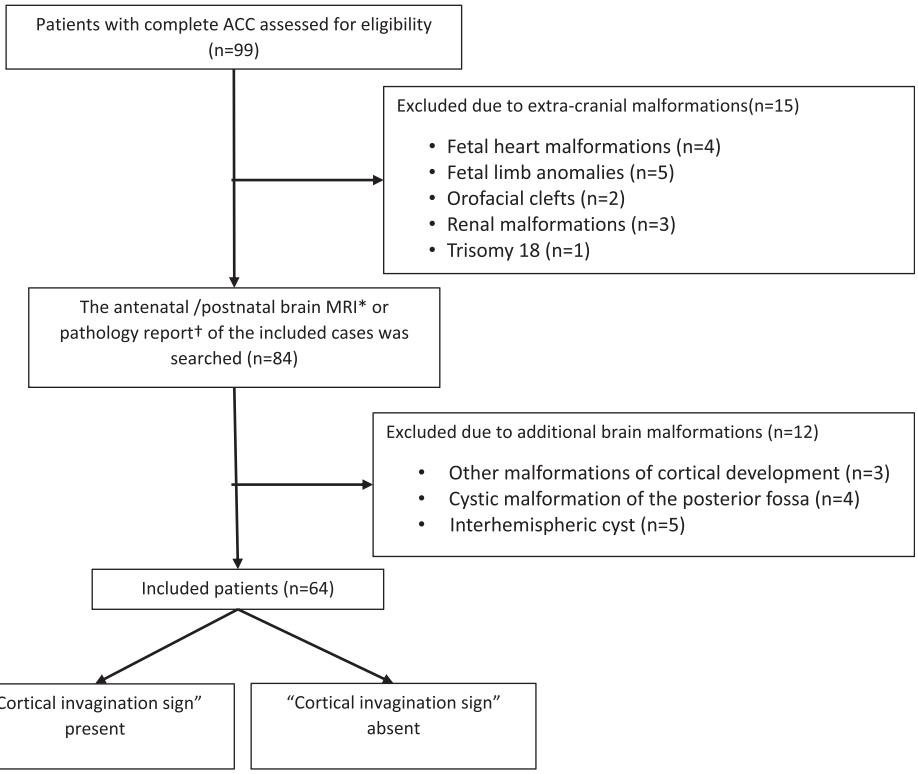
FIGURE 3
Flowchart (according to the STROBE guideline) of patient enrollment in the study



ACC, agenesis of the corpus callosum; *MRI*, magnetic resonance imaging; *STROBE*, Strengthening the Reporting of Observational Studies in Epidemiology.

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TABLE

Baseline maternal and fetal characteristics of the overall population and according to the presence or absence of the "cortical invagination sign" at magnetic resonance imaging.

Characteristic	Overall	ACC without the "cortical invagination sign"	ACC with the "cortical invagination sign"	*P* value
	N=64	n=49 (76.6%)	n=15 (23.4%)	
Maternal age (y)	33.3±5.6	33.4±5.9	32.7±4.2	.65
BMI at booking (kg/m^2)	22.5±4.3	22.3±4.3	23.2±4.7	.49
GA at inclusion (wk)	21 1/7±1 0/7	21 2/7±0 6/7	21 0/7±1 3/7	.41
Fetal gender				.06
Male	38 (59.4%)	26 (53.1%)	12 (80.0%)	
Female	26 (40.6%)	23 (46.9%)	3 (20.0%)	
Pregnancy outcome				.02
TOP	50 (78.1%)	35 (71.4%)	15 (100.0%)	
Delivery	14 (21.9%)	14 (28.6%)	0 (0.0%)	

Data are presented as mean±standard deviation or number (percentage), unless otherwise indicated.

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"cortical invagination sign"—and this finding can be easily documented at axial midtrimester brain ultrasound or MRI.

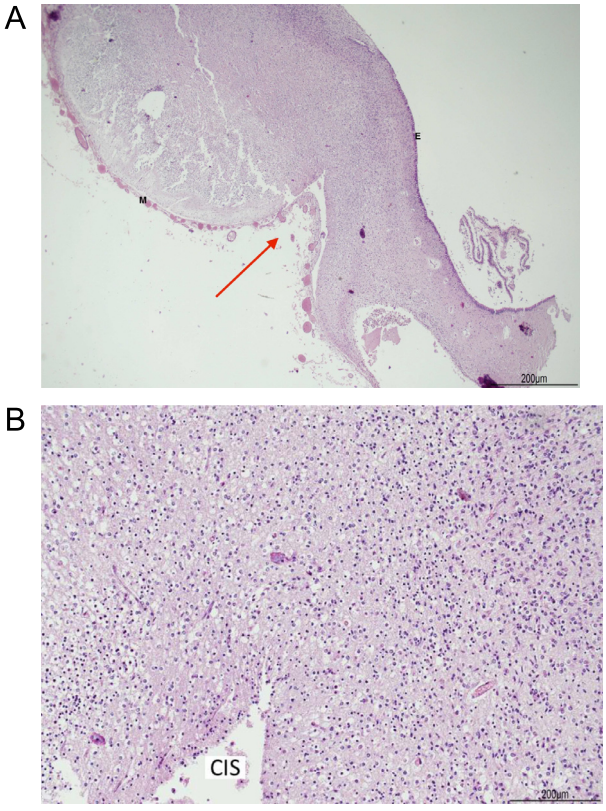
Results in the context of what is known

ACC is a midline malformation of the brain, and it is commonly associated with other brain malformations, such as MCD.[10–13] The "cortical invagination sign" can be defined as an abnormal invagination of the mesial cortical surface in the frontal-parietal lobe, which we have found to occur along the widened interhemispheric fissure unilaterally and exclusively on the left cerebral hemisphere. We propose that this "cortical invagination sign" belongs to the group of focal cortical dysgyria; however, the cellular mechanism underlying such macroscopic features cannot be elucidated at present. It is pivotal to underline how the concept of "dysgyria" has to be taken into account to indicate a wide, still not sharply defined, pool of MCD or "nonorthodox" brain sulcation at imaging, whose morphologic variability is very prominent (ie, encompassing different forms of too deep sulci isolated or in a cluster, hippocampus or parahippocampal sulci malrotation-orientation, coarse sulcation, and sulci in unexpected location) according to the current neurodevelopmental medicine.[21] In our cases, the "cortical invagination sign" was histologically described as an irregular cortical neuronal accumulation—a putative sign of local cell migration or organization impairment.

The "cortical invagination sign" has not been reported previously at antenatal ultrasound among fetuses with ACC. Recently, a study using brain MRI described an association between a similar type of unilateral focal cortical malformation and complete ACC.[18] In this retrospective work conducted on a cohort of 45 fetuses with complete ACC, most focal cortical malformations were located in the frontal-parietal region. In line with these findings, we reported a similar pattern of unilateral focal anomaly cortical surface profile mainly seen at the mesial aspect of the left frontal-parietal lobe in fetuses affected by complete ACC.

Because of the spatial contiguity between the area that is normally occupied by the corpus callosum and the mesial surface of the frontal-parietal cortex, this cortical surface aberrant invagination seems to have a deterministic relationship with the callosal anomaly; however, this is difficult to explain. Callosal defects are considered to be a manifestation of disruption of the normal axonal guidance in the early stages of development of the corpus callosum. In some cases, this disruption might be due to mechanical weakness, such as focal cortical dysgyria, which might explain this association.[18,22] Furthermore, we cannot provide with our data a clear explanation for the unilaterality of our findings exclusively affecting the left cerebral hemisphere. However, it has to be mentioned that some asymmetry between cerebral hemispheres in the timing of gyrification trajectory is well known to occur not only in normal cortical development but also in ACC.[13] Therefore, we cannot exclude that some asymmetry may arise in the tissular framework (within subplate, intermediate zone) underneath the cortical plate in ACC, and this can play a role in the unilateral mesial focal cortical plate invagination. Of note, most of our cases were imaged at a relatively early gestation of 20 to 22 weeks, so the morphologic evolution of such anomaly at imaging is not known, and the possibility of its development at the contralateral side later in gestation cannot be excluded as well (our cases resulted in TOP soon after diagnosis).

FIGURE 4
Histological picture of the "cortical invagination sign"



A, Histological picture of the "cortical invagination sign" (*red arrow*) in hematoxylin and eosin, 2 high-power field. **B,** Histological picture of the "cortical invagination sign" in hematoxylin and eosin, 10 high-power field. Note the irregular accumulation of the neurons in the cortex, with no clear distinction of cortical layers. CIS, "cortical invagination sign".

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Clinical and research implications

The neurodevelopmental outcome of fetuses affected by ACC is mainly determined by the presence of additional central nervous system anomalies.[6–10] Complete ACC associated with MCD has been found to have worse adverse neurodevelopmental outcomes than isolated ACC.[9,10] However, we cannot say whether the cortical invagination sign carries a worse prognosis for fetuses with complete ACC as commonly acknowledged for cases with MCD or if the outcome of such cases might overlap with those with isolated complete ACC. Furthermore, we cannot exclude that this abnormal invagination may represent a "paraphysiological" epiphenomenon of sulcation progression in fetuses with a typical complete ACC. Further large prospective studies are needed to evaluate the neurodevelopmental outcomes of fetuses affected by ACC and the "cortical invagination sign."

Here, we failed to demonstrate a common genetic background for cases with complete ACC and the "cortical invagination sign." We found a predominance of male fetuses (4:1) affected with ACC and "cortical invagination sign," although this difference did not reach statistical significance (P=.06). This association has been previously reported in the literature[18] and might suggest that some X-linked genetic disorder might be associated with the presence of such a finding.[18,22,23] Unfortunately, we could not confirm this hypothesis as none of the fetuses affected by the "cortical invagination sign" underwent exome sequencing. Future studies might be able to test this hypothesis.

Strengths and limitations

The main strength of our study lies in its originality. Moreover, we employed strict inclusion criteria, specifically selecting cases exclusively affected by complete ACC without additional brain malformations except for the "cortical invagination sign." Our rationale for this decision was a recent meta-analysis that showed a great heterogenicity in the definition of corpus callosum anomalies other than complete ACC.[24] This approach allowed us to avoid the inclusion of cases with ambiguously defined corpus callosum dysplasia or hypoplasia. In addition, the "cortical invagination sign" was observed on the transventricular axial plane, which is the plane used for routine screening of fetal anomalies and does not require a high level of expertise to be acquired on prenatal ultrasound.

The main limitation of our study is its retrospective design. However, data used in this study had been prospectively collected for other research purposes. The few cases that underwent clinical exome sequencing might be seen as a limitation. However, this test was just offered routinely to women with a fetus affected by ACC from 2021 onward, when this option became available in the participating centers. Future studies should evaluate whether the "cortical invagination sign" is associated with any genetic disorder. Finally, we lacked follow-up data regarding postnatal neurodevelopmental outcomes for cases affected by complete ACC and "cortical invagination sign" because all our cases resulted in TOP. Thus, our study does not provide insights into specific prognosis factors of the "cortical invagination sign."

Conclusion

Our study describes a marker of focal cortical dysgyria (deviation from expected normal sulcation trajectory), which seems to characterize a large group of fetuses (especially males) with complete ACC. Further studies are

needed to assess the etiology, pathophysiology, and prognostic significance of the "cortical invagination sign." ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.101198.

References

1. Raybaud C, Girard N. Malformations of the telencephalic commissures. Pediatric neuroradiology: brain. Berlin Heidelberg. Germany: Springer; 2005. p. 41–69.

2. Glass HC, Shaw GM, Ma C, Sherr EH. Agenesis of the corpus callosum in California 1983–2003: a population-based study. Am J Med Genet A 2008;146A:2495–500.

3. Morris JK, Wellesley DG, Barisic I, et al. Epidemiology of congenital cerebral anomalies in Europe: a multicentre, population-based EUROCAT study. Arch Dis Child 2019;104:1181–7.

4. Rydberg C, Tunón K. Detection of fetal abnormalities by second-trimester ultrasound screening in a non-selected population. Acta Obstet Gynecol Scand 2017;96:176–82.

5. Fadda GM, Capobianco G, Balata A, et al. Routine second trimester ultrasound screening for prenatal detection of fetal malformations in Sassari University Hospital, Italy: 23 years of experience in 42,256 pregnancies. Eur J Obstet Gynecol Reprod Biol 2009;144:110–4.

6. Romaniello R, Arrigoni F, De Salvo P, et al. Long-term follow-up in a cohort of children with isolated corpus callosum agenesis at fetal MRI. Ann Clin Transl Neurol 2021;8:2280–8.

7. Folliot-Le Doussal L, Chadie A, Brasseur-Daudruy M, et al. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. Early Hum Dev 2018;116:9–16.

8. Yeh HR, Park HK, Kim HJ, et al. Neurodevelopmental outcomes in children with prenatally diagnosed corpus callosal abnormalities. Brain Dev 2018;40:634–41.

9. Romaniello R, Marelli S, Giorda R, 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;32:60–71.

10. Tang PH, Bartha AI, Norton ME, Barkovich AJ, Sherr EH, Glenn OA. Agenesis of the corpus callosum: an MR imaging analysis of associated abnormalities in the fetus. AJNR Am J Neuroradiol 2009;30:257–63.

11. Hetts SW, Sherr EH, Chao S, Gobuty S, Barkovich AJ. Anomalies of the corpus callosum: an MR analysis of the phenotypic spectrum of associated malformations. AJR Am J Roentgenol 2006;187:1343–8.

12. Alby C, Malan V, Boutaud L, et al. Clinical, genetic and neuropathological findings in a series of 138 fetuses with a corpus callosum malformation. Birth Defects Res A Clin Mol Teratol 2016;106:36–46.

13. Tarui T, Madan N, Farhat N, et al. Disorganized patterns of sulcal position in fetal brains with agenesis of corpus callosum. Cereb Cortex 2018;28:3192–203.

14. Santo S, D'Antonio F, Homfray T, et al. Counseling in fetal medicine: agenesis of the corpus callosum. Ultrasound Obstet Gynecol 2012;40:513–21.

15. ENSO Working Group. Role of prenatal magnetic resonance imaging in fetuses with isolated anomalies of corpus callosum: multinational study. Ultrasound Obstet Gynecol 2021;58:26–33.

16. Griffiths PD, Bradburn M, Campbell MJ, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Lancet 2017;389:538–46.

17. Prayer D, Malinger G, De Catte L, et al. ISUOG Practice Guidelines (updated): performance of fetal magnetic resonance imaging. Ultrasound Obstet Gynecol 2023;61:278–87.

18. Vola EA, Griffiths PD, Parazzini C, et al. Complete agenesis of corpus callosum and unilateral cortical formation anomalies detected on fetal MR imaging: a phenotype strongly associated with the male fetuses. Eur Radiol 2023;33:2258–65.

19. Lanna M, Scelsa B, Cutillo G, et al. Long-term outcome of consecutive case series of congenital isolated agenesis of corpus callosum. Ultrasound Obstet Gynecol 2022;60:494–8.

20. Elm E von, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8.

21. Severino M, Geraldo AF, Utz N, et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain 2020;143:2874–94.

22. Kidron D, Shapira D, Ben Sira L, et al. Agenesis of the corpus callosum. An autopsy study in fetuses. Virchows Arch 2016;468:219–30.

23. Menkes JH, Philippart M, Clark DB. Hereditary partial agenesis of corpus callosum; biochemical and pathological studies. Arch Neurol 1964;11:198–208.

24. Mahallati H, Sotiriadis A, Celestin C, et al. Heterogeneity in defining fetal corpus callosal pathology: systematic review. Ultrasound Obstet Gynecol 2021;58:11–8.

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Received Aug. 18, 2023; revised Sept. 12, 2023; accepted Oct. 9, 2023.

The authors report no conflict of interes.t

This study received no funding.

The results of this study were presented as oral communication at the World Congress of Perinatal Medicine, Milan, Italy, May 7–10, 2023, and at the Fetal Medicine Foundation World Congress, Valencia, Spain, June 25–29, 2023.

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