

Acceptance date: 18/02/2025

CORPUS CALLOSUM AGENESIS: A REVIEW

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Abstract: The corpus callosum (CC) connects the two brain hemispheres through axonal fiber tissues, being important for the functional integration of sensory, motor, visuomotor and cognitive processes, in addition to processing and management of social and emotional stimuli. Agenesis of the corpus callosum (ACC) is a congenital brain malformation defined by anatomy (complete or partial absence of the corpus callosum), rarely occurring in isolation and is a specific and relatively easy to detect phenotypic marker for developmental disorders. The prevalence of ACC in the general population is extremely variable and probably underestimated due to the asymptomatic course, the usual range is 0.020–0.025%, in individuals with neurodevelopmental impairment this defect has a prevalence of 1 to 3%. Etiology that varies, from maternal alcohol consumption, to prenatal infections, chromosomal errors or genetic mutations. Fetal alcohol syndrome (FAS) is the most important non-genetic congenital cause of ACC, with an incidence of approximately 7% in FAS cases, but the most frequent cause of ACC are genetic mutations related to axonal guidance pathways, ciliary development, cell adhesion, proliferation, differentiation and migration. Patients with ACC can be divided into three groups: the first including individuals with “syndromic” ACC who commonly present severe neurocognitive deficiency that obscures the deficiencies directly caused by the absence of CC generally associating cerebral malformations, non-cerebral structural defects, altered patterns of growth and development, in addition to progressive neurological symptoms and sensory impairment; the second presents with neurodevelopmental diseases in which ACC has been suggested to play a role; and the final includes patients with isolated complete or partial ACC who remain neurologically asymptomatic and have normal intelligence, however, in-depth neuropsychological screening can often reveal mild beha-

vioral and cognitive deficits. In recent decades, magnetic resonance imaging (MRI) has been implemented, a tool that has increased the recognition of fetal diagnosis, which is performed in three planes and is useful in identifying associated anomalies. The use of MRI is essential and must be done together with a complementary fetal ultrasound exam, with the midsagittal plane parallel to the CC being ideal for evaluation. Multiplanar fetal neurosonography is the best imaging test to evaluate the fetus from the 20th week of gestation onwards. Most brain abnormalities remain undiagnosed until midway through the first trimester, and may go undetected due to small fetal brain structures. Between the 11th and 13th weeks, ultrasound can highlight changes that are incompatible with life. Multiplanar neurosonography is indicated in the middle of the first trimester of pregnancy, including non-axial plane scanning. The sonographer’s knowledge of fetal anatomy and sonoembryology results in early diagnosis.

INTRODUCTION

The corpus callosum is the largest of the interhemispheric white matter tracts that connect the cerebral hemispheres. It can be divided into four main parts: rostrum, genu, body and splenium (Ferreira et al., 2022). “Complete agenesis of the corpus callosum” is the terminology used to describe its complete absence, while “partial agenesis of the corpus callosum” refers to a reduction in its anteroposterior length as a result of the absence of one or multiple segments, such as the splenium and the rostrum, there are also other abnormalities which include dysgenesis (abnormal shape) and hyper/hypoplasias (Hofman et al., 2020). The prevalence of agenesis of the corpus callosum in the general population ranges from 1:4,000 to 1:5,000, which may be underestimated due to the generally asymptomatic course (Hofman et al., 2020). Genetic factors have been described as the most com-

mon etiology, with agenesis being associated with more than 200 genetic syndromes and chromosomal abnormalities (Pânzaru et al., 2022). It can occur in an isolated presentation or as a component of different syndromes that course with neuroanatomical malformations (Hofman et al., 2020). There is suspicion or the diagnosis is confirmed, in the prenatal period during routine ultrasound screening between 20 and 22 weeks of gestation, magnetic resonance imaging is useful after the 20th week of gestation to demonstrate associated brain anomalies that may go unnoticed (Sileo et al., 2021). Approximately one-third of patients with isolated agenesis of the corpus callosum, whether complete or partial, have normal neurodevelopment, while the remainder have motor and cognitive deficits ranging from moderate to severe. (Mancuso et al., 2019).

OBJECTIVES

This article aims to review the scientific literature in order to highlight the agenesis of the corpus callosum in its etiology, epidemiology, symptoms, pathophysiology and its intrauterine diagnosis. Furthermore, this study aims to encourage the development of new research on the topic, due to the scarce number of research papers surrounding the disease.

METHODS

This narrative literature review adheres to the methodological guidelines stipulated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The investigation draws upon the following databases: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature (Lilacs), and PubMed. The search strategy employed encompassed the utilization of the search descriptors “agenesis of the corpus callosum” and “corpus callosum agenesis, across all aforementioned databases.

The inclusion criteria encompassed original articles, clinical trials or series, systematic and literature reviews, meta-analyses, and randomized controlled trials, published between the years 2012 to 2022 in either English or Portuguese, with free full text. These selected studies were constrained to the pediatric population and aligned with the research’s defined objectives. Conversely, the exclusion criteria encompassed book chapters, duplicated abstracts, as well as studies focused on adult populations.

RESULTS

Following the implementation of the PRISMA framework, the outcomes revealed the following distribution across databases: PubMed produced 97 articles, SciELO 5 articles meeting the criteria, and Lilacs generated 8 articles. Subsequent scrutiny of the retrieved articles against the stipulated inclusion and exclusion criteria specified in the methodology resulted in: 14 from PubMed, 1 article from SciELO and only 1 article fulfilled the criteria from Lilacs, that pertinently discussed the isolated agenesis of the corpus callosum.

DISCUSSION

The corpus callosum (CC) connects the two brain hemispheres through axonal fiber tissues, being important for the functional integration of sensory, motor, visuomotor and cognitive processes (language, abstract reasoning and integration of complex sensory information), in addition to processing and management of social and emotional stimuli (Restrepo et al. 2019). The CC can be anatomically divided into 4 regions: rostrum, genu, body and splenium. The rostrum and genu connect the frontal and premotor regions of the cerebral cortex, the body connects the motor, somatosensory, and parietal regions, while the splenium links the temporal and occipital cortices on both sides (Pânzaru et al.,

2020). At birth, the CC already has its characteristic shape, its thickness generally increases throughout childhood and adolescence, with growth in the anterior sections being more pronounced in the first 10 years of life, and posterior growth predominating during adolescence (Edwards et al., 2014).

Agenesis of the corpus callosum (ACC) is a congenital brain malformation defined by anatomy (complete or partial absence of the corpus callosum) and not by behavioral abnormalities. It rarely occurs in isolation and is a specific and relatively easy to detect phenotypic marker for developmental disorders (Brown et al. 2019). The prevalence of ACC in the general population is extremely variable and probably underestimated due to the asymptomatic course, the usual range is 1:4,000 to 1:5,000 live births (0.020–0.025%), whereas in individuals with neurodevelopmental impairment this defect has a prevalence of 1 to 3% (Hofman et al. 2020).

CC development begins around the 12th week of gestation and follows well-orchestrated events: neuronal and glial planning, neuronal migration and planning, midline patterning, axonal growth and orientation, and post-orientation refinement, becoming recognizable around the 14 to 15th week of gestation, while the splenium becomes predominant around the 18th to 19th week of gestation. This process is complex and involves several pathways, such as Semaphorin/Plexin/Neuropilin, Slit/Robo, Eph/Ephrin, Netrin/DCC/Unc5, Wnt/Ryk and FGF8/MAPK (Pânzaru et al., 2020).

ACC has an etiology that varies, from maternal alcohol consumption, to prenatal infections, chromosomal errors or genetic mutations. Fetal alcohol syndrome (FAS) is the most important non-genetic congenital cause of ACC, with an incidence of approximately 7% in FAS cases (Guadarrama-Ortiz et al., 2020). The most frequent cause of ACC are genetic mutations related to axonal guidance

pathways, ciliary development, cell adhesion, proliferation, differentiation and migration, which can present as an isolated anomaly or as a component of a complex disorder (Hofman et al., 2020).

Pânzaru et al. (2020) describes the existence of several genes associated with CC development events, which may contribute to a possible change in structure, density or quantity of CC commissure fibers. The described genetic alterations are grouped into chromosomal anomalies, monogenic alterations and those related to the isolated form of ACC. Among the chromosomal anomalies are trisomies 18, 13 and 21, mosaic 8, monosomy X, 8p inverted duplication/deletion syndrome, 1q43q44, 6q27 and 17q21.31 microdeletions, in addition to several other variations in the number of chromosomes which were reported in ACC cases. Among the monogenic alterations, which are found in 8 to 35% of the cases of ACC, are the acrocallosal syndrome (ACS), the tubulinopathies, the FOXP1 syndrome, the Andermann syndrome (ACC–neuropathy), the Aicardi syndrome, Proud syndrome (ACC-abnormal genitalia), pyruvate dehydrogenase complex (PDC) deficiency, pyridoxine-dependent epilepsy (PDE), congenital mirror movements (CMM), split-brain syndrome (horizontal gaze palsy with progressive scoliosis) and septo-optic dysplasia (SOD). Regarding the isolated presentation of ACC, heterozygous missense of the CDK5RAP2 gene and missense mutations of the DCC (deleted in colorectal cancer) gene are described, the latter with some emphasis (Marsh et al. 2018).

The DCC gene encodes the DCC receptor netrin-1 (NTN1), a transmembrane protein necessary for the orientation of commissural axons. Germinal mutations in this gene interrupt the development of the greater commissures causing loss of their physiological function leading to congenital mirror movements, isolated ACC or both. A significant, level-dependent increase in DCC gene expression is observed in

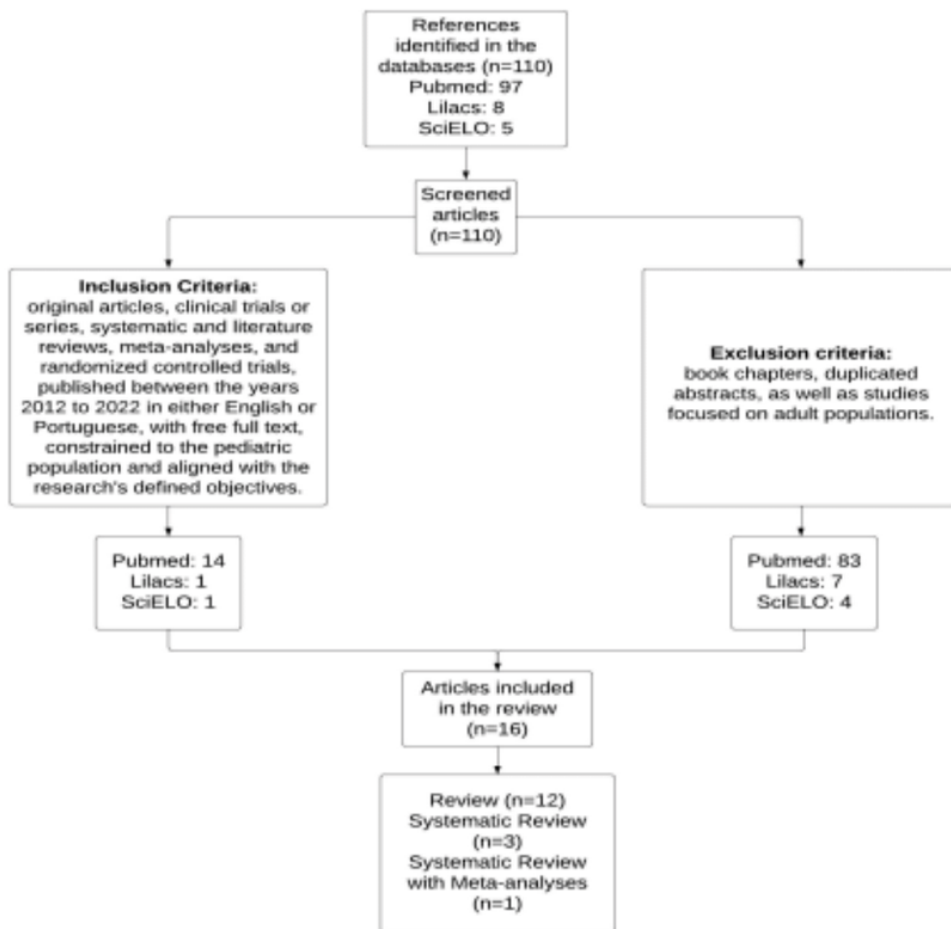


Figure 1. Flowchart of search mechanism based on the PRISMA-P 2015.

Reference (Author / Year)	Study	Results
BROWN; PAUL, 2019	The neuropsychological syndrome of agenesis of the corpus callosum	The cores syndrome includes: (1) reduced interhemispheric transfer of sensory-motor information; (2) reduced cognitive processing speed; and (3) deficits in complex reasoning and novel problem-solving. These domains do not appear to reflect different neuroanatomical abnormalities, but rather different domains of expression of reduced interhemispheric communication from callosal absence.
EDWARDS et al., 2014	Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes	Callosal agenesis rarely occurs in isolation, and is a specific and relatively easy-to-detect phenotypic marker for developmental disorders. Mouse models have vastly improved our understanding of the mechanisms of normal corpus callosum formation, and have paved the way for a developmental classification system based on the clinical and genetic features of human ACC syndromes.
FERREIRA FURTADO et al., 2022	The role of neuroplasticity in improving the decision-making quality of individuals with agenesis of the corpus callosum: A systematic review	Patients with ACC present considerable decision-making difficulties mainly due to the functional connectivity impairment in the frontal lobes. Neuroplasticity was characterized by increased anterior commissure width as compared with controls. No studies were conducted on cognitive therapists managing this type of disease. Although the reorganization of inter-hemispheric bundles on anterior commissure has demonstrated the main natural neuroanatomic strategy in ACC, further evidence will be needed to clarify whether cognitive stimulus could improve the decision-making quality.

GUADARRAMA-ORTIZ; CHOREÑO-PARRA; DE LA ROSA-ARREDONDO, 2020	Isolated agenesis of the corpus callosum and normal general intelligence development during postnatal life: a case report and review of the literature	AgCC is not an innocuous brain malformation even if it occurs isolated, and patients with this defect require a strict neurocognitive follow-up despite normal cognitive function during childhood.
HOFMAN et al., 2020	Corpus callosum agenesis: An insight into the etiology and spectrum of symptoms	ACC is a malformation with varied clinical presentation, depending on multiple factors. Its prenatal detection using imaging techniques and genetic analysis enables future planning of adequate care, which is particularly crucial in cases of metabolic diseases.
LÁBADI; BEKE, 2016	A corpus callosum agenesis vizsgálódás és kognitív profilja - összefoglaló	The results indicate that individuals with agenesis of corpus callosum have deficiency in social-cognitive domain (recognition of emotions, weakness in paralinguistic aspects of language and mentalizing abilities). The impaired social cognition can be manifested in behavioral problems like autism and attention deficit hyperactivity disorder.
LIPA; POOH; WIELGOŚ, 2017	Three-dimensional neurosonography — a novel field in fetal medicine	Detailed neurosonograms provide valuable data about the morphology of the fetal brain. Systematic, high-resolution transvaginal approach for the evaluation of fetal CNS with the use of multidimensional imaging techniques may significantly increase the overall detection rate of CNS.
MAHALLATI et al., 2021	Heterogeneity in defining fetal corpus callosal pathology: systematic review	In comparison to the postnatal literature, in the prenatal literature there is much greater heterogeneity in the nomenclature and definition of CC anomalies other than complete agenesis. This heterogeneity and lack of standard definitions in the prenatal literature make it difficult to develop large multicenter pooled cohorts of patients who can be followed in order to develop a better understanding of the genetic associations and neurodevelopmental and psychological outcomes of patients with CC anomalies.
MANCUSO et al., 2019	Brain functional connectivity in individuals with callosotomy and agenesis of the corpus callosum: A systematic review	The reduction of interhemispheric functional connectivity (ihFC) observed after callosotomy implies that the CC is the main structure dedicated to supporting interhemispheric connectivity. The preservation of ihFC between areas virtually disconnected in cases of partial callosotomy highlights the importance of heterotopic connectivity of the CC, as well as of ipsilateral associative pathways that could help distribute information within each hemisphere.
MARSH et al., 2018	DCC mutation update: Congenital mirror movements, isolated agenesis of the corpus callosum, and developmental split brain syndrome	Mutations in DCC disrupt the development of predominantly commissural tracts in the CNS and cause a spectrum of neurological disorders ranging from MMs and iACC with a normal or favorable developmental outcome, to DSBS with a poor developmental outcome. Utilization of advanced neuroimaging modalities, such as diffusion MRI-based tractography and functional MRI, will also aid our understanding of how the brains of these affected individuals is wired in the context of DCC dysfunction or LoF during development.
NISHIKIMI; OISHI; NAKAJIMA, 2013	Axon guidance mechanisms for establishment of callosal connections	Development of interhemispheric connections such as the CC is guided by molecules in the axonal environment, under the regulation of a number of different control mechanisms. Midline glial and neuronal populations express and secrete guidance molecules, and “pioneer” axons help in the axon pathfinding of the callosal neurons. Disruption of these navigational mechanisms may cause dysgenesis of the corpus callosum.
PÂNZARU et al., 2022	Genetic heterogeneity in corpus callosum agenesis	There are still conditions of unclear etiology in ACC-associated syndromes. Incomplete penetrance and variable expressivity, unexplained by the type of mutation, suggest the existence of genetic modifiers. Detection of associated anomalies and genetic causes is essential in prenatal detected cases, given the variable outcome, oscillating between the normal cognitive level and severe psychomotor delay.

RANGASAMI et al., 2020	Magnetic resonance imaging findings in fetal corpus callosal developmental abnormalities: A pictorial essay	The definitive diagnosis of CCA can be made by ultrasound, if a midsagittal plane parallel to the CC could be obtained. But due to fetal position, it is rarely obtained and hence three-dimensional ultrasound comes handy to provide the plane that is needed once a volume of fetal head is obtained. MRI is a complementary modality to sonography in the assessment of fetal CC due to its multiplanar capability and contrast resolution.
RODRÍGUEZ RESTREPO et al., 2019	Abordaje diagnóstico de las alteraciones del cuerpo calloso: estado del arte / Diagnostic Approach to the Alterations of the Corpus Callosum: State of the Art	There are several indirect signs that allow a diagnosis of these alterations in prenatal ultrasound. However, when this diagnosis is made difficult by certain limitations, it is necessary to perform a prenatal MRI. MRI made a diagnosis of the complete absence of the corpus callosum and, in addition, found additional neurological abnormalities, such as heterotopia, anomalies of the circumvolutions and asymmetry of the cerebral hemispheres.
SILEO et al., 2021	Role of prenatal magnetic resonance imaging in fetuses with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic review and meta-analysis	The rate of associated anomalies detected exclusively at fetal MRI in isolated ACC undergoing neurosonography is lower than previously reported. Cortical and posterior fossa anomalies are among the most common anomalies detected exclusively at MRI, thus confirming the crucial role of fetal MRI in determining the prognosis of these fetuses.
VOLPE et al., 2021	First-trimester fetal neurosonography: technique and diagnostic potential	In the first trimester it is therefore not possible to suspect callosal agenesis based on the lack of its direct visualization on grayscale ultrasound imaging. However, some authors have proposed seeking indirect signs of callosal absence at 11–13 weeks. In 80% of fetuses that had agenesis of the corpus callosum diagnosed later in gestation, there is an increased ratio between the diencephalon diameter (from midbrain to falx, including third ventricle and thalami) and the falx diameter. This sonographic marker seems to reflect early in gestation the upward displacement and dilatation of the third ventricle, which is commonly noted in the midtrimester in fetuses with absent corpus callosum.

Table 1. Description of the studies and research outcomes in AgCC, according to database research authors described above. *Source: Table prepared by the authors.*

testosterone-treated neural stem cells derived from human embryonic stem cells, suggesting that isolated ACC may occur when DCC gene expression is below a critical level during CC development (Marsh et al, 2018).

In general, patients with ACC can be divided into three groups according to their clinical and neurocognitive characteristics. The first group includes individuals with “syndromic” ACC who commonly present severe neurocognitive deficiency that obscures the deficiencies directly caused by the absence of CC. These patients generally associate cerebral malformations, non-cerebral structural defects, altered patterns of growth and development, in addition to progressive neurological symptoms and sensory impairment. A second group of patients presents with neurodevel-

opmental diseases in which ACC has been suggested to play a role. The final group includes patients with isolated complete or partial ACC who remain neurologically asymptomatic and have normal intelligence, however, in-depth neuropsychological screening can often reveal mild behavioral and cognitive deficits (Guarrama-Ortiz et al., 2020).

The syndromic presentation results from a reduction in the interhemispheric transfer of sensorimotor information, an increase in cognitive processing time and a deficient processing of complex information and unknown tasks with a consequent greater vulnerability to increased cognitive demands. However, because these cognitive impairments are typically mild to moderate, they are often not easily recognized. The degree of involvement is

directly related to the areas of deficient development and whether the malformation is partial or total, factors that affect quality of life and treatment. There is a change in social cognition, emotion recognition, mentalization and linguistic skills, in addition to a greater tendency towards the autism spectrum and attention deficit disorder (Brown et al., 2019).

Guadarrama-Ortiz et al. (2020) reports a case in which an 8-year-old male patient with ACC was fully identified intrauterine by means of ultrasound (US), requiring a cesarean section at 36 weeks due to hydrocephalus, without perinatal complications or any other abnormality suggestive of the syndrome. congenital. Magnetic resonance imaging (MRI) of his brain at school age demonstrated, in addition to the total ACC, an enlargement of the lateral ventricles with dilated occipital horns (colpocephaly). During follow-up, he did not present any disturbances on neurological examination, behavioral/psychiatric disorders or intellectual disabilities.

In a quantitative analysis with clinical cases where the authors evaluated neuroplasticity in patients with ACC, there were described decision-making difficulties which occur due to impaired connection of the commissural fibers within the frontal lobes, with growth in the thickness of the anterior commissure being seen in patients with neuroplasticity when compared to controls (Nishikimi et al., 2013). Although the increase in the size of the anterior commissure constitutes the main event of anatomical neuroplasticity in patients with ACC, no current evidence is available to recommend an efficient cognitive therapy to improve the quality of decision making, explaining the heterogeneity between patients. More experimental studies will be necessary, especially in the use of molecular markers to clarify this field of knowledge (Ferreira et al., 2022).

Since 1985, ACC has been diagnosed through fetal ultrasound. This assessment was incoherent and divergent, meaning that the evaluator,

at that time, was unable to distinguish complete agenesis from the partial form (Mahallati et al., 2020). In recent decades, magnetic resonance imaging (MRI) has been implemented, a tool that has increased the recognition of fetal diagnosis, which is performed in three planes and is useful in identifying associated anomalies. The use of MRI is essential and must be done together with a complementary fetal ultrasound exam, with the midsagittal plane parallel to the CC being ideal for evaluation (Rangasami, R. et al, 2020).

In a systematic literature review and meta-analysis study, in which 14 studies were included totaling 798 fetuses, evaluating the type of ultrasound evaluation (neurosonography versus standard axial evaluation), gestational age on fetal MRI and anomaly rates detected postnatally, in search of greater sensitivity and effectiveness in diagnosis. According to the type of ultrasound assessment, the rate of associated anomalies detected only on fetal MRI was 5.7% with dedicated neurosonography and 18.5% with standard axial assessment. In fetuses with isolated partial ACC, 13.4% and 16.2% of additional anomalies were detected by fetal or postnatal MRI, respectively. According to the type of ultrasound assessment, the rate of associated anomalies detected only on fetal MRI was 11.4% when dedicated neurosonography was performed. Cortical and posterior fossa anomalies are among the most common anomalies detected exclusively on MRI, thus confirming the crucial role of fetal MRI in determining prognosis. However, some anomalies still go unnoticed during prenatal care and this should be highlighted during parental counseling (Sileo et al., 2020).

Multiplanar fetal neurosonography is the best imaging test to evaluate the fetus from the 20th week of gestation onwards. Most brain abnormalities remain undiagnosed until midway through the first trimester, and may go undetected due to small fetal brain structures. Between the 11th and 13th weeks, ultrasou-

nd can highlight changes that are incompatible with life. Multiplanar neurosonography is indicated in the middle of the first trimester of pregnancy, including non-axial plane scanning. The sonographer's knowledge of fetal anatomy and sonoembryology results in early diagnosis (Volpe et al., 2020; Lipa et al., 2017).

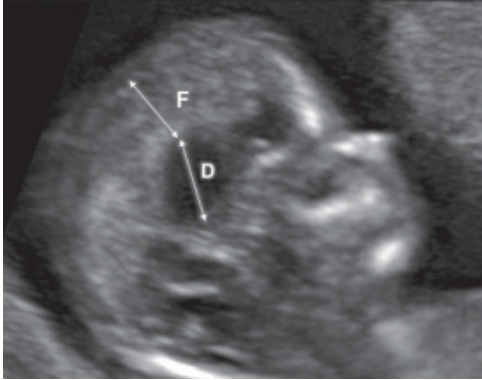


Fig. 1: Agenesis of corpus callosum in midsagittal ultrasound view in first trimester, showing increased ratio between diencephalon (D) and falx (F) diameters. In 80% of fetuses that had agenesia of the corpus callosum diagnosed later in gestation, there was an increased ratio between the diencephalon diameter (from midbrain to falx, including third ventricle and thalami) and the falx diameter. Adapted from Volpe et al. 2021.

CONCLUSION

ACC is a rare condition with a variety of causes, including genetic, environmental, and infectious factors. This malformation can be asymptomatic or cause a variety of symptoms, which vary depending on the severity of the malformation. The most common symptoms include developmental delay, seizures, learning and behavioral deficits, and physical and motor disabilities.

Dedicated ultrasound has high sensitivity for detecting malformations in the Central Nervous System during the prenatal period, so the diagnosis of ACC is usually made by fetal ultrasound. Magnetic resonance imaging should be used as a complementary method to detect associated anomalies and provide data for better perinatal care. The use of magnetic resonance imaging combined with neurosonography may result in a better prognosis for the patient.

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