Corpus callosum agenesis: prenatal diagnosis and neurodevelopmental outcome

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ABSTRACT

Introduction: The corpus callosum (CC) is the main commissural pathway in the brain and has an important role in the integration of information between the two cerebral hemispheres. The CC can be partially or completely absent and this anomaly can be isolated or complex (coexisting with other abnormalities). The prevalence of corpus callosum agenesis (CCA) is approximately 1:4000-1:5000 live births. The combination of antenatal ultrasound (US) and magnetic resonance imaging (MRI) is capable of diagnosing isolated forms of CCA. The purpose of this review is to assess current knowledge regarding prenatal diagnosis of CCA and the neurodevelopmental outcome of affected individuals, with a view to allowing clinicians to offer appropriate prenatal counseling.

Material and Methods: A systematic review of 62 articles regarding CCA was performed using the following databases: PubMed, Cochrane Library, Scientific Electronic Library Online (SciELO), and online Knowledge Library (B-ON). The search was restricted to English-language articles published from 1984 to 2016.

Results: In isolated CCA detected by means of US and MRI, medium- and long-term neurodevelopment is expected to be normal in approximately 75% of cases. With regard to outcomes, borderline/moderate and severe neurodevelopmental impairment have been reported in 14.92% and 12.52% of children, respectively. Fine motor control was affected in 11.74 % of cases, and 16.11% of these children suffered from epilepsy. As a result, counseling in isolated cases has been changing, and many parents choose not to terminate pregnancy when there are no other abnormalities in their fetus. However, these children may still need long-term follow up: subjects who eventually have a normal neurodevelopmental outcome may have transient mild symptoms in early life, while in other cases, abnormalities may appear later in life.

Conclusion: During the second trimester, three axial planes of the head should be obtained to assess the fetal central nervous system. Assessment of the cavum septum pellucidum (CSP) is important to rule out CCA. In the case of absence or abnormal shape of the CSP, the CC must be assessed in the mid-sagittal view of the brain. A detailed US, MRI and fetal karyotype with chromosomal microarray analysis should be offered if there is a suspicion of CCA or CCPA. Several prenatal studies have reported similar neurodevelopmental outcomes in fetuses with CC partial agenesis (CCPA) and in those with complete CCA, with delay reported in about 25–30% of cases. Nevertheless, follow up of these children is necessary in order to evaluate their neurological development. When other abnormalities are associated, the prognosis is more severe.

KEYWORDS

Corpus callosum agenesis, prenatal diagnosis, neurodevelopment, chromosomal microarray analysis (CMA).

Introduction

The corpus callosum (CC) is the largest white matter tract in the human brain, containing about 200 million axons that connect the left and the right cerebral hemispheres. It is one of the five main cerebral commissures. Its principal function is the connection and transfer of information between the two cerebral hemispheres, aiding cognition and neurological function. This interhemispheric communication is important for the functional integration of sensory, motor and visuomotor information, as well as higher cognitive functions such as language and abstract reasoning [1]. The CC has traditionally been divided into four anatomically defined regions: the rostrum, genu, body and splenium; the narrowing between the body and splenium is called the isthmus [2].

By 18–20 weeks of gestation, the CC assumes its final shape. The CC can present the following abnormalities: hypoplasia, hyperplasia and agenesis. Corpus callosum agenesis (CCA) can be complete (total absence of the CC) or partial (partial absence of the CC). The developmental sequence is

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thought to be important to understand the etiology of CCA: if partial CCA involves the anterior portion, it is usually due to a disruptive event (such as a vascular or infectious cause) [3,4]. Conversely, if the posterior portion is absent, it may suggest an arrest in development [3]. The reported prevalence of CCA is approximately 1:4000-1:5000 live births [5]. CCA can be isolated (with no other abnormalities) or complex (coexisting with other abnormalities) [6]. By combining antenatal ultrasound (US) and magnetic resonance imaging (MRI), isolated forms of CCA can be diagnosed. The purpose of this review is to assess current knowledge regarding prenatal diagnosis of CCA and the neurodevelopmental outcome of affected individuals, with a view to allowing clinicians to offer appropriate prenatal counseling.

Material and methods

A systematic review of 62 articles regarding CCA was performed using the PubMed, Cochrane Library, MEDLINE, Scientific Electronic Library Online (SciELO), and online Knowledge Library (B-ON) databases. The search was restricted to English-language articles published from 1984 to 2016.

Results

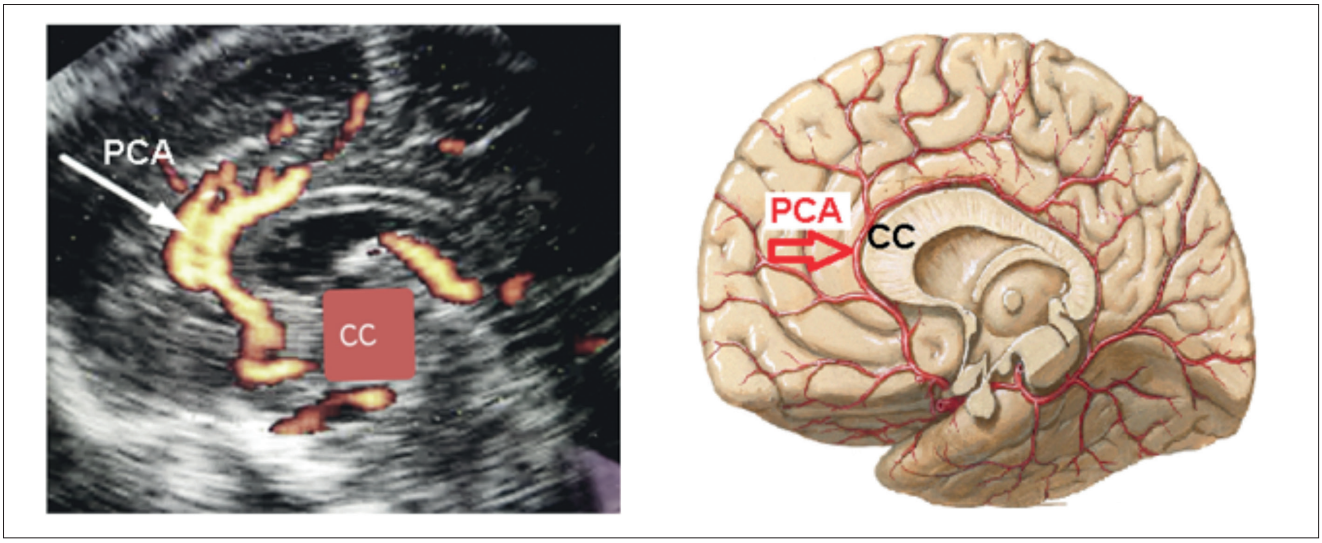
In normal fetuses, the CC can be visualized in mid-sagittal views of the brain by the end of the 20th week of gestation. It appears as a thin anechoic space, bordered superiorly and inferiorly by two echogenic lines [7]. The pericallosal artery, which develops in close association with the CC, can act as a useful marker when direct visualization of CC is difficult due to maternal obesity or fetal position (Figure 1). Mid-sagittal and mid-coronal scans of the fetal brain are the best planes with which to visualize the CC and can be obtained with standard transabdominal US if the fetus is in breech or with transvaginal US if the fetus is in cephalic presentation [7-9]. According to guidelines of the International Society of Ultrasound in Obstetrics and Gynecology, three axial planes (transventricular, transcerebellar and transthalamic) are used to investigate the fetal central nervous system using US. Using this method, it is possible to detect the head shape, lateral ventricles (including choroid plexus), cavum septum pellucidum (CSP), midline falx, thalami, cerebellum, and cisterna magna [10]. Usually, the additional scanning planes of fetal neuro US (mid-sagittal and coronal views) are needed in fetuses with suspicious findings on basic examinations [9]. Failure to visualize the CSP is the main indirect finding in case of CCA (Figure 2).

While complete CCA is often suspected on fetal US due to absence of the CSP, detecting CC partial agenesis (CCPA) is extremely difficult. CCPA with absence of the CSP has been reported, with rates ranging from 10% to 20% [11-13]. This means that in 80% to 90% of cases the axial view of the fetal head is often unremarkable [11]. That said, an association between partial CCPA and an abnormal shape of the septum pellucidum has been demonstrated [14]. The appearance of the CSP is variable in fetuses; a recent evaluation showed that in the transventricular plane, the CSP had a rectangular shape in 73% of normal cases, whereas in the other 27% it was triangular with an anterior base [15].

The detection rate of CCPA can be improved by means of observation of the associated abnormal shape of the CSP and its objective quantification using the CSP ratio [14]. The CSP ratio is the relation of CSP length to width and it has to be measured in the axial plane of the fetal head. The width of the CSP is measured at the level of the middle of the CSP [16]. To measure CSP length, the calipers are placed on the echogenic borders: the callosal sulcus anteriorly and the fornix posteriorly.

Fetuses with a normal CC have a rectangular-shaped CSP, with a CSP ratio >1.5 during the second half of pregnancy (Figure 3). Most fetuses with CCPA have an abnormally shaped, wide and short CSP, with a decreased CSP ratio [14]. In all suspicious cases, the examiner should obtain a mid-sagittal view to either confirm the hook-shaped structure of the CC, or exclude its abnormal size and appearance. In CCA, the CC is absent, while in CCPA, it is interrupted or short, with an anteroposterior length < 5th centile [17-18].

Figure 1 On the right: 20-week scan showing pericallosal artery (PCA) surrounding the corpus callosum (CC). On the left: anatomical appearance of the brain.



CCA has been associated with cranial and extracranial anomalies. Careful imaging in a center with a high level of expertise is necessary in order to make a full assessment and to exclude coexisting abnormalities, which occur in about 46% of fetuses, because their presence increases the likelihood of a later neurological impairment.

The most frequently reported brain abnormalities associated with CCA are posterior fossa abnormalities, interhemispheric cysts and neuronal migration disorders.

MRI should be a part of the assessment when CCA is suspected. It allows direct and better visualization of the CC and, in addition, it can reduce the false-positive rates shown by US. Moreover, MRI may detect other brain abnormalities, such as anomalies of gyration and heterotopia [19-21].

In a recent systematic review, prenatal MRI was associated with detection of additional abnormalities in 22.5% of cases compared with US [2].

Prenatal karyotype testing and chromosomal microarray analysis (CMA) should be offered in CCA [22]. The overall chromosomal abnormality rate is 18%, which is high but includes both isolated and complex CCA; more recent studies suggest that chromosomal abnormalities are rare in isolated cases [23]. Chromosomal microdeletions may be connected with CCA and therefore chromosomal analysis using comparative genomic hybridization should be considered.

CCA has been correlated with autosomal dominant, autosomal recessive and X-linked modes of inheritance [24, 25]. The most common genetic causes of CCA are the following:

- Aicardi syndrome: found almost exclusively in girls, this is inherited as an X-linked dominant trait; it is characterized by the presence of CCA associated with chorioretinal abnormalities, infantile seizures and mental retardation [26];
- Andermann syndrome: a rare autosomal recessive disorder characterized by CCA, progressive motor- sensory neuropathy and mental retardation [27].

Given the uncertain prevalence of CCA, it is very difficult to establish the frequency of underlying genetic syndromes [28].

Apart from genetic syndromes, CCA can be caused by

Figure 2 On the right: Axial view of the brain showing absence of the cavum septum pellucidum (CSP) (indirect sign), on the left: Mid-sagittal view showing absence of the corpus callosum (CCA) (direct sign).

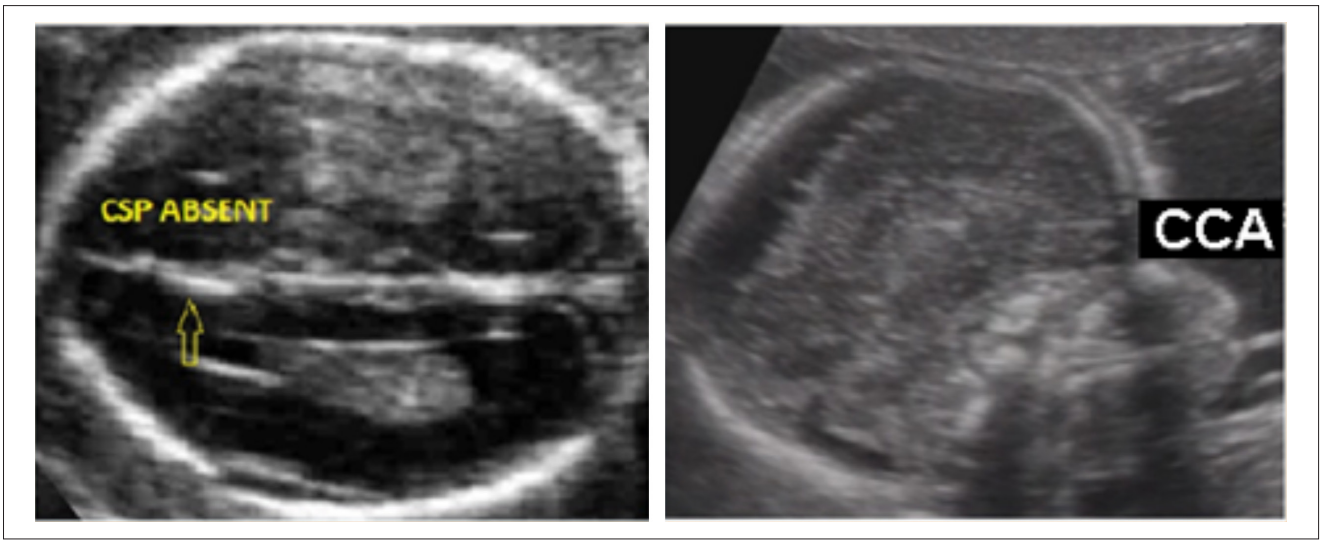


Figure 3 20-week scan showing: A: typical rectangular-shaped cavum septum pellucidum; B: hook-shaped corpus callosum on a sagittal US scan.

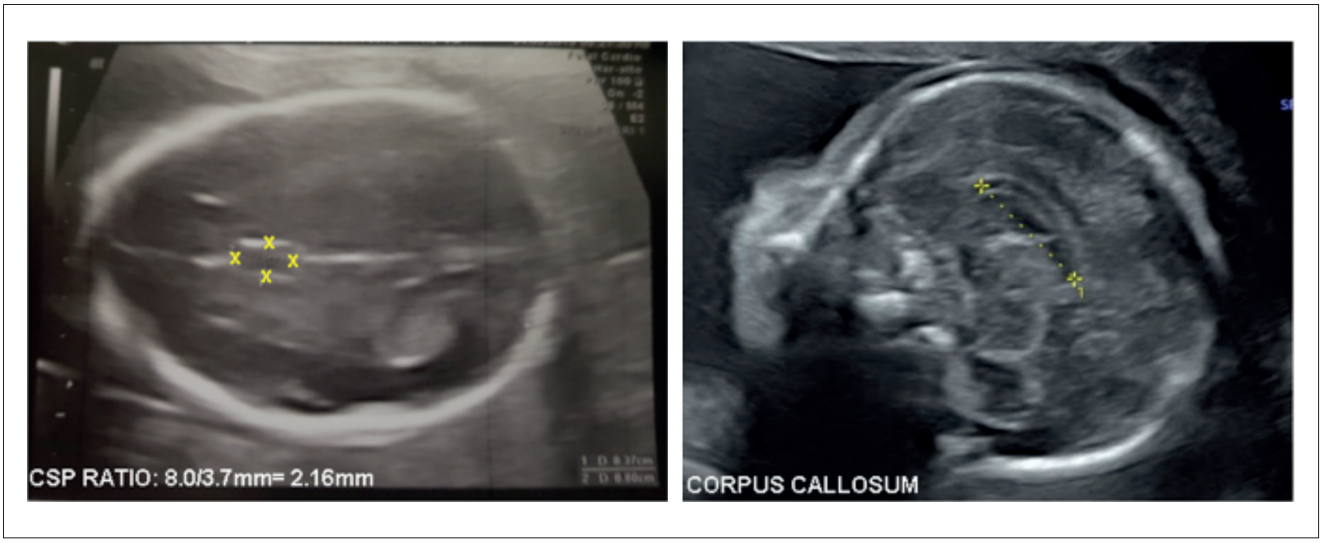
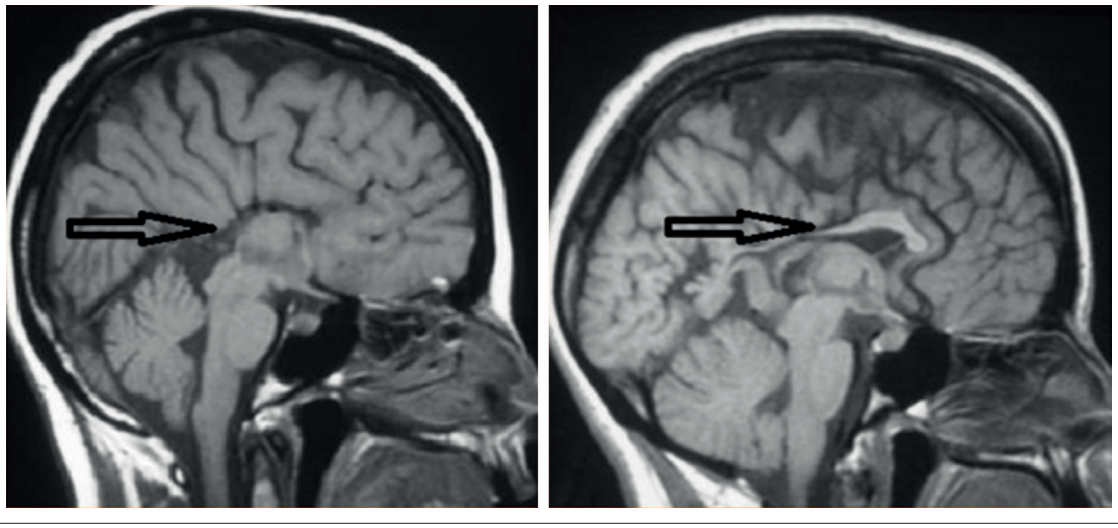


Figure 4 MRI showing complete (right) and partial agenesis of the corpus callosum (left).



non-syndromic conditions such as fetal alcohol syndrome and metabolic disorders [29].

The prognosis in CCA depends on the coexistence of other abnormalities; these may include alterations of cortical development, which can only be assessed with advancing gestation. Therefore, additional detailed fetal US examination should be considered, in order to search for cerebral and extra-cerebral abnormalities that could be misinterpreted during the second trimester.

In the presence of associated anomalies, the prognosis depends largely on them, because they can lead to severe mental and psychomotor retardation [30-34]. The isolated nature of CCA is defined by the absence of other neurological (including ventriculomegaly > 15 mm) and extra-neurological alterations observed after a detailed prenatal morphological US, as well as MRI, carried out at around 32 weeks with negative karyotype.

Hypoplasia of the CC and of CCPA are more difficult to diagnose prenatally than complete CCA, although prenatal diagnosis of these conditions is feasible by means of targeted US [31]. Each type of CCA is likely to reflect a distinct malformation spectrum and seems to share the same neurodevelopmental prognosis when isolated [31-33]. The combination of antenatal US and MRI is sufficient for diagnosing isolated forms of CCA (Figure 4). Overall, 15% of cases thought to be isolated proved to be associated with other abnormalities after birth. Prenatal counseling should take into account that in 5-20% of cases diagnosed prenatally as isolated CCA, other abnormalities could be detected later [19,31,35]. The rate of neurodevelopmental delay in infants with a prenatal diagnosis of isolated CCA is about 25–30%, and this appears to be similar in both complete and partial forms [2]. With regard to outcomes, borderline/moderate and severe neurodevelopmental impairment have been reported in 14.92% and 12.52% of children, respectively. Fine motor control was affected in 11.74% of cases, and 16.11% of these children presented epilepsy [36]. In isolated CCA, medium- and long-term neurodevelopment is expected to be normal in approximately 75% of cases [2]. As a result, counseling is decisive with regard to the parents' choice and, many opt not to terminate when isolated CCA is diagnosed [24].

Conclusion

Fetal abnormalities are multifactorial, and among them it is necessary to consider conditions with chromosomal or infectious origins [37-40]. During the second trimester, three US axial planes of the head should be obtained to assess the fetal central nervous system. Visualization of the CSP is important to rule out CCA. In the case of absence or an abnormal shape of the CSP, the CC must be assessed in the mid-sagittal view of the brain.

A detailed US should be performed and when there is a suspicion of CCA, MRI is compulsory for a complete evaluation of the cerebral structures, while fetal karyotype testing and CMA should be offered for genetic framing [22].

When the defect is isolated, the prognosis is less negative: several prenatal studies have reported similar neurodevelopmental outcomes in children prenatally diagnosed with CCPA versus complete CCA, with delay reported in about 25–30% of cases [16,18,41-42]. Children with a prenatal diagnosis of isolated CCA show several degrees of impairment in motor control, coordination, language and cognitive status [36]. Follow up of these children is, in any case, necessary in order to evaluate their neurological development. When other abnormalities are associated, the prognosis is more severe.

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