Antenatal diagnosis and outcome of agenesis of corpus callosum: A retrospective review of 33 cases

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Abstract

Objective: To present antenatal sonographic findings and postnatal outcome of a population of foetuses diagnosed with agenesis of corpus callosum.

Material and Methods: The database of our ultrasound laboratory was retrospectively searched for cases of agenesis of the corpus callosum suspected at antenatal sonography between 2002 and 2012. The following variables were assessed: maternal age, gestational age at diagnosis, gender, any additional cerebral and extra-cerebral malformations, results of karyotype analysis and pregnancy and foetal/neonatal outcomes.

Results: During the study period, 33 foetuses with agenesis of the corpus callosum were identified antenatally, with a male preponderance. The mean maternal age was 28.48 years. In all cases, pre/postnatal MRI and/or necropsy were performed in order to confirm the diagnosis. Among those, there were additional brain findings in 23 (69.7%) and additional extra-cerebral anomalies in 3 (9.1%) foetuses. Karyotype analysis was performed in 21 of 33 (63.6%) cases. As for pregnancy outcome, the pregnancy was terminated in 14 (42.4%) of the remaining 19 foetuses; eighteen (54.5%) were delivered near term and one (3.1%) who was delivered prematurely died during the neonatal period.

Conclusion: The diagnosis of congenital brain malformation is a challenging issue, since additional findings have a considerable effect on prognosis; detailed examination with genetic counselling should be performed.

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Key words: Agenesis of corpus callosum, foetal MRI, prenatal diagnosis, ultrasound

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Introduction

The corpus callosum (CC) is the main junction between the two cerebral hemispheres, comprised of approximately 180 million axons, extending from the frontal lobe anteriorly to above the quadrigeminal plate posteriorly (1). Functionally, CC permits not only the information transfer between cerebral hemispheres, but also inhibition of concurrent activity in the contralateral hemisphere (1). From anterior to posterior it has 4 parts, namely the rostrum, genu, body and splenium (1). The anterior portion of the genu forms at the same time as the posterior callosal body, after which the splenium forms, and the last part to develop is the rostrum (1). By the end of the 20th week of gestation, the CC is well established with a shape similar to that of the adult, but with less myelination, reaching adult size by the age of two (1). The prevalence of agenesis of corpus callosum (ACC) varies in different studies, depending on the population studied and the diagnostic criteria, between 0.3% and 0.7% in the general population and 2% and 3% in the developmentally disabled population (2). Sonographic findings of ACC were first described by Comstock et al. (3), divided into direct findings such as the complete or partial absence of CC in the midsagittal plane, and indirect findings, such as colpocephaly, obliteration of the cavum septum pellucidum, elevation and dilatation of the 3rd ventricle and abnormal course of the pericallosal artery (4). Congenital anomalies of CC are commonly associated with other cerebral and extra-cerebral malformations, aneuploidies, genetic syndromes or inborn errors of metabolism, but can also be found in asymptomatic individuals with normal intelligence (5).

By the help of advanced foetal imaging techniques, antenatal diagnosis of complete callosal agenesis is feasible with midtrimester sonography. Beside this, accurate diagnosis of ACC and differentiation between partial and complete forms is still a challenge. Due to the uncertainty of postnatal outcome, giving a prognosis is extremely difficult. Our aim in this study is to report the results of follow-up and perinatal outcomes of cases with ACC between 2002 and 2012.

Material and Methods

Data were collected from our Maternal-Fetal Medicine Unit database. A retrospective database search for ACC was performed and all of the cases with a diagnosis of ACC were selected between 2002 and 2012. The informed consent of

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each participant was taken. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA). For each case, the following variables were assessed: maternal age, gestational age at diagnosis time, foetal gender, additional cerebral and extra-cerebral malformations, karyotype analysis, pregnancy and foetal/neonatal outcome. The diagnoses were confirmed at follow-up by pathology or postnatal neuroimaging with ultrasonography and magnetic resonance imaging (MRI).
Ultrasound investigations were carried out using Siemens Sonoline Antares (Siemens AG, North Rhine-Westphalia, Germany) and Voluson 730 pro (GE Healthcare, Milwaukee, WI, USA).

Results

During the study period, 33 foetuses with ACC were identified antenatally; the general features are given in Table 1. The mean age of the pregnant women was 28.48±5.60 years. The mean gravida was 2.21±1.38 and 39.39% of the patients were primipara. The mean gestational age at initial diagnosis was 24.06±4.50 weeks. Twenty-four of the 33 foetuses (72.7%) were male and 9 (27.3%) were female.
Postnatal sonography and MRI were available in 14 cases (42.4%) and autopsy reports were available in ten of the fourteen cases in which a post-mortem examination had been performed (71.4%).
Among the 33 foetuses with ACC, seven (21.2%) showed isolated ACC. Additional findings were given in Table 1. Following sonographic diagnosis, foetal brain MRI was performed in four cases and confirmed the ultrasound findings in all of them. Additional cerebral findings were encountered in 23 foetuses (69.7%). Additional extra-cerebral anomalies were recognised in three foetuses (9.1%), including cerebro-oculo-fascio-skeletal syndrome, multicystic dysplastic kidney and single umbilical artery with a single kidney.
Eighteen of 33 foetuses had complete ACC (54.5%). Thirteen of these cases had additional cerebral findings (72.2%), 1 had multicystic dysplastic kidney (5.5%) and the remaining 4 were isolated cases of complete ACC (22.3%). Four out of 18 cases had chromosomal abnormalities (22.3%), including mosaic trisomy 8, ring chromosome 14, trisomy 18 and the partial duplication of 6p. All of these chromosomal abnormalities were found in complete ACC cases presenting with additional cerebral findings. Ten out of 18 cases were terminated (55.6%); the remaining 8 were alive in the neonatal period (44.4%).
Fifteen of 33 foetuses had partial ACC (45.5%). Ten of these cases had additional cerebral findings (66.7%), 2 presented with cerebro-oculo-fascio-skeletal syndrome and single umbilical artery with single kidney (13.3%) and the remaining 3 were isolated cases of partial ACC (20.0%). Two out of 15 cases had chromosomal abnormalities (13.3%), one case each of trisomy 21 and trisomy 18. Both of these chromosomal abnormalities were found in partial ACC cases presenting with additional cerebral findings. Four out of 15 cases were terminated (26.6%), 10 were alive in the neonatal period (66.7%) and one (6.7%) who was delivered prematurely at 32 weeks, died during the neonatal period because of necrotising enterocolitis. The details are given in Table 1.
Twelve out of 33 (36.4%) cases did not undergo karyotype analysis due to the late admission in 6 (50.0%), and patient preference in the other 6 (50.0%). Postnatal karyotype analysis was not performed on the basis of the initial postnatal evaluation. Three cases presenting with additional extra-cerebral findings, as mentioned before, had normal karyotype analysis results.

Discussion

Agenesis of corpus callosum is one of the most common central nervous system (CNS) abnormalities diagnosed in the antenatal period (4). ACC can present in different forms, complete or partial, isolated or associated with other cerebral and extra-cerebral abnormalities. In the literature, it has been recommended to evaluate the development of corpus callosum between the 20th and 24th gestational weeks since it is difficult to estimate the presence of callosal abnormalities before the 18th gestational week. In accordance with the literature, we diagnosed ACC with a mean gestational age of 24 weeks.
Vasudevan et al. (1) reported that isolated ACC accounts for approximately 50% of patients diagnosed with ACC. In the other half, various CNS abnormalities were described (1). In our study, we found that 7 out of 33 (21.2%) had isolated ACC. On the other hand, Mangione et al. (6) reported a large series of 175 patients in which CNS abnormalities were found in 50% of isolated ACC cases. It has also been shown that the presence of extra-cerebral abnormalities occurs in about 65% of antenatally diagnosed ACC patients (7). Consistent with the literature, we found that 3 out of 33 cases had extra-cerebral malformations. Since these cerebral and extra-cerebral malformations play a serious role in the prognosis, they should be mentioned during counselling.
It is difficult to estimate the exact prognosis because of the limited data due to the relatively low incidence of this disorder. In the literature, there is great variability among the studies evaluated. Some assessed ACC cases with additional cerebral malformations; while the others assessed ACC cases with extra-cerebral malformations. It is well known that associated cerebral and extra-cerebral abnormalities result in poor prognosis (1). The sonographic finding of ACC should be a guide for the clinician for further assessment of not only the subtle cerebral anomalies but also the additional extra-cerebral abnormalities. It is also known that 5-20% of patients who were thought to have isolated ACC in antenatal imaging were found to have associated anomalies postnatally (6). In this perspective, foetal MRI plays a critical role in detecting them (1). If available, magnetic resonance imaging should be performed since it allows direct visualisation of CC. It can reduce false-positive rates on ultrasound while confirming ACC, and it can assess whether this is complete or partial. Beside these advantages it can also help to detect coexisting brain abnormalities not seen on ultrasound (8). In our study, 5 out of 33 of patients had foetal MRI to confirm the sonographic diagnosis of ACC; overall, 4 out of 5 (80%) had additional cerebral malformations, including hydrocephalus and ventriculomegaly, while one had isolated ACC on foetal MRI.

Table 1. Patient characteristics

ACC Types	Week of diagnosis (week)	Week at birth	Pregnancy outcome	Birth weight	Sex	Karyotype analysis	Additional findings
Complete ACC with additional anomaly	21 w	37 w	Alive	3440 g	female	Normal	Ventriculomegaly
Complete ACC with additional anomaly	17 w	24 w	ToP	840 g	male	Normal	Ventriculomegaly
Complete ACC	18 w	34 w	Alive	2180 g	male	Normal	None
Partial ACC with additional anomaly	26 w	41 w	Alive	3900 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	19 w	20 w	ToP	160 g	female	Abnormal, trisomy 18	Hydrocephalus
Complete ACC with additional anomaly	29 w	37 w	Alive	3000 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	22 w	23 w	ToP	340 g	male	Normal	Multicystic dysplastic kidney
Partial ACC with additional anomaly	26 w	39 w	Alive	2990 g	male	Normal	Ventriculomegaly
Partial ACC with additional anomaly	28 w	38 w	Alive	3200 g	male	Absent	Ventriculomegaly
Partial ACC with additional anomaly	19 w	20 w	ToP	390 g	male	Abnormal, trisomy 21	Dandy-Walker syndrome
Partial ACC with additional anomaly	22 w	23 w	ToP	730 g	male	Abnormal, trisomy 18	Ventriculomegaly
Complete ACC with additional anomaly	32 w	35 w	Alive	2650 g	male	Absent	Hydrocephalus
Partial ACC	29 w	38 w	Alive	2960 g	female	Absent	None
Partial ACC with additional anomaly	26 w	26 w	ToP	780 g	male	Normal	Cerebro-oculo-fascio-skeletal syndrome
Partial ACC with additional anomaly	27 w	40 w	Alive	4140 g	male	Absent	Ventriculomegaly
Complete ACC with additional anomaly	24 w	24 w	ToP	950 g	male	Normal	Hydrocephalus
Complete ACC with additional anomaly	33 w	38 w	Alive	3530 g	male	Absent	Hydrocephalus
Complete ACC with additional anomaly	18 w	21 w	Top	350 g	male	Abnormal, mosaic trisomy 8	Hydrocephalus
Partial ACC	21 w	38 w	Alive	3370 g	male	Absent	None
Complete ACC with additional anomaly	15 w	23 w	ToP	850 g	female	Abnormal, partial duplication of 6 p	Hydrocephalus
Complete ACC with additional anomaly	29 w	29 w	ToP	1230 g	female	Normal	Dandy-Walker syndrome
Partial ACC with additional anomaly	23 w	39 w	Alive	2860 g	male	Normal	Dandy-Walker syndrome
Partial ACC with additional anomaly	22 w	38 w	Alive	3010 g	female	Normal	Ventriculomegaly
Partial ACC with additional anomaly	24 w	24 w	ToP	1100 g	male	Normal	Single umbilical artery with single kidney
Complete ACC with additional anomaly	28 w	34 w	Alive	2400 g	male	Absent	Hydrocephalus
Partial ACC with additional anomaly	23 w	38 w	Alive	3580 g	male	Absent	Absence of splenium
Partial ACC	26 w	37 w	Alive	2810 g	female	Normal	None
Partial ACC with additional anomaly	24 w	32 w	Neonatal Exitus	1840 g	male	Absent	Hydrocephalus
Complete ACC	31 w	37 w	Alive	3130 g	female	Absent	None
Complete ACC	19 w	20 w	ToP	450 g	male	Normal	None
Complete ACC	28 w	37 w	Alive	3070 g	female	Normal	None
Complete ACC with additional anomaly	24 w	26 w	ToP	1140 g	male	Abnormal, ring Ch 14	Inter-hemispheric porencephalic cyst
Complete ACC with additional anomaly	21 w	24 w	ToP	720 g	male	Normal	Porencephaly and schizencephaly

ACC: Agenesis of corpus callosum; w: Week; ToP: Termination of pregnancy; Ch: Chromosome

Moutard et al. (9) reported that during postnatal neuropsychological follow-up, the median intellectual quotient (IQ) was within the normal range, regardless of whether ACC is complete or partial. Since distinguishing these two by foetal ultrasonography is difficult, the clinician should pay more attention to associated cerebral and extra-cerebral anomalies.

In conclusion, the diagnosis of a congenital brain malformation creates great anxiety among the parents. In our clinical practice, since findings of additional cerebral and extra-cerebral abnormalities have a considerable effect on prognosis, we performed detailed examination with genetic counselling. Although a male preponderance was observed in our study, a gender-based research protocol is not advisable. In isolated cases of ACC, long-term neurodevelopmental outcome is expected to be normal in approximately 75% of cases, meaning that continuation of pregnancy can be preferred (5). On the other hand, if the case is not an isolated one, to the best of our knowledge, termination should be offered because of poor neurodevelopmental prognosis. For an exact diagnosis, the evaluation of CC should be postponed until after 20 weeks of gestation and foetal MRI should be offered in cases of uncertainty about termination versus continuation of pregnancy. In continuing pregnancies, delivery should be performed in multidisciplinary centres for the benefit of the infant.

Ethics Committee Approval: *Ethics committee approval was not obtained because this study was designed as a retrospective case series study.*

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