Fetal Diagnosis and Therapy

Review Article

Fetal Diagn Ther 2021;48:88–95
DOI: 10.1159/000512534

Received: June 15, 2020
Accepted: October 22, 2020
Published online: January 29, 2021

Neurodevelopmental Outcomes following Prenatal Diagnosis of Isolated Corpus Callosum Agenesis: A Systematic Review

Sara Bernardes da Cunha[a] Maria Carolina Carneiro[a] Maria Miguel Sa[b]
Andrea Rodrigues[c] Carla Pina[a]

[a]Gynaecology and Obstetrics Department, Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal; [b]Family Doctor, UCSP Moscavide, Lisbon, Portugal; [c]Occupational Medicine, Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal

Keywords
Abnormalities of corpus callosum · Neurodevelopmental outcomes · Prenatal counseling · Isolated corpus callosum abnormalities

Abstract
Abnormalities of corpus callosum are one of the most common brain anomalies. Fetuses with isolated corpus callosum agenesis (CCA) have a better prognosis than those with additional anomalies. However, unpredictable neurodevelopmental outcomes of truly isolated CCA make prenatal counseling a challenge. The aim of this review is to evaluate neurodevelopmental outcomes in children with prenatal diagnosis of isolated CCA. Controlled clinical trials published between May 23, 2009, and May 23, 2019, using the MeSH term "agenesis of corpus callosum" were reviewed. A total of 942 articles were identified, and 8 studies were included in the systematic review depending on the inclusion criteria. These studies included 217 fetuses with isolated CCA and no other anomalies at prenatal assessment. Neurodevelopmental outcome was reported to be normal in 83 children with a prenatal diagnosis of isolated CCA confirmed at birth within 128 completed assessments. About 45 children presented borderline, moderate, or severe neurodevelopmental outcome. In this review, neurodevelopment was favorable in two-thirds of the cases, but mild disabilities emerged in older children. Despite this, disabilities can occur later beyond school age and a low risk of severe cognitive impairment exists. Our study highlights the essential early diagnosis and proper supportive therapy.

Introduction

Corpus callosum (CC) agenesis (CCA) is among the most common central nervous system (CNS) malformations diagnosed on prenatal ultrasound (US). The true prevalence is difficult to estimate because of a proportion of asymptomatic patients and challenging diagnosis [1], but 2–3% is described in the developmentally impaired population [1–6].

The most common anomalies involving the CC are complete CCA (cCCA) or partial CCA (pCCA) [1, 2, 7], hypo-hyperplasia of the CC and dysplasia. Dysgenesis of the CC refers to the CC being present but malformed in some way, including pCCA and CC hypoplasia (hCC) [8].

Abnormalities of CC (ACC) can result from alterations on the embryological development or from external

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

Sara Bernardes da Cunha
Gynaecology and Obstetrics Department
Centro Hospitalar de Entre Douro e Vouga, Rua Principal
No. 794; 3º Esquerdo-sul, PT–4410-129 São Félix da Marinha – Gaia (Portugal)
sara.bernardes.cunha@gmail.com

insults. Vascular, toxic, genetic, and infectious (TORCH and Zika virus) etiologies have been described [6]. However, only <50% of the underlying cause is achieved [9, 10].

Genetic factors are among the most common causes of CCA [11]. Monogenic causes are found in 35%, a syndrome in 45% of the cases with a genetic cause, and chromosomal abnormalities concur in 18% of these, mostly trisomy 18, 13, and mosaic 8 [12]. In a study involving 138 fetuses, etiologic assessment could not justify 67% of the causes. Of the causes established, this study counts with 1 case of maternal metabolic disease, 1 case of cytomegalovirus infection, 23 chromosome alterations, and 21 Mendelian abnormalities [13]. Among the 138 cases, the underlying etiology was found in 46 cases: diabetes (1 case), cytomegalovirus infection (1 case), 23 chromosome abnormalities, and 21 Mendelian conditions.

Conventional abnormal karyotype occurs in 4.8% of cCCA and in 7.5% of pCCA, respectively, thus highlighting the need for prenatal assessment of fetal karyotype in these cases [11]. Fetuses with CNS anomalies and normal karyotype have been shown to have a significantly higher risk of genetic anomalies at chromosomal microarray analysis (CMA). In fetuses with apparently isolated CCA, the rate of significant pathological copy number variations and normal karyotype has been reported to be 5.7% [11]. A recent joint committee opinion of the American College of Obstetricians and Gynecologists (ACOG) and the Society of Maternal-Fetal Medicine (SMFM) recommended that CMA analysis should be performed in all fetuses undergoing invasive procedures for major structural anomalies detected on US [11, 14–16]. Nevertheless, these techniques cannot detect discrete gene mutations involved in various monogenic disorders [11, 15, 16].

Advances in new genetic diagnostic techniques, such as next-generation sequencing, whole-genome sequencing (WGS), and particularly whole-exome sequencing (WES) [14–17], may help determine the underlying cause of CCA especially in those cases not presenting with the classical clinical features of a syndromic condition [14–16] and in fetuses with normal karyotype and CMA. WGS analyzes the entire genome. Exons generally have greater clinical relevance and applicability to patient care. However, the routine use of WES for prenatal diagnosis is not recommended outside clinical trials [14]. Due to CCA genetic heterogeneity, these techniques may play an important role on identifying the children with ACC who are at a higher risk of intellectual disability [11].

CCA is diagnosed prenatally by US at a mean gestational age of 22 weeks [1]. Prenatal ultrasonographic diagnosis of CCA can be challenging, often associated with the absence of total ACC or partial (pACC) visualization of CC in the midsagittal plane of the fetal head [11, 18].

Visualization of the CSP is fundamental to assess the integrity of CC, which cannot be identified on axial views of the brain but requires sagittal and coronal planes. Yet, visualization of the CC is difficult, and diagnosis of CCA is based on typical sonographic signs that have been described as either direct (complete or partial absence of the CC in the midsagittal plane) or, more often, indirect signs (colpocephaly, elevation and dilatation of the third ventricle, and an abnormal course of the pericallosal artery). In case of pACC, the shape of CSP can be variable. In the main cases, the shape is abnormal, and is considered an indirect sign of partial agenesis and possibly the only diagnostic clue [19]. Despite this importance, a direct visualization of the CC is not required on the standard examination of the fetal CNS performed at the time of routine scans, thus explaining the relatively low detection rate for ACC, in particular for pACC reported in the literature [11, 18].

Recently, US assessment of the anterior complex, defined as the group of all anatomical structures visible on the routine transventricular plane of the fetal brain, has been proposed to improve the detection rate of supratentorial midline anomalies [11, 18]. New imaging modalities are being used in the study of normal and abnormal development of the fetal brain like three-dimensional US, magnetic resonance imaging (MRI), and newly functional neuroimaging techniques (such as high-resolution diffusion tensor imaging tractography) [20, 21].

Fetal MRI is commonly performed in fetuses with suspected CNS anomalies. The yield of "clinically relevant information" provided by MRI in comparison with neurosonography (NSG) ranges from 7 to 40% [20]. A particular area of controversy is the clinical usefulness of MRI for the diagnosis or as an adjunct to NSG, the latter being defined as US examination of the fetal brain performed by an experienced sonologist using a multiplanar, possibly transvaginal approach, as reported in the recently published guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [18].

In a recent systematic review including only fetuses with isolated CCA, associated anomalies not detected on US were diagnosed on fetal MRI in 7.83 and in 11.86% of total ACC and pACC [11]. The large majority of such additional anomalies included neuronal migration disorders, which can be detected preferentially from the third trimester of pregnancy. In Meridian Study, a multicenter

prospective cohort study involving over 800 pregnancies with a fetal brain abnormality undergoing US and MRI the first 2 weeks of life, the diagnostic accuracy for detecting ACC was 40.0% for US and 92.7% for MRI. More importantly, prognostic information given to the women changed in 45.6% of the cases after MRI. Nonetheless, latter work revealed limitations to this study, with one of the most important being the suboptimal performance of US, leading to potential erroneous conclusions [22].

In contrast, Paladini et al. [20] considered that expert NSG is capable of characterizing most CNS abnormalities and that MRI is only needed in selected cases with specific indications or queries. They also proposed that MRI added clinically relevant information on 7.9% of the cases undergoing expert NSG and MRI, which, depending upon the sonologist's experience and the spectrum of CNS anomalies, may represent 10–20% of all fetuses with CNS malformations referred to a tertiary center [20]. Despite all these arguments, US is the primary technique for detecting ACC, while MRI should be performed in centers where expertise in NSG is not available and weighed against the availability of economic and human resources.

The presence of associated anomalies is one of the major prognosis determinants of fetuses affected by ACC. These may include abnormalities of cortical development, which can only be assessed with advancing gestation. Although the actual contribution of MRI compared to US in fetal CNS anomalies is difficult to quantify due to the large heterogeneity among the previously published studies, MRI is routinely used in clinical practice particularly beyond 30 weeks of gestation to confirm diagnosis and to look for associated anomalies in case of ACC (such as cortical anomalies).

Some of the adverse outcomes related to ACC include delays in motor and cognitive functions, and epilepsy, in addition to behavioral, social, and language deficits; autism; and schizophrenia. Attention-deficit disorders have also been described [9, 10].

A recent integrative review highlighted that in truly isolated CCA, neurodevelopmental outcomes can range from normal development in about 75% of the individuals to different levels of intellectual disability. About 12% of the individuals in this series had severe intellectual disability [4, 11], which made it challenging for antenatal counseling, when a fetus is diagnosed with apparently isolated CCA [5–7, 10]. For this reason, a cognitive outcome of isolated CCA remains a major concern with uncertain prognosis. The aim of this review is to evaluate neurodevelopmental outcomes following prenatal diagnosis of isolated CCA.

Material and Methods

A systematic review of the literature was performed using PubMed (Medline), Cochrane Database, Dare, Bandolier, and BMJ, considering a time period of 10 years (May 23, 2009–May 23, 2019) applying the MeSH terms "agenesis of corpus callosum." The use of wide research criteria was made because the relevant evidence is scarce. In order to be eligible, studies would have to fulfill the following criteria: controlled clinical trial, multicenter study, or observational study; and studies assessing neurological or neurodevelopmental outcomes in children with isolated CCA.

The authors screened the articles by title/abstract. Afterward, a full-text review was performed. The reference lists of included articles were screened for further studies considered being relevant. In studies deemed to be eligible, data were extracted regarding population, type of callosal agenesis (cCCA and pCCA), type of imaging assessment, and neurodevelopmental outcomes. If more than 1 article was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Results

Neurodevelopmental Outcomes

A total of 942 articles were identified. A full-text review was performed for 29 articles, and finally, 8 studies were included in the systematic review (Fig. 1; Table 1). These 8 studies included 217 fetuses with isolated CCA. Additional anomalies not detected at prenatal US were diagnosed postnatally in 12 children. Of these children, 10 were excluded because they were lost to follow-up, and 1 was excluded for late-onset follow-up (i.e., initially lost to follow-up, but recurred again to the clinic at a later age). Sixty-seven women performed termination of pregnancy, and in 1 case, intrauterine fetal death occurred.

Neurodevelopmental outcomes were assessed in 128 children. It was reported to be normal in 83 children with a prenatal diagnosis of isolated CCA confirmed at birth. The other 45 children presented borderline, moderate, or severe neurodevelopmental outcomes.

Considering only children with development follow-up, the findings from this systematic review suggested that about two-thirds of the children showed a normal neurodevelopmental outcome (64.8%) and one-third (33.6%) presented borderline, moderate, or severe neurodevelopmental outcomes. These results are similar to those of other studies [10].

The limitations of these studies were their inclusion criteria; lack of consensus on the meaning of normal outcome and mild, moderate, and severe disability; retrospective and study designs; small number of cases included; paucity of population-based studies; lack of a stan-

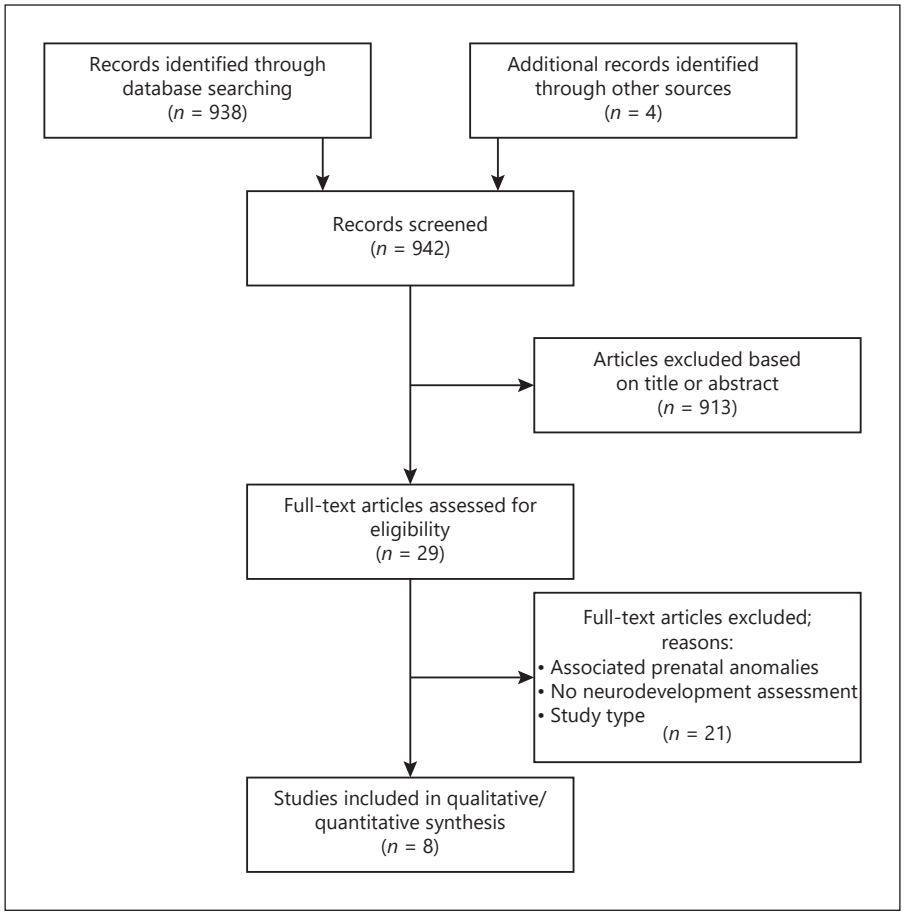

Fig. 1. Flow diagram of included studies.

dardized prenatal and postnatal medical workup protocol; and heterogeneity of psychometric tools adopted. Moreover, the majority of these studies do not take into account the social, cultural, or educational level of the family in the interpretation of outcomes, which could have hampered any detailed cognitive analysis. Furthermore, the relatively short period of follow-up after birth did not allow a precise estimation of the overall rate of additional anomalies detected only after birth and missed prenatally (Table 1).

Discussion

Yeh et al. [5] revealed that hCC or pCCA was often associated with concomitant non-CNS anomalies. The rate of severe disability in the later was higher than that in patients with cCCA; however, this difference was not statistically significant. The study has some methodological limitations, including its retrospective design and the application of 2 different tests, BSID II and KICD, nonrandomly chosen. Both neurophysiological scoring tests were designed for patients younger than 5 years, and development assessment at a median age of 24.8 months may not be ideal to exclude the possibility of behavior or learning disorders [5].

In the Folliot-Le Doussal et al. [1] study, neurodevelopmental outcome was favorable in 88% of the children. This study has some limitations with restrictive inclusion criteria, and despite a long follow-up period, few children were included regarding age at diagnosis. Indeed, mild disabilities can appear later, when children reach school age. They did not take into account the social, cultural, or educational level of the family in the interpretation of outcomes [1].

Des Portes et al. [6] conducted a prospective study over an 11-year period, where intellectual quotient is normal (IQ > 85) in approximately two-thirds of the children and borderline in just over a quarter of patients. In this study, they could not determine any difference, between cCCA and pCCA, possibly due to the small number of patients with pCCA. This study does not take into ac-

Table 1. General characteristics of the included studies

Article/year/ study type/country	Number of cases/ follow-up (range)	Neurodevelopmental tool	Type of the corpus callosum abnormality	Length of follow-up	Outcomes
Yeh et al. [5] Retrospective South Korea	16 cases/24.8 months (average follow-up 10–60 months)	BSID-II; KICDT	Isolated agenesis or hypoplasia of the corpus callosum in 16 (32.7%) patients – other associated CNS abnormalities in 28 (57.1%) patients and non-CNS abnormalities in 11 (22.4%) patients	24 months	4 – lost to follow-up 7 – normal development 5 – development delay (all had language delay, 1 had gross motor delay, 2 had fine motor delay, 4 had personal-social delay, and 3 cognitive delays.) None had moderate-to-severe global delayed development, and 1 had microcephaly
Folliot-le Doussal et al. [1] Retrospective France	25 cases/24 years (average follow-up 8±5 years)	WISC-IV; WPPSI-III; WISC-III; FSIQ; ADHD	Isolated ACC	8±5 years	9 – normal neurodevelopment (6 had cCCA and 3 had pCCA) 13 – mild disabilities (8 with cCCA, 2 with pCCA, and 3 with hCC) 3 – moderate/severe disabilities (3 cCCA)
Des portes et al. [6] Prospective France	34 cases/11 years	WPPSI-III, WPPSI-IV, WISC-IV test; brain MRI PIQ; VIQ; FSIQ	Isolated ACC	7 years	16 – good learning skills 6 – mild learning difficulties 10 – multiple learning disabilities 2 – severe intellectual disabilities
Li et al. [17] Prospective USA	14 cases/6 years (average follow-up 3–5 years)	Neuropediatric and pediatric psychologists follow-up Bayley mental scale (MDI) and motor scale (PDI)	Isolated or non-isolated ACC abnormalities	3 years of age	2 – TOP 5 – additional CNS abnormalities on postnatal imaging or autopsy 8 – normal or mild delays that resolved 1 – mild delays that persisted 3 – moderate to severe delays/abnormalities
Moutard et al. [23] Prospective France	17 cases/10 years	WISC III Dellatolas protocol Pegboard test, Rey-Osterrieth complex Figure Test	Isolated CCA	10 years of age	5 – lost to follow-up 1 – additional anomalies were diagnosed postnatally (fetal alcohol syndrome) 11 – follow-up until the age of 10; no patient present epilepsy, all cases had normal neurological examination, neurodevelopment (FSIQs) was in the normal lower range despite having more difficulties with visual-motor skills and difficulties in perception, analysis, and synthesis of a complex, slow learning; short-term memory was in the normal range No behavioral problems were noted
Mangione et al. [24] Prospective France	88 cases/50 months (average follow-up 30–74 months)	CDI	Isolated ACC additional anomalies were diagnosed postnatally in 15%	5 years	60 – TOP 1 – intrauterine fetal death 1 – excluded late-onset follow-up 14 months 4 – additional anomalies were diagnosed postnatally 22 – followed up: 4 – had neurodevelopmental delay 18 – normal neurodevelopment
Cignini et al. [25] Prospective Italy	17 cases/4 years	Binet-Simon Scale revised from Stanford	Isolated complete ACC	4 years	1 – TOP 1 – lost to follow-up 2 – excluded due to associated abnormalities 12 – regular psychomotor and cognitive development 1 – mild hypotonia, coordination deficit, and mild degree of mental retardation
Ghi et al. [26] Retrospective Italy	6 cases/3–8 years	Standard neurologic examination	Hypoplasia and partial agenesis	3 years	4 – TOP 1 – normal development at 8 years of age 1 – normal development at 3 years of age

CCA, corpus callosum agenesis; cCCA, complete corpus callosum agenesis; CNS, central nervous system; hCC, corpus callosum hypoplasia; pCCA, partial corpus callosum agenesis; TOP, termination of pregnancy; BSID-II, Bayley Scales of Infant Development; KICDT, Korean Infant and Child Development Test; WISC-IV, Wechsler Intelligence Scale for Children IV; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence III; WISC-III, Wechsler Intelligence Scale for Children III; FSIQ, Full-Scale Intelligence Quotient; ADHD, attention deficit hyperactivity disorder; PIQ, performance/visuospatial IQ; VIQ, verbal IQ; MDI, Mental Development Index; PDI, Psychomotor Development Index; CDI, Ireton's Child Development Inventory.

count the degree of ventricle dimension, in contrast with other series. Conversely, they excluded hCC [6].

The study of Li et al. [17] revealed that additional CNS abnormalities missed by the prenatal US exam were detected by postnatal exams in 5 children (35.7%). In this study, among those who survived the neonatal period, neurodevelopmental outcome was normal or showed only mild delays that resolved in 8/12 (67%) children with prenatally diagnosed isolated CCA. Diagnosis of additional CNS abnormalities in association with callosal abnormalities impacted prognosis. They found additional CNS abnormalities in 5 of the 12 surviving children who were thought at the time of prenatal diagnosis to have isolated CCA. However, the patients with prenatal isolated callosal abnormalities in this study showed a worse development outcome than did similar patients in other studies. This is because they included in the group with isolated callosal abnormalities those cases with additional abnormalities found postnatally. This study has some limitations, as it includes ventriculomegaly cases, and cannot exclude the possibility that fetuses with callosal abnormalities without ventriculomegaly might have bet-

ter or worse postnatal outcomes. The statistics of this study showed substantial but not perfect agreement between US and MRI in the prenatal diagnosis of callosal abnormalities [17].

In the study by Moutard et al. [23], all cases had normal neurological examination; neurodevelopment (FSIQs) was in the normal lower range despite having more difficulties with visual-motor skills and difficulties in perception, analysis, and synthesis of a complex and slow learning. Short-term memory was in the normal range. Although no children exhibited mental retardation in this CCA population, the frequency of borderline intelligence was higher in this group (33%) than in the general population (16%). More children in this study had borderline FSIQs at the age of 10, confirming that neuropsychological impairments may emerge as children grow older. However, all the children with borderline IQ were born from mothers with a low socioeducational level, whereas children with normal-to-low IQ levels, except for one, were from mothers with a relatively higher socioeducational level [23].

In the study by Mangione et al. [24], of the 22 children who were followed up, with no additional anomalies, 18 had normal neurodevelopment and 4 had some delay. The study reports on children up to the age of 6 years, whereas some psychopathological or cognitive disorders can only be evaluated later in life [24].

In the study by Cignini et al. [25], a regular psychomotor and cognitive development was present in 12 children (92.3%) with prenatally diagnosed isolated CCA. Among 13 cases of isolated CCA, after a 4-year follow-up period, only 1 child showed a mild deficit of motor coordination, mild hypotonia, and mild degree of mental retardation and 92.8% of the children showed a regular psychomotor development at 4 years of age [25].

The study by Ghi et al. [26] had a high number of termination of pregnancy (66.6%) after diagnosis of isolated CCA. In the 2 cases with isolated pCCA in which the pregnancy was not terminated, neurological outcome of the infants was reported to be normal at follow-up (1 at 3 and 1 at 8 years old). In pCCA or hCC, neurological outcome is reported by some to be similar to that in cases with cCCA, while according to others a worse outcome should be expected for cases with the later due to the greater disruption of neuronal function. In this study, the limited number of surviving infants with isolated underdevelopment of the CC does not allow us to draw any conclusions [26]. In this systematic review, children with prenatally isolated CCA had favorable psychomotor development (normal neurodevelopmental outcome or mild abnormalities) in two-thirds of the cases; however, despite "normal" IQ reported in a majority of patients, the rates of learning disabilities and severe outcome (ranging from 0 to 20%) are not clearly established, and that can occur later beyond school age.

Therefore, a low risk of severe cognitive impairment exists. Neurodevelopmental outcomes in isolated CCA are variable, even between children who share similar neuroanatomic profiles and implicate multiple overlapping pathways in their etiology. The presence of extracallosal brain anomalies is not the only major predictive factor, and probably the underlying neurogenetic cause has a stronger effect on the clinical phenotype and outcome [26].

Conclusion

The limitations of these studies were their inclusion criteria; lack of consensus on the meaning of normal outcome and mild, moderate, and severe disabilities; retrospective and study designs; small number of cases included; paucity of population-based studies; lack of a standardized prenatal and postnatal medical workup protocol; and heterogeneity of psychometric tools adopted. Moreover, the majority of these studies do not take into account the social, cultural, or educational level of the family in the interpretation of outcomes, which could have hampered any detailed cognitive analysis. Furthermore, the relatively short period of follow-up after birth did not allow a precise estimation of the overall rate of additional anomalies detected only after birth and missed prenatally.

Many studies report that fetuses with isolated CCA have a better prognosis than those with additional CNS anomalies, but the actual percentages of normal outcome differ. Many children had subtle speech, attention, and reasoning difficulties that began to appear with increasing age. Of the 4 children with prenatally diagnosed isolated CCA with persistent delays, 2 had an additional CNS finding postnatally of polymicrogyria. This emphasizes the fact that counseling of patients at the time of prenatal diagnosis of ACC needs to be tempered by the fact that additional abnormalities may become apparent later in gestation or postnatally [18].

CCA is one of the most common brain anomalies diagnosed in utero. However, and according to the literature, prenatal counseling is still challenging and quite difficult. For this reason, cognitive outcomes remain a major concern. Although children with prenatal diagnosis of isolated CCA have favorable psychomotor development, they often have mild disabilities including speech disor-

ders at school age and behavior and attention deficit disorders that can emerge at a later stage.

Efforts must be taken for accurate CCA diagnosis (particularly pCCA and hCC), confirmation of its isolated nature (entire fetal anatomy, karyotype, CMA, WES, and NSG/MRI), to enhance information for prospective counseling [22]. New genetic techniques can add precious value in order to confirm the "truly" isolated nature of CCA. Despite high diagnostic yield of WGS/WES, their use in the prenatal setting is currently limited, mostly because of lack of time and financial resources, and another major restraint is the likelihood of unsolicited findings such as variants of unknown significance; unrelated to the phenotype and of late-onset diseases, a significant proportion of syndromes or anomalies may become evident only after birth. These variants can also be found with CMA, but WES presumably retrieves them at a higher rate which results in difficult counseling.

Clinician's experience in imaging interpretation of fetal CNS abnormalities could affect the ability to recognize and appropriately diagnose callosal abnormalities. MRI can also be valuable in postnatal setting, allowing for diagnosis confirmation and the rule out of associated CNS disorders, especially in cases of pCCA or hCC.

Children should undergo a prolonged and strict neurodevelopment follow-up, including beyond school age, in order to early identify disabilities, which can be favorable for supportive therapy. Therefore, at the time of prenatal diagnosis, parents should be counseled that prenatal workup medical protocol does not completely rule out all anomalies.

It seems essential to consider these evidences, aligned with realistic resources as a whole (both human and financial), to make decisions and help with parents' counseling and options. Future studies must be performed using functional neuroimaging techniques, such as high-resolution diffusion tensor imaging tractography, in order to understand this pathology, the fetal brain plasticity, and compensation mechanisms, for a better prospective counseling.

Different methodologies compromise prognosis and outcomes. Consequently, this highlights the need for large prospective studies to be performed as well as a strict and long-term follow-up beyond school age. This is essential to provide early diagnosis and adequate supportive therapy.

The comprehensive approach including a better understanding of imaging (including functional neuroimaging) and genetics may contribute to determining the true nature of isolated CCA and neuropsychological outcome of these children. This will enable understanding about how these factors contribute to cognitive abilities and childhood and adolescence development and competencies, in order to empower parents with better counseling. Indeed, large prospective studies are needed to assess the neurodevelopmental and psychological performance of children with isolated CCA using standardized tools of neurodevelopment assessment at appropriate time intervals to ascertain the actual neuropsychological performance and intellectual impairment.

In conclusion, the wide heterogeneity and limitations of previous studies do not allow extrapolation of objective evidence on the actual burden of neurodevelopmental disabilities affecting fetuses with isolated CCA. Longer assessment periods seem to represent potential aspects to take into account for future studies, as early neuropsychological examination may not accurately predict neurodevelopmental outcomes during later life, while late assessment may be biased by the influence of socioeconomic, parenting, environmental, and educational factors, which may significantly affect the development measures.

Acknowledgement

The authors certify that this material has not been published previously and is not under consideration by another journal. We further certify that all authors have had substantive involvement in the preparation of this manuscript and are fully familiar with its content.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

There was no funding assigned to this work.

Author Contributions

Sara Cunha, Andrea Rodrigues, and Carla Pina were responsible for the conception and drafting of the work. Sara Cunha, Maria Carneiro Maria Miguel Sá, Andrea Rodrigues, and Carla Pina were responsible for the acquisition, analysis, and interpretation of information contained within the manuscript. Carla Pina contributed to the design of the work, to revision, and to approval of the final manuscript. All authors approve the final version to be published and ensure that aspects related to the integrity/accuracy are accomplished.

References

1 Folliot-Le Doussal L, Chadie A, Brasseur-Daudruy M, Verspyck E, Saugier-Veber P, Marret S. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. Early Hum Dev. 2018;116:9–16.

2 Al-Hashim AH, Blaser S, Raybaud C, MacGregor D. Corpus callosum abnormalities: neuroradiological and clinical correlations. Dev Med Child Neurol. 2016;58(5):475–84.

3 Paul LK, Erickson RL, Hartman JA, Brown WS. Learning and memory in individuals with agenesis of the corpus callosum. Neuropsychologia. 2016;86:183–92.

4 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.e1–5.

5 Yeh HR, Park HK, Kim HJ, Ko TS, Won HS, Lee MY, et al. Neurodevelopmental outcomes in children with prenatally diagnosed corpus callosal abnormalities. Brain Dev. 2018;40(8):634–41.

6 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;22(1):82–92.

7 Siffredi V, Spencer-Smith MM, Barrouillet P, Vaessen MJ, Leventer RJ, Anderson V, et al. Neural correlates of working memory in children and adolescents with agenesis of the corpus callosum: an fMRI study. Neuropsychologia. 2017;106:71–82.

8 Palmer EE, Mowat D. Agenesis of the corpus callosum: a clinical approach to diagnosis. Am J Med Genet C Semin Med Genet. 2014;166c(2):184–97.

9 Contro E, Nanni M, Bellussi F, Salsi G, Grisolia G, Sanz-Cortès M, et al. The hippocampal commissure: a new finding at prenatal 3D ultrasound in fetuses with isolated complete agenesis of the corpus callosum. Prenat Diagn. 2015;35(9):919–22.

10 D'Antonio F, Pagani G, Familiari A, Khalil A, Sagies TL, Malinger G, et al. Outcomes associated with isolated agenesis of the corpus callosum: a meta-analysis. Pediatrics. 2016;138(3):e20160445.

11 Leombroni M, Khalil A, Liberati M, D'Antonio F. Fetal midline anomalies: diagnosis and counselling part 1: corpus callosum anomalies. Eur J Paediatr Neurol. 2018;22(6):951–62.

12 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.

13 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.

14 Committee Opinion No. 682. Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016;128(6):e262–e8.

15 Reches A, Hiersch L, Simchoni S, Barel D, Greenberg R, Ben Sira L, et al. Whole-exome sequencing in fetuses with central nervous system abnormalities. J Perinatol. 2018;38(10):1301–8.

16 Lenberg JL, Pretorius DH, Rupe ES, Jones MC, Ramos GA, Andreasen TS. Whole-exome sequencing reveals novel USP9X variant in female fetus with isolated agenesis of the corpus callosum. Clin Case Rep. 2019;7(4):656–60.

17 Li Y, Estroff JA, Khwaja O, Mehta TS, Poussaint TY, Robson CD, et al. Callosal dysgenesis in fetuses with ventriculomegaly: levels of agreement between imaging modalities and postnatal outcome. Ultrasound Obstet Gynecol. 2012;40(5):522–9.

18 Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram'. Ultrasound Obstet Gynecol. 2007;29(1):109–16.

19 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.

20 Paladini D, Quarantelli M, Sglavo G, Pastore G, Cavallaro A, D'Armiento MR, et al. Accuracy of neurosonography and MRI in clinical management of fetuses referred with central nervous system abnormalities. Ultrasound Obstet Gynecol. 2014;44(2):188–96.

21 Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, Jarvis D, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Lancet. 2017;389(10068):538–46.

22 Malinger G, Paladini D, Pilu G, Timor IE. Fetal cerebral magnetic resonance, neurosonography, the multiverse and the brave new world of fetal medicine. Ultrasound Obstet Gynecol. 2017;50(6):679–80.

23 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;32(3):277–83.

24 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.

25 Cignini P, D'Emidio L, Padula F, Girgenti A, Battistoni S, Vigna R, et al. The role of ultrasonography in the diagnosis of fetal isolated complete agenesis of the corpus callosum: a long-term prospective study. J Matern Fetal Neonatal Med. 2010;23(12):1504–9.

26 Ghi T, Carletti A, Contro E, Cera E, Falco P, Tagliavini G, et al. Prenatal diagnosis and outcome of partial agenesis and hypoplasia of the corpus callosum. Ultrasound Obstet Gynecol. 2010;35(1):35–41.