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Diagnostic Profile of Corpus Callosum Anomalies at a Tertiary Center: A Retrospective Cross-sectional Study

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ABSTRACT Objective: This study aimed to define the frequency and type of additional accompanying anomalies in cases with various anomalies of the corpus callosum (ACCs) in our tertiary center in the last 8 years. **Material and Methods:** This retrospective cross-sectional study included the data of 152 cases of prenatally diagnosed ACCs in a tertiary referral center between October 2012 and November 2020. We evaluated central nervous system and other organ system structural abnormalities, chromosomal abnormalities, and syndromes accompanying in non-isolated forms. **Results:** During the study period, a total of 152 cases with callosal anomaly were diagnosed throughout the study course in a population of 117,450 live births, resulting in an overall prevalence of 12.9 per 10,000 live births. Of the 152 cases ascertained, 105 (69%) were total agenesis, 38 (25%) were partial agenesis, and 9 (6%) were hypoplasia of the corpus callosum. Of these 152 cases, 80 (52.6%) had isolated ACC and the remaining 72 (47.4%) cases had at least one associated anomaly, including chromosomal anomalies, recognized syndromes, and multiple congenital abnormalities. **Conclusion:** ACCs are clinically and etiologically heterogeneous, and prenatal diagnosis is possible. Even in isolated cases, the neurodevelopmental prognosis is uncertain and mostly associated with other structural abnormalities, chromosomal and genetic diseases. Due to the underlying etiological cause, accompanying additional anomalies and uncertainty regarding developmental outcomes, chromosomal, syndromic, and additional structural disorders may be clues in antenatal ultrasonographic observation in ACC cases should be investigated with the more detailed sonographic examination and genetic tests.

Keywords: Central nervous system; corpus callosum; ultrasonography; prenatal

The corpus callosum (CC) is the largest connective structure located in the midline of the brain. It plays an important role in the integration and exchange of information between both brain hemispheres. It transfers motor, sensory and cognitive information between the two hemispheres.[1] Anomalies of the CC (ACCs) occur when midline fibers do not develop or cannot cross the midline.[2,3] Callosal abnormalities have been described in various congenital metabolic diseases, chromosomal abnormalities, and syndromes.[2-5] Probable CC abnormalities include complete or partial agenesis, an increased (hyperplasia) or reduced thickness (hypoplasia), or an abnormal configuration (dysgenesis/dysplasia).[6]

The exact incidence of agenesis of CC is difficult to estimate because the reported data usually include case series from tertiary referral centers.[7,8] Also, the prevalence could be underestimated frequently due to a large proportion of asymptomatic cases eluded detection. Emerging studies reported that the combined prevalence of agenesis of the CC or hypoplasia of the CC (HCC) was 1.4-1.8 per 10,000 live births.[9,10]

All CC abnormalities can be isolated without additional anomalies or may occur together with other cerebral or extracerebral congenital defects.[11-13] The reported prevalence of associated anomalies accompanying ACC in different studies varies widely be-

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tween 39.6% and 86.5%.[9,14] Studies have limited data on the relationship of ACC with specific types of other congenital defects and which organ systems are most affected by associated anomalies, and the results of studies are inconsistent.

This study aimed to define the frequency and type of additional accompanying anomalies in cases with various ACCs in our tertiary center in the last 8 years.

MATERIAL AND METHODS

This retrospective cross-sectional study included the data of 152 cases of prenatally diagnosed ACCs in Kanuni Sultan Süleyman Training and Research Hospital, which was a tertiary referral center in Turkey, between October 2012 and November 2020. Ethical approval was obtained from the Ethics Committee of Kanuni Sultan Süleyman Training and Research Hospital for the study (date: 15.05.2020, no: 2020.05.10). The study was performed in accordance with the Helsinki Declaration.

We included all cases with callosal anomalies diagnosed at the routine second-trimester ultrasound (US) scan in our hospital or referred from other hospitals to our perinatology unit. The ACCs were classified as complete agenesis (total absence of all the structurally defined zones of the CC), partial agenesis (absence of at least one zone of the CC, a small residual always existing), and HCC (a smaller and thinner CC than expected for a gestational week with a normal anterior-posterior extent).[15] The non-structural abnormalities associated with corpus callosum, including intracranial hemorrhage, hypoxic-ischemic encephalopathy-related findings, and US signs suggestive of congenital infections, were excluded.

We obtained the data concerning medical records and prenatal US results from the hospital database system. All ultrasonographic fetal cranial examinations were conducted by expert sonographers with advanced training in prenatal diagnosis, transabdominally and also transvaginally when the fetus is in cephalic presentation, using high-resolution ultrasound devices (Voluson 730 Expert and/or Voluson E6, GE Medical Systems, Milwaukee, Wisconsin, USA) with a convex probe (3.5-5 MHz for transabdominal examinations, 5-6.5 MHz for transvaginal examinations). The central nervous system (CNS) was examined with detailed neurosonography following the International Society of Ultrasound in Obstetrics and Gynecology practice guidelines.[16] We obtained the axial, sagittal, and coronal views of the fetal brain in all cases. Also, entire fetal anatomy was evaluated to determine any associated cerebral and extracerebral malformations.

We conducted the direct visualization of the CC in midsagittal views. In the case of complete agenesis of the CC, indirect characteristics are frequently present in the axial plane. These indirect findings were colpocephaly, increased lateral separation of the frontal horns, ventriculomegaly, the absence of cavum septum pellucidum (CSP), and elevation of the 3rd ventricle.[6,7] Previous definition of Malinger et al. was used for the diagnosis of partial agenesis of the CC and HCC.[17] Fetal cranial magnetic resonance imaging (MRI) was recommended in ongoing pregnancies after 24 weeks of gestation or in fetuses with complicated brain pathology to investigate for associated anomalies not identifiable by US examination. In fetuses where fetal intrauterine growth restriction (IUGR) was suspected, we performed a Doppler US exam of the fetal umbilical arteries.[18] Chromosomal analysis was recommended to all patients, but chromosomal microarray tests were not available in our hospital setting during the study period. Isolated ACC was defined when there were no other anomalies accompanying ACC. Non-isolated ACC was defined as the presence of additional cerebral malformations (other than the indirect features of ACC), extracerebral anomalies, chromosomal abnormalities, and syndromes.[6]

STATISTICAL ANALYSIS

IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical analysis of our research data. A descriptive analysis of the records was performed following the completion of the audit. We presented the categorical variables as frequencies and percentages.

RESULTS

During the study period, 9,517 pregnant women underwent a mid-trimester US scan. A total of 152 cases

with callosal anomaly were diagnosed throughout the study course in a population of 120,829 deliveries and 117,450 live births, resulting in an overall prevalence of 12.6 per 10,000 deliveries and 12.9 per 10,000 live births. The mean age of the mothers was 27.17±3.71 years.

Of the 152 cases ascertained, 105 (69%) were total agenesis, 38 (25%) were partial agenesis, and 9 (6%) were HCC. Of these 152 cases, 80 (52.6%) had isolated ACC and the remaining 72 (47.4%) cases had at least one associated anomaly, including chromosomal anomalies, recognized syndromes, and multiple congenital abnormalities (Table 1, Table 2).

A total of 37 (24.3%) pregnant women underwent fetal cranial MRI. Of these, 27 had fetuses with isolated callosal anomaly and 10 had fetuses with non-isolated ACC. The termination rate in our study cohort was 23.0%. Also, 22.5% of pregnancies with isolated ACC and 23.6% of pregnancies with non-isolated ACC underwent pregnancy termination. Five

TABLE 1: Isolated and associated anomalies in 152 cases with callosal anomalies.

	n	%
Non-isolated callosal anomalies	72	47.4
Recognized syndromes, spectra	5	3.3
Chromosomal abnormalities	6	4
Multiple congenital anomalies	61	40.1
Isolated callosal anomalies	80	52.6
Total	152	100

TABLE 2: Recognizable and unrecognizable anomalies in 72 cases with non-isolated abnormalities of the corpus callosum.

	Total (n)	%
Recognized situations		
Chromosomal abnormalities	6	8.3
Trisomy 18 (n=2, 33.3%), Trisomy 13 (n=2, 33.3%), Trisomy 21 (n=1, 16.7%), others (n=1, 16.7%)		
Nonchromosomal abnormalities	5	6.9
Dandy Walker malformation (n=3, 60.0%), Fetal akinesia deformation sequence (n=2, 40.0%)		
Unrecognized situations		
Central nervous system	51	70.8
Arachnoid cyst (n=3, 5.9%), Cerebellar hypoplasia (n=9, 17.6%), Interhemispheric cyst (n=13, 25.5%), Hydrocephalus (n=8, 15.7%), Microcephaly (n=5, 9.8%), Lissencephaly (n=3, 5.9%), Hemimegalencephaly (n=1, 1.9%), Encephalocele (n=1, 1.9%), Polymicrogyria (n=1, 1.9%), others (n=7, 13.7%)		
Congenital heart defects	32	44.4
Ventricular septal defect (n=13, 40.6%), Aortic coarctation (n=4, 12.5%), Tetralogy of fallot (n=1, 3.1%), Transposition of the great arteries) (n=1, 3.1%), Atrioventricular septal defect (n=3, 9.4%), Double outlet right ventricle (n: 3, 9.4%), others (n=7, 21.9%)		
Musculoskeletal system	16	22.2
Pes equinovarus (n=7, 43.8%), Polydactyly (n=1, 6.2%), Limb reduction defect (n=2, 12.5%), others (n=6, 37.5%)		
Facial	10	13.8
Cleft lip and palate (n=5, 50.0%), others (n=5, 50.0%)		
Urinary system	6	8.3
Multicystic kidney (n=3, 50.0%), Horseshoe kidney (n=1, 16.7%), Double collector system (n=1, 16.7%), others (n=1, 16.7%)		
Eye	5	6.9
Microophthalmitis (n=2, 40.0%), Hypotelorism (n=1, 20.0%), Hypertelorism (n=1, 20.0%), Cataract (n=1, 20.0%)		
Abdominal wall	5	6.9
Omphalocele (n=5, 100.0%)		
Genital system	2	2.7
Ambigious genitalia (n=2, 100.0%)		
Respiratory system	2	2.7
Hydrothorax (n=2, 100.0%)	2	2.7
Diaphragmatic hernia	2	2.7
Total	131	

pregnant women experienced in utero fetal demise in our study cohort (Figure 1).

The prevalence of chromosomal abnormalities was 8.3% (n=6) in the cases with non-isolated ACC. Of these, two had trisomy 18, two had trisomy 13, one had trisomy 21, and one had 22q11 deletion. Three cases had Dandy-Walker syndrome and two cases had fetal akinesia syndrome. All these syndromes were clinical diagnoses. There was a single associated malformation in 39 cases, two malformations in 15 cases, and three or more associated malformations in 18 cases. CNS anomalies (n=51, 70.8%), cardiovascular system (CVS) anomalies (n=32, 44.4%), musculoskeletal system anomalies (n=16, 22.2%), facial anomalies (n=10, 13.8%) were the most common accompanying anomalies, respectively. The most common associated CNS anomalies were interhemispheric cyst (n=13, 25.5%), cerebellar hypoplasia (n=9, 17.6%) and hydrocephalus (n=8, 15.7%), respectively. The most common associated CVS anomalies were ventricular septal defect (n=13, 40.6%) and aortic coarctation (n=4, 12.5%), respectively. Accompanying anomalies in each organ system are shown in Table 2.

DISCUSSION

The accurate prevalence of ACCs varies depending on the studied population. While its prevalence is 1.8 per 1000 births in the general population, it increases up to 3% among children with developmental disabilities.[9,19] In this study, the prevalence of ACCs was 1.29 per 1,000 births.

Callosal anomalies may develop in isolation or in association with other CNS anomalies or systemic malformations (ranging from 39.6% to 86.5%).[9,14] Non-isolated forms could be a feature of a more complex syndrome and lead to neurodevelopmental delay and neurologic symptoms.[20] The common causes of callosal anomalies include single-gene disorders, known syndromes, chromosomal abnormalities, teratogens, and unknown causes. In the existence of additional congenital anomalies, the prognosis depends primarily on these malformations and whether they cause psychomotor and mental retardation.[1] The improvement in US technologies led to the identification of a growing number of isolated ACC cases. However, previous studies reported a wide range of outcomes in isolated agenesis of CC cases, from totally healthy (85%) to severely impaired neurodevelopment, behavioral disorders, or seizures.[20-22] Therefore, the counseling for isolated cases is challenging due to the uncertainty in the prognosis. Isapof et al. reported that most of the parents choose to refuse (79.6%) pregnancy termination related to the high possibility of a good prognosis when isolated ACC was detected in their fetuses.[23] Despite this, Rouleau reported that ACC was the most common

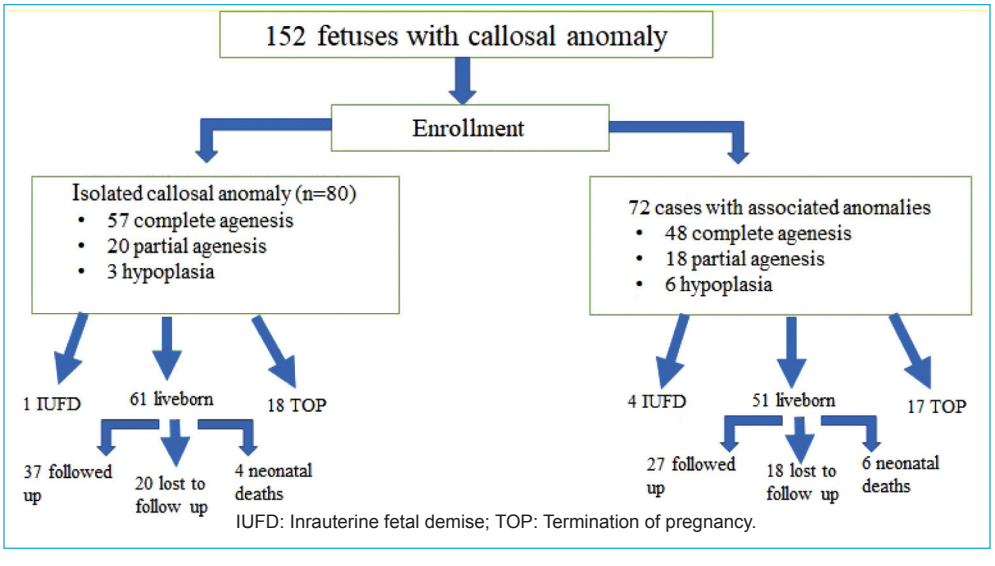

FIGURE 1: Flow chart of the study.

cause for pregnancy termination among CNS-related malformations after 24 weeks of pregnancy.[24] Fratelli et al. reported that 79% of parents elected pregnancy termination due to callosal anomalies, and in the non-isolated group, this rate was 89%.[25] Ballardini et al. found a 41.2% of pregnancy termination rate.[10] In our study, 47.4% (n=72) of the cases had associated anomalies. The termination rate in our study cohort was 23.0%. Also, 22.5% of pregnancies with isolated ACC and 23.6% of pregnancies with non-isolated ACC underwent pregnancy termination. We consider that the lower rate of pregnancy termination might be related to the socio-cultural and religious factors of the parents.

Chromosomal anomalies were reported to be present in the range from 2.6% to 40% in ACC cases.[14,26] In this study, chromosomal anomalies were detected in 6 cases (8.3%) with non-isolated callosal anomalies. Consistent with the literature, trisomy 18 and trisomy 13 were the most common chromosomal anomalies in our cases with available karyotype.[26,27] de Wit et al. stated that in fetuses with isolated complete ACC on US examination and without causal abnormalities on single nucleotide polymorphism (SNP) array, MRI and physical evaluation of the infant exposed additional physical abnormalities. They concluded that microarray should be recommended in cases of isolated ACC on US scan.[28] It was indicated that 3.1-7.9% of fetuses with a normal karyotype and a structural US anomaly in one system will demonstrate submicroscopic genetic copy number variants, which presents data for the prognosis of the fetus.[29] However, chromosomal microarray tests were not available in our hospital setting during the study period.

Previous studies reported that associated CNS anomalies were the most common other anomalies in the cases with callosal anomalies with a range between 17.4-52.6%.[26,27] Likewise, in our study, the prevalence of associated fetal cerebral anomalies was 34.4% in cases with ACCs, and 70.8% among fetuses with non-isolated callosal anomalies. Also, interhemispheric cysts were the most common associated cerebral malformation among cases in our study. Bedeschi et al. found that 38.1% of the patients with ACC manifested other CNS malformations. They demonstrated that partial agenesis of the CC was frequently associated with posterior fossa malformations and complete agenesis was mostly correlated with malformations of the cortical development.[30] Sotiriadis et al. indicated that abnormalities of migration, sulcation, and gyration such as nodular heterotopia and pachygyria would be potentially undiagnosable by the US and these cases tended to have a much worse prognosis than correctly isolated cases.[20] Thus, prenatal counseling should consider that there is about a 20% risk of false-negative diagnosis for fetuses with isolated CC anomalies in the US.[6]

Among the numerous organ system anomalies stated in previous studies in fetuses with callosal anomalies with associated malformations, there were significant variances in the case series. Likewise our study, previous studies reported that anomalies in the cardiovascular, musculoskeletal, and urogenital systems were the most common additional anomalies after CNS malformations in the fetuses with ACC.[27,30,31] Ballardini et al. stated that given the doubtful neurological prognosis, pregnancy termination may be elected especially when a callosal anomaly is associated with additional malformations.[10] Also, associated anomalies may lead to an earlier diagnosis or earlier diagnosis may permit the election of pregnancy termination.[10]

The main strength of this study is that a well-identified group of patients in which all pregnant women were examined by expert sonographers with advanced training in prenatal diagnosis in a well-organized tertiary center. However, there are some limitations to this study. This study has been designed retrospectively and has the potential to contain limitations of such studies. Since our hospital is a tertiary referral center, a preadmission selection bias may exist. The other limitation is the relatively low sample size and the lack of long-term follow-up data on the survived infants with callosal anomalies.

CONCLUSION

Prenatal diagnosis of ACCs is possible with expert sonographers. They are mostly associated with other structural abnormalities, chromosomal and genetic diseases. The actual prevalence of ACC and the pres-

ence of additional accompanying anomalies may vary depending on both the difference in diagnostic methods and the population studied. Also, the number of cases overlooked in routine prenatal follow-up is unknown. ACC is clinically and etiologically heterogeneous. Neurodevelopmental prognosis is uncertain even in isolated cases. Care should be taken in anticipating developmental expectations. In the literature series, there are significant differences among organ system malformations accompanying ACC cases. Due to the underlying etiological cause, accompanying additional anomalies and uncertainty regarding developmental outcomes, chromosomal, syndromic, and additional structural disorders that may be clues in antenatal ultrasonographic observation in ACC cases should be investigated with a more detailed sonographic examination and genetic tests.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zeynep Gedik Özköse, Süleyman Cemil Oğlak, Mustafa Behram, İsmail Özdemir;* ***Design:*** *Zeynep Gedik Özköse, Süleyman Cemil Oğlak, Fatma Ölmez, İsmail Özdemir;* ***Control/Supervision:*** *Zeynep Gedik Özköse, Ayşegül Bestel, Sema Süzen Çaypınar, İsmail Özdemir;* ***Data Collection and/or Processing:*** *Zeynep Gedik Özköse, Mustafa Behram, Ayşegül Bestel;* ***Analysis and/or Interpretation:*** *Zeynep Gedik Özköse, Fatma Ölmez, Sema Süzen Çaypınar, İsmail Özdemir;* ***Literature Review:*** *Zeynep Gedik Özköse, Süleyman Cemil Oğlak;* ***Writing the Article:*** *Zeynep Gedik Özköse, Süleyman Cemil Oğlak;* ***Critical Review:*** *Zeynep Gedik Özköse, Süleyman Cemil Oğlak, Ayşegül Bestel;* ***References and Fundings:*** *Zeynep Gedik Özköse, Sema Süzen Çaypınar.*

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