The ultrasound evaluation of corpus callosum in the routine screening is not recommended, because we know less than we see

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ABSTRACT

The corpus callosum serves as a link between the two hemispheres, with an important role in cognitive mechanisms, also integrating motor and sensitive information and processing stimuli. Evaluation of the morphologic structure of the corpus callosum in order to diagnose structural anomalies such as hyperplasia, hypoplasia, as well as indirect signs of corpus callosum agenesis can be realized using ultrasonography during the mid-trimester screening. At present, it is recommended to perform a targeted evaluation only in high-risk cases of central nervous system abnormalities; the International Society of Ultrasound in Obstetrics and Gynaecology has not included the corpus callosum evaluation in the routine second-trimester screening. Callosal anomalies present uncertainty in the fetal prognosis: 75% of cases of isolated corpus callosum agenesis develop normally; on the other hand, they could develop various degrees of neurological impairment from language or social deficiency to autism or schizophrenia. We, therefore, highlight the importance of corpus callosum evaluation, as the agenesis of the corpus callosum can be an isolated defect, but it can also be associated with other extracerebral anomalies or it could be a part of a syndrome. Completing the diagnosis often requires magnetic resonance imaging and genetic tests.

Keywords: corpus callosum agenesis, hypoplasia, fetal prognosis, ultrasound

INTRODUCTION

The corpus callosum represents a structure that incorporates white fiber tracts connecting the two cerebral hemispheres [1]. It is involved in motor and sensitive information integration, cognitive mechanisms and stimuli processing [2].

The following regions are included in the structure of the corpus callosum: the rostrum, genu, body, isthmus and splenium [2]. The corpus callosum neurons derive from the cingulate cortex. The development of the corpus callosum debuts from genu to splenium areas, the rostrum being the last part forming. All these regions can be distinguished after the 20th gestational week. Between 20 to 30 gestational weeks, a thickening process of the corpus callosum occurs. Following this, thickness is reduced in the second postnatal month and from now on the myelination process continues until the age of 9 [2].

Disorders of the corpus callosum include agenesis of the corpus callosum (ACC), hypoplasia and hyperplasia. Agenesis of the corpus callosum can be complete, when all the components are missing, or partial when a remnant structure can be observed (the posterior regions of the corpus callosum are usually absent) [3,4]. Hypoplasia is described as thinning of the corpus callosum, while hyperplasia is described as the thickening of corpus callosum [4]. The corpus callosum’s length between 18 and 22 weeks of gestation varies between 11.1-29.9 mm, with a median of 19.7±2.8 mm, and corpus callosum thickness varies between 0.97-4.47 mm, the median thickness being 1.98±0.4 mm [5].

Agenesis of the corpus callosum has a prevalence between 1.85 and 2.49 per 10,000 births and it can be isolated or associated with other disorders in 39.6-86.5% of cases [6]. Hypoplasia of the corpus callosum has a prevalence of 0.4 per 10,000 births [7].

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Causes for agenesis of corpus callosum include chromosomal abnormalities (7.3-40%), fetal alcohol syndrome, and infectious, ischemic, teratogenic and metabolic diseases [3,4]. Among genetic causes, the most common are Aicardi syndrome and Anderman syndrome. Aicardi syndrome is characterized by agenesis of the corpus callosum in association with infantile convulsions, cognitive retardation, and chorioretinal anomaly and it predominantly affects girls. Anderman syndrome has a recessive autosomal inheritance and it is characterized by agenesis of the corpus callosum, cognitive retardation and progressive motor-sensory neuropathy [4]. Infectious causes include cytomegalovirus, influenza, rubella virus and toxoplasmosis [4].

Extracerebral anomalies are present in 60% of cases, most of them affecting the heart and the genitourinary tract. Cardiac abnormalities include ventricular septal defect and coarctation of the aorta. Genitourinary abnormalities include renal agenesis, cystic kidneys, ureteral anomalies and hypospadias. Agenesis of the corpus callosum can also be associated with digestive tract abnormalities such as oesophageal atresia, duodenal atresia and intestinal malrotation. In 46% of cases, agenesis of the corpus callosum is associated with other brain malformations such as Dandy-Walker syndrome, polymicrogyria, grey matter heterotopia and vermian dysgenesis. Lipomas and interhemispheric cysts can also occur in the midline [3,6].

CORPUS CALLOSUM—NORMAL ULTRASOUND ASPECTS

Regarding fetal ultrasound, the corpus callosum can be evaluated in several planes. In the transudate (coronal) plane, the body of the corpus callosum appears as a hypoechoic region between the frontal horns and above cavum septi pellucid. Corpus callosum can also be evaluated in the midsagittal anterior plane which can be acquired through the anterior fontanelle [8]. In this section, the corpus callosum appears as a hypoechoic structure delimited superiorly and inferiorly by two echogenic lines (Figure 1 a, b) [9]. All the components of the corpus callosum should be present in this section [8]. Doppler ultrasound can be used in order to evaluate the pericallosal artery (Figure 2) and it can be helpful especially when the mother has a large body mass index (BMI) or the fetus has a position that does not facilitate the evaluation [4,9].

Biometry of the corpus callosum was indicated in the past [4]. At present, the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) recommends that measurements of the corpus callosum should be done with caution in order to diagnose hypoplasia; smaller or larger dimensions of the corpus callosum are not necessarily signs of the disorder. The assessment should focus on qualitative evaluation and not on quantitative one [8]. Transabdominal ultrasound should be performed for fetuses in breech or transverse presentation and transvaginal ultrasound should be performed for fetuses in vertex presentation [9].
AGENESIS OF THE CORPUS CALLOSUM – ULTRASOUND ASPECTS

Diagnosis of corpus callosum agenesis is established by the lack of visualization of this structure. Besides this aspect, there are several indicators that can suggest agenesis of the corpus callosum [4].

1. Cavum septum pellucidum-related indicators:
In complete agenesis, cavum septum pellucidum is absent or completely disorganized whereas in partial agenesis, cavum septum pellucidum is present in the majority of cases [4,9], it can have a normal appearance, it can be dysmorphic or it can be presented as an uncommonly short and wide structure in the axial plane [3]. There is a screening marker that was proposed for diagnosing partial agenesis of corpus callosum represented by a <1.5 cavum septum pellucidum length-to-width ratio [3]. It should be mentioned that the absence of cavum septum pellucidum is not pathognomonic for agenesis of the corpus callosum, this abnormality being also present in disorders such as holoprosencephaly and encephalocoele [4]. Corpus callosum and cavum septum pellucidum have the same embryonal origin, which can explain their simultaneous absence [3].

2. Ventricles-related indicators:
The third ventricle can be increased in size and situated higher at the level of lateral ventricles in the axial or coronal plane. Lateral ventricles can have the aspect of a bull's horn due to a fiber tract named bundle of Probst which cause lateral displacement of the bodies of the lateral ventricles. Another indicator of corpus callosum agenesis is colpocephaly as a result of the missing posterior region of the corpus callosum [4]. These modifications, described as the tear-drop sign, consist in the exaggerated enlargement of the occipital horns compared to the frontal horns, medial walls of the ventricles being parallel to each other and to de midline. Dilatation of the ventricles is more often as gestational age advances [3]. These ultrasound modifications are also present in partial agenesis of the corpus callosum, but they tend to be less pronounced [3].

3. Pericallosal artery-related indicators:
Complete agenesis of the corpus callosum is associated with the absence of the pericallosal artery [4]. In this case, branches of the anterior cerebral artery have a radiate arrangement ascending linearly [9]. Partial agenesis of the corpus callosum is associated with a pericallosal artery that is present only in the anterior part of the corpus callosum, the posterior region of the corpus callosum being absent and the artery taking a posterior oblique trajectory [4].

4. Interhemispheric fissure-related indicators:
Agenesis of the corpus callosum causes enlargement of the interhemispheric fissure. This aspect on ultrasound imaging is suggested by three parallel echogenic lines. The lateral lines are the medial margins of the hemispheres and the medial line is represented by the falx cerebri [4].

5. Cerebral convolutions related indicators:
Agenesis of corpus callosum is responsible for a radial disposition of the sulci on the medial surface of the hemispheres [4].

ADDITIONAL DIAGNOSTIC METHODS

Due to the associated cardiac malformations described, a fetal echocardiography is recommended [3]. Magnetic resonance imaging (MRI) is superior to ultrasound imaging in detecting associated brain abnormalities and given that ultrasonography has a false-positive rate between 0-20%, MRI testing should be included in agenesis of corpus callosum diagnosis. This can be especially useful when isolated agenesis is suspected, since simultaneous brain abnormalities may diminish the chances of a good prognosis [3,4].

Due to the fact that 17% of agenesis of corpus callosum cases are associated with chromosomal abnormalities, genetic testing is indicated. The initial approach consists of a karyotype analysis or fluorescence in situ hybridization. If the results of this method are normal, a chromosomal microarray analysis should be performed. There are cases that may require gene panel testing or exome sequencing since chromosomal microarray analysis cannot identify single-gene disorders. Cell-free DNA screening is an alternative for patients who refuse a complete evaluation [3].

Screening for infectious causes has an uncertain role [4].

PROGNOSIS

Patients presenting callosal affections have a very variable prognosis. Outcomes include motor and cognitive impairment, epilepsy, language and social deficiency, autism, and schizophrenia [10].

Regarding isolated agenesis of the corpus callosum, neurodevelopmental outcomes are normal in 75% of cases whereas 12% of patients have variable levels of cognitive impairment [11]. Between the prognosis of complete and partial agenesis of the corpus callosum, there are only subtle differences [12].

CONCLUSIONS

Ultrasonographic diagnosis of corpus callosum agenesis is still difficult before 17 weeks gestation. Corpus callosum agenesis or hypoplasia is not a life-threatening disorder but the specific outcomes are difficult to predict. The actual recommendations include performing a targeted evaluation in case of increased risk of central nervous system abnormali-
ties. The International Society of Ultrasound in Obstetrics and Gynaecology guideline recommends a routine evaluation only for the following structures: spine, cerebellum, cavum septum pellucidum, lateral ventricles, thalami, cisterna magna.

There are several ultrasound indicators that can suggest agenesis of the corpus callosum including the appearance of cavum septum pellucidum, cerebroventricles, pericallosal artery, interhemispheric fissure and cerebral convolutions. It is highly recommended that the ultrasound assessment should focus on qualitative evaluation and not on quantitative one. In addition to the ultrasonographic evaluation, diagnosis can be completed with the help of MRI and genetic testing.

Simultaneous brain disorders are associated with a worse prognosis while isolated complete and partial agenesis have a better prognosis and similar outcomes. Important variability in outcomes makes prenatal counselling challenging, especially in isolated cases of disease as parents can experience anger, sadness, anxiety and psychological distress due to the ambiguity of diagnosis.

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**REFERENCES**