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# Children with corpus callosum anomalies: clinical characteristics and developmental outcomes

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## Abstract

**Introduction.** Corpus callosum abnormalities are complex, aetiologically diverse, and clinically heterogeneous conditions. Counselling parents regarding their causes and associated syndromes, and predicting the neurodevelopmental and seizure risk prognosis, is challenging.

**Material and methods.** We describe the clinical characteristics, associated anomalies, and neurodevelopmental outcomes of children with agenesis of corpus callosum (ACC). Fifty-one neonates with ACC/hypoplasia of the corpus callosum were identified over a 17-year period, and their medical records were retrospectively reviewed.

**Results.** Patients were classified into two groups depending on the presence or absence of associated abnormalities. The first group (17 patients, 33.4%) presented with isolated callosal anomalies. The second group included 34 patients (66.6%) with associated cerebral and extracerebral anomalies. We achieved an identifiable genetic aetiology in 23.5% of our cohort. Magnetic resonance imaging was performed in 28 patients (55%), and of these 39.3% had additional brain anomalies. During the study period, five patients died early in the neonatal period and four were lost to follow up. Of the 42 followed patients, 13 (31%) showed normal neurodevelopment, 13 (31%) showed mild delay, and 16 (38%) had a severe delay. Fifteen (35.7%) had epilepsy.

**Conclusions and clinical implications.** We have confirmed that callosal defects are frequently accompanied by brain and somatic anomalies. Additional abnormalities were shown to be significantly associated with developmental delay and increased risk of epilepsy.

We have highlighted essential clinical features that may provide diagnostic clues to physicians and we have given examples of underlying genetic disorders. We have provided recommendations about extended neuroimaging diagnostics and widespread genetic testing that may impact upon daily clinical practice. Paediatric neurologists may therefore use our findings to help base their decisions regarding this matter.

**Key words:** agenesis of corpus callosum, developmental delay, somatic anomalies, brain malformation, genetic anomalies

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## Introduction

The corpus callosum (CC) is the largest connective structure of the brain, joining the two cerebral hemispheres [1, 2].

Development of the ACC comprises variable mechanisms of neurogenesis and neuronal migration in which multiple genes are involved. Agenesis of the corpus callosum (ACC) can result from disruption of its formation at numerous developmental stages, leading to a total or partial absence of the CC, when one of its components (rostrum, genu, body, isthmus, or splenium) is missing. It may also present as hypoplasia of the CC (HCC), when the CC is fully formed, but thinner. ACC can

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occur as an isolated condition, or in association with various brain and extracranial malformations, as well as with a broad range of genetic disorders [3–8].

ACC can result from antenatal infections, vascular or toxic factors. Foetal alcohol spectrum disorders (FASD) and inborn errors of metabolism are also considered as causes of ACC [6, 8–10]. The reported prevalence of callosal anomalies ranges between 1.47–2.05 per 10,000 live births to 2.49 per 10,000 births [10–13].

Prenatal diagnosis of ACC is possible on the mid-trimester ultrasound, when there is a failure in visualisation of CC in mid-sagittal plan [14–16]. Callosal anomalies can also be detected based on the presence of indirect ultrasound signs, such as the absence of the cavum septi pellucidi (CSP), colpocephaly (dilatation of the occipital horns of the lateral ventricles), increased separation of the hemispheres, abnormally elevated third ventricle, and lack of pericallosal arteries [15, 17].

The clinical course of ACC varies remarkably widely, ranging from asymptomatic cases to severe developmental delays. A lack of CC affects intelligence and behaviour, leading to motor and intellectual disability, epilepsy, and social and language deficits [3, 6, 18]. Parental counselling as to its causes and associated syndromes, and predicting the prognosis for neurodevelopment and seizures is difficult. Asymptomatic neonates without an antenatal diagnosis of ACC can be discharged without a congenital callosal defect being recognised. Thus, early diagnosis and prediction of long-term complications can help towards earlier intervention and better outcomes.

### Objective

The clinical and diagnostic features of a group of children with CC anomalies born in a single tertiary perinatal care centre were analysed to show the possible diagnostic difficulties encountered in paediatric practice. Isolated and non-isolated cases were compared to show the impact of extracallosal abnormalities on long-term outcomes. We focused on the key steps in the diagnosis, assessment, investigation, and management of neonates and children presenting with ACC. We wanted to highlight any essential clinical features that could provide diagnostic clues to physicians.

## Materials and methods

This study was conducted at the Department of Neonatology of the University Clinical Centre in Gdansk associated with the Medical University of Gdansk, Poland.

We evaluated prenatal findings and postnatal outcomes of neonates who presented with a congenital anomaly diagnosis during hospitalisation in our centre from 1 January, 2001 to 31 December, 2017.

Fifty-seven neonates demonstrating CC anomalies were found during this 17-year study period. Of these, we eliminated six infants in whom the CC was missing due to the presence of severe destructive central nervous system (CNS) lesions (two cases of holoprosencephaly, two neonates with bilateral schizencephaly, one with schizencephaly and hemisphere atrophy, and one with hemisphere atrophy coexisting with hypoplasia of the CC after intracranial haemorrhage following prematurity).

This left a total of 51 cases with callosal anomalies included in the study. Of these, 43 (84.3%) underwent postnatal head ultrasound following prenatal suspicion of congenital defects, including callosal anomalies and other brain or organ defects. The remaining eight (15.7%) cases underwent ultrasound due to prematurity (one case), intrauterine growth restriction (one case), the presence of dysmorphic features (four cases), being a neonate of a diabetic mother (one case), and coexisting prematurity, dysmorphic features and other anomalies, namely congenital heart defect and cleft lip and palate (one case).

Children with anomalies of the CC were initially identified during their stay in the Neonatal Department. The following data was assessed: gestational age (GA) at birth, birth weight (BW), gender, prenatal and postnatal diagnoses, brain magnetic resonance imaging (MRI) if carried out, genetic test results (if available), and the presence of additional cerebral and extracerebral malformations. Mothers were asked to complete a questionnaire regarding pregnancy course, parity, comorbidities and place of residence. Prenatal diagnoses were also taken into consideration. After assigning an identification number and anonymisation, data was transferred to the hospital database. Written informed consent was obtained from parents or authorised representatives of all the subjects included in this study. Informed consent to collect subsequent patient observations and patient information to be published was also provided. Clinical records of the selected patients were retrospectively reviewed for additional examinations (e.g. brain neuroimaging, genetic tests), developmental course, and neurological status by researching the hospital database.

Patients showing callosal anomalies were classified into two groups depending on the presence or absence of accompanying anomalies.

### Group 1

Isolated callosal anomalies; no other malformations identified. Patients with an interhemispheric cyst, a lipoma, or colpocephaly were included in this group, as we considered these findings to be a part of callosal anomalies [1, 2, 7, 11, 12].

### Group 2

Callosal anomalies associated with both CNS and other organ anomalies, including genetic disorders.

The main characteristics and developmental outcomes of each group were compared.

The extent of the defects in each baby was defined based on head ultrasound; MRI was performed in 28 patients (55% of the 51 studied). In cases of neonatal death, post mortem reports were available. Callosal defects were classified as

either agenesis of the CC, complete — ACC, or agenesis of the ACC, partial — pACC, or HCC, according to the description provided by the radiologist or pathologist. The assessment of neurological development was conducted by paediatricians or paediatric neurologists during hospitalisations or follow-up visits. The patient's age at the time of the last examination was taken into consideration. We relied on clinical descriptions of neurological conditions from children's medical records, as this was a retrospective study. The phrase "children with motor delay" is a description of patients who were not diagnosed with an intellectual disability, but who did show delayed motor milestones. Intellectual disability, social problems, and speech delay were defined by hospital psychologists without providing the type of tools used for the diagnosis.

### Statistical analysis

Data was analyzed using Statistica 13.3 software (TIBCO, Palo Alto, CA, USA). Descriptive statistics were calculated separately for groups of patients with callosal defects. Analysis of variance (ANOVA) and Chi-square test were used to compare data between groups of children with ACC depending on the ACC pattern. Contrast analysis and Fisher's LSD test were used to evaluate the differences between these groups. A P-value < < 0.05 was considered statistically significant.

### Ethical approval

This study is consistent with the Helsinki Declaration, and was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk, Poland, approval number NKBBN/65/2014.

## Results

Over the study period, 36,145 neonates were born at our centre. Congenital malformations were identified in 1,163 (3.2%) infants. CNS anomalies were found in 217 cases (18.7% of all inborn defects and 0.6% of the general population). Of them, 51 infants had ACC/HCC diagnosed, resulting in a prevalence of 14.1 per 10,000 births.

In patients with ACC, the mean GA at birth was 37.1 weeks (range 24–41) and the mean BW was 2,891.4 g (range 600––4,730). Newborns with an isolated ACC/HCC had a significantly higher BW (3,433.8 g) than those presenting with additional somatic and CNS defects (2,614.0 g, p = 0.027). Similarly, they had a significantly higher GA at birth (38.6 weeks), than the remaining patients (36.3 weeks, p = 0.018). There were 30 (58.8%) males and 21 (41.2%) females. Twenty-eight (55%) neonates had complete ACC, 14 (27.4%) had pACC, and nine (17.6%) had HCC.

A prenatal diagnosis was made in 11 (21.5%) foetuses. Mean GA at diagnosis was 25 weeks (range 21–30). Finding one of the indirect signs of failed commissuration was strongly associated with a prenatal diagnosis of ACC (Table 1). Ventriculomegaly (VM) was found in five (45.5%) of 11 foetuses with a correct diagnosis of ACC and in 33 (82.5%) of 40 cases without antenatal diagnosis (p = 0.102). There were 40 (78.5%) cases in which CC anomalies were not suspected during pregnancy despite other abnormalities being diagnosed. In this group, the most common abnormality was hydrocephalus in 17 foetuses, VM in seven, Dandy Walker Syndrome in four, cardiac defects in three (Hypoplastic Left Heart Syndrome, Ebstein anomaly, dextrocardia), chromosomal aberration in one, and arm and leg deformations in two foetuses.

**Table 1.** Correlation between presence of indirect symptoms and prenatal diagnosis of agenesis of corpus callosum

| Prenatal diagnosis of colpocephaly | Prenatal diagnosis of ACC | | |
|---|---|---|---|
| | Not diagnosed (%) | Diagnosed (%) | Row (%) |
| Not diagnosed | 38 (95.0) | 5 (45.5) | 43 |
| Diagnosed | 2 (5.0) | 6 (54.5) | 8 |
| Totals | 40 (100.0) | 11 | 51 |
| p = 0.00059 | | | |
| **Prenatal finding of interhemispheric cyst or widening of interhemispheric fissure** | **Prenatal diagnosis of ACC** | | |
| | **Not diagnosed (%)** | **Diagnosed (%)** | **Row (%)** |
| Not diagnosed | 39 (97.5) | 8 (72.7) | 47 |
| Diagnosed | 1 (2.5) | 3 (27.3) | 4 |
| Totals | 40 (100) | 11 (100) | 51 |
| p = 0.028 | | | |
| **Non-visualisation of cavum septi pellucidi** | **Prenatal diagnosis of ACC** | | |
| | **Not diagnosed (%)** | **Diagnosed (%)** | **Row (%)** |
| Not diagnosed | 40 (100) | 7 (63.6) | 47 |
| Diagnosed | 0 | 4 (36.4) | 4 |
| Totals | 40 (100) | 11 (100) | 51 |
| p = 0.00132 | | | |

ACC — agenesis of corpus callosum

In total, 29 (57%) neonates were born by caesarean delivery (CD) and 22 (43%) by vaginal delivery (VD). Newborns with a prenatal diagnosis of CNS anomalies were more likely to be born by CD, either planned or emergency (p = 0.060). Prenatal diagnosis of ACC did not affect the plan of delivery (Tab. 2).

There was no difference in the level of care received by neonates born by CD and VD (p = 0.466). Six (20.7%) neonates born by CD and five (22.7%) born by VD received normal neonatal care, and 18 (62.0%) born by CD and 13 (59.1%) by VD required special care in the Neonatal Intermediate Care Unit. Five (13.7%) born by CD and two (9.1%) born by VD required admission to the Neonatal Intensive Care Unit, and two (9.1%) born by VD received palliative care.

**Table 2.** Impact of prenatal diagnosis on mode of delivery

| | Mode of delivery | | | Row n (%) | p-value |
|---|---|---|---|---|---|
| | Elective CD n (%) | Emergency CD n (%) | VD n (%) | | |
| Prenatally diagnosed ACC | 4 (36.5) | 2 (18.0) | 5 (45.5) | 11 (100) | 0.525 |
| Prenatally diagnosed CNS anomalies | 14 (52.0) | 4 (15.0) | 9 (33.0) | 27 (100) | 0.060 |
| Prenatally diagnosed other organ anomalies | 1 (20.0) | 2 (40.0) | 2 (40.0) | 5 (100) | 0.817 |
| Cases without prenatal diagnosis | 1 (12.5) | 1 (12.5) | 6 (75.0%) | 8 (100) | 0.042 |
| | 20 (39.2) | 9 (17.8) | 22 (43.0) | 51 (100) | |

ACC — agenesis of corpus callosum; CD — caesarean delivery; CNS — central nervous system; VD — vaginal delivery

Patients were classified into two groups on the basis of accompanying anomalies. Group 1 included 17 (33.4%) patients who presented with isolated callosal anomalies. In one child, a congenital cytomegalovirus infection was diagnosed postnatally; this baby died at the age of one year. Three cases were lost to follow-up. The characteristics of this group are set out in Table 3.

Group 2 comprised 34 (66.6%) patients who presented with CC anomalies associated with extracallosal CNS anomalies and/or other organ anomalies or genetic syndromes. The characteristics of this group are set out in Tables 4–6. The most frequent extracallosal brain anomalies were agenesis of the septum pellucidum (9/51; 17.6%) and hydrocephalus (8/51; 15.6%).

Of the 28 (55%) patients who underwent MRI, 11 (39.3%) had additional brain abnormalities, including cortical malformations (seven cases), and septo-optic dysplasia, Chiari syndrome, lack of other cerebral commissures, and stenosis of aqueduct of Sylvius (one case each, see Tab. 4–6).

Genetic testing was conducted in 43% (22/51) of cases, including karyotype analysis, fluorescence in situ hybridisation, and array comparative genomic hybridisation (aCGH). Two of our patients were screened for FRAS1 and EPG5 mutations. An underlying diagnosis was found in 12 of the 51 patients (23.5%). Chromosomal disorders were confirmed in seven patients (13.7%), with one case each of mosaic trisomy chromosome 8, sex chromosome aneuploidy (47, XYY), trisomy 13/trisomy 18 mosaicism, 22q11.2 deletion syndrome, 5p deletion syndrome, and Vici syndrome. The last of these newborns had a disorder of sex development, in which the female phenotype did not correspond to the genetic sex (46, XY). In five (9.8%) cases, the genetic analysis did not reveal any abnormalities, although specific dysmorphic features were present. The following genetic syndromes were recognised: Fraser syndrome (one case), Smith-Lemli-Opitz syndrome (one case), Rubinstein-Taybi syndrome (one case), and Apert syndrome (two cases). The main features of these patients are set out in Table 6. In eight (15.6%) patients demonstrating unspecific dysmorphic features, the genetic basis remained unknown.

Neurodevelopmental outcomes were available for 42 (82.3%) of our patients. Four children were lost to follow-up, and five died early in the neonatal period. The mean age at the last neurological assessment was 4.7 years (range 4 months to 18 years).

Development at the last follow-up was normal in 31% (13/42) of patients. Of these, nine were in the isolated ACC group, while four were in the other group (p = 0.001, Tab. 7).

Of 14 patients who presented with isolated ACC, five had transient hypotonia, two had speech delay in early childhood, one had learning difficulties at school age, one demonstrated cognitive and social problems, and one developed epilepsy (see Tab. 3).

All of the 12 infants with chromosomal disorders or known genetic syndromes had mild to severe developmental delay (see Tab. 6).

Epilepsy occurred in 35.7% (15/42) of children. The risk of seizures was almost 13-fold higher for babies with additional abnormalities (OR = 12.99; 95% confidence interval (CI): 1.49–111.11), compared to cases with isolated callosal defects. Of 28 patients with callosal defects accompanied by other abnormalities, 14 (50%) developed epilepsy, while in the 14 patients with isolated callosal anomalies, only one (7.1%) had epilepsy (p = 0.008).

In a total of 51 ACC cases, nine deaths occurred (15.6%). The presence of extracallosal anomalies significantly affected mortality. Infants with ACC/HCC accompanied by additional defects were 10 times more likely to die compared to those with an isolated ACC/HCC (OR = 10.70; 95% CI: 1.20–95.23).

## Discussion

The detection of callosal anomalies in infants always raises concerns among parents and healthcare professionals. The diagnosis of ACC is possible antenatally, which could allow for medical care for the mother and her child to be optimised after birth [10, 15, 19]. Postnatal detection of ACC may be limited, as ACC can be asymptomatic, especially if not associated with other anomalies. Head ultrasound in neonates is usually undertaken following prenatal suspicion of congenital anomalies, or as a neuroimaging investigation in newborns who have neurological abnormalities or risk factors for intracranial lesions [20].

The current study confirmed a relatively high frequency of clinical indications for brain imaging in the context of

**Table 3.** Characteristics of patients with isolated anomalies of corpus callosum

| Sex GA at birth/ /weeks | Mode of delivery | Neonatal care | GA at diagnosis (weeks); Reason for referral (Initial antenatal findings ID); Antenatal diagnosis (AD) | Postnatal findings; Postnatal MRI (pMRI) results | Age at last exam | Neurodevelopmental outcome; Epilepsy | Death |
|---|---|---|---|---|---|---|---|
| F<br>40 | VD | Normal | GA 22: ID: non-visualisation of CC;<br>AD: IHF widening, fMRI: IHF widening, 46XX, Isolated ACC | ACC<br>pMRI: confirmed diagnosis | 3 years | Normal development;<br>Epi (–) | (–) |
| M<br>41 | VD | NIMCU admission | GA 25: ID: VM;<br>AD: colpocephaly OH 17–18 mm, CSP absence, fMRI: colpocephaly OH 18 mm, Isolated ACC | ACC<br>Colpocephaly: right OH 17 mm, left OH 20 mm<br>pMRI: confirmed diagnosis | 2 years | 1st year of life — hypotonic, mild speech delay;<br>Epi (–) | (–) |
| M<br>35 | CD emerg | NIMCU admission | GA 28: ID: IHF widening, ACC;<br>AD: IHF widening, Isolated pACC | pACC<br>pMRI: (–) | 3 years | Normal development;<br>Epi (–) | (–) |
| M<br>41 | VD | NIMCU admission | GA 30: ID: VM;<br>AD: CSP absence, colpocephaly OH 16.2 mm, Isolated ACC | HCC<br>Colpocephaly OH 8 mm<br>pMRI: (–) | 6 years | 1st year of life — hypotonic.<br>Mild speech delay, dyspraxia, cognitive problems, speech delay, social problems;<br>Epi (–) | (–) |
| M<br>38 | CD elect | NIMCU admission | AD: GA 24: VM OH 16 mm,<br>GA 30: hydrocephalus OH 20 mm | ACC<br>pMRI: (–) | Lost | (–) | (–) |
| F<br>40 | VD | NIMCU admission | (–) | ACC<br>pMRI: confirmed diagnosis | 1 year | Mild developmental delay, hypotonic;<br>Epi (–) | (–) |
| F<br>38 | VD | Normal | AD: GA 33: hydrocephalus OH 22 mm | ACC; 46, XX<br>pMRI: confirmed diagnosis | 3 years | 3 months of age — hypotonic;<br>Normal development; Epi (–) | (–) |
| M<br>39 | CD elect | Normal | AD: GA 23: VM ventricle width 10 mm | ACC<br>Colpocephaly<br>pMRI: (–) | 2 years | Normal development;<br>Epi (–) | (–) |
| F<br>37 | CD elect | NIMCU admission | AD: GA 20: hydrocephalus OH 20 mm | ACC<br>pMRI: midline cyst | 12 years | Normal development,<br>Learning difficulties; Epi (–) | (–) |
| F<br>38 | VD | Normal | AD: GA 18: VM ventricle width 15 mm | ACC<br>Colpocephaly<br>pMRI: lipoma | 5 years | Normal development;<br>Epi — Yes | (–) |
| M<br>40 | VD | NIMCU admission | AD: GA 39: VM, colpocephaly OH 18 mm | ACC<br>pMRI: (–) | 5 months | Severe developmental delay;<br>Congenital cytomegalovirus infection;<br>Epi (–) | 1st year |
| F<br>40 | CD elect | NIMCU admission | AD: GA 20: hydrocephalus OH 30 mm | pACC<br>pMRI: (–) | 3 years | Normal development;<br>Epi (–) | (–) |

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**Table 3 cont.** Characteristics of patients with isolated anomalies of corpus callosum

| Sex GA at birth/ /weeks | Mode of delivery | Neonatal care | GA at diagnosis (weeks); Reason for referral (Initial antenatal findings ID); Antenatal diagnosis (AD) | Postnatal findings; Postnatal MRI (pMRI) results | Age at last exam | Neurodevelopmental outcome; Epilepsy | Death |
|---|---|---|---|---|---|---|---|
| M 37 | VD | NIMCU admission | AD: GA 36: VM ventricle width 10 mm | pACC pMRI: (–) | 4 years | Normal development; Epi (–) | (–) |
| F 38 | VD | Normal | (–) | pACC pMRI: (–) | 2 years | Normal development; Epi (–) | (–) |
| F 38 | VD | NIMCU admission | (–) | pACC pMRI: (–) | Lost | (–) | (–) |
| M 39 | CD elect | NIMCU admission | AD: GA30: VM ventricle width 18 mm | HCC pMRI: (–) | Lost | (–) | (–) |
| M 38 | CD elect | NIMCU admission | (–) | HCC pMRI: (–) | 3 years | Mild developmental delay, hypotonia; Epi (–) | (–) |
| N = 17 | | | (–) | | | | |

ACC — agenesis of corpus callosum; ASP — agenesis of septum pellucidum; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; CSP — cavum septi pellucidi; Epi — epilepsy; F — female; fMRI — foetal magnetic resonance imaging; GA — gestational age; HCC — hypoplasia of corpus callosum; IACC — isolated agenesis of corpus callosum; IHF — interhemispheric fissure; M — male; NIMCU — Neonatal Intermediate Care Unit; pMRI — postnatal magnetic resonance imaging; OH — occipital horn; pACC — partial agenesis of corpus callosum; VD — vaginal delivery; VM — ventriculomegaly

**Table 4.** Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations

| Sex, GA at birth weeks | Mode of delivery | Neonatal care | GA at antenatal diagnosis (weeks); Antenatal diagnosis AD | Postnatal findings: Other brain and other organ anomalies; Genetic test results | Age at last exam | Neurodevelopmental outcome | |
|---|---|---|---|---|---|---|---|
| | | | | | | Epilepsy | Development; Death |
| M 34 | CD elect | NIMCU admission | AD: GA 23; hydrocephalus, HPE, Schizencephaly | ACC; hydrocephalus, ASP 46,XY | 3 years | Yes | Severe developmental delay |
| M 40 | VD | Normal | AD: GA 28; VM, ventricle width 12 mm, CSP absence, Isolated ACC | ACC; ASP | 7 years | Yes | Mild developmental delay |
| M 32 | VD | NIMCU admission | AD: GA 25; VM colpocephaly OH 18 mm | ACC; ASP | 2 years | No | First year of life — hypotonia, Normal development |
| F 36 | CD elect | NIMCU admission | AD: GA 30; hydrocephalus | ACC; microcephaly, optic nerve atrophy | 3 years | Yes | Severe developmental delay |
| M 39 | CD elect | NICU admission | AD: GA 24; hydrocephalus, HLHS; | ACC; DWS HLHS | (–) | (–) | Neonatal death |
| M 36 | CD elect | NIMCU admission | AD: GA 22; hydrocephalus | ACC; ASP Dysmorphism, genitourinary anomalies, musculoskeletal defects | 4 months | No | Severe developmental delay |

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**Table 4 cont.** Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations

| Sex, GA at birth weeks | Mode of delivery | Neonatal care | GA at antenatal diagnosis (weeks); Antenatal diagnosis AD | Postnatal findings: Other brain and other organ anomalies; Genetic test results | Age at last exam | Neurodevelopmental outcome | |
|---|---|---|---|---|---|---|---|
| | | | | | | Epilepsy | Development; Death |
| M 37 | CD emerg | NIMCU admission | AD: GA 33; hydrocephalus, shortened foetal limbs | ACC; Hydrocephalus, midline cyst; Dysmorphism, genitourinary anomalies, musculoskeletal defects, 46, XY | 9 months | No | Severe developmental delay |
| M 29 | VD | NICU admission | (–) | ACC dysmorphism | (–) | (–) | Neonatal death |
| F 24 | VD | Palliative care | AD: GA 22; fMRI: colpocephaly OH: 10–11 mm, TAC, hydronephrosis, 46, XX, complex ACC | ACC; TAC, hydronephrosis | (–) | (–) | TOP |
| F 37 | VD | NIMCU admission | AD: GA 22; DWS, cardiac disease suspicion, mother refused further investigation | HCC; DWS; dysmorphism, VSD; 46, XX, aCGH — no abnormalities | 1 year | No | Mild global developmental delay, hypotonia |
| M 40 | CD emerg | NIMCU admission | AD: GA 16; hydrocephalus, DWS | pACC; DWS; 46,XY | 3 years | No | Severe developmental delay |
| F 38 | CD elect | Normal | AD: GA 24; midline cyst | pACC; genitourinary anomalies; 46,XX | (–) | (–) | Lost |
| F 38 | VD | Normal | AD: GA 21; VM, fMRI: colpocephaly OH: 14 mm, Interthalamic adhesion, 46, XX, Isolated ACC | pACC, colpocephaly 12/15 mm; VSD, 46,XX | 3 years | No | Normal development |
| N = 13 | | | | (–) | | | |

ACC — agenesis of corpus callosum; aCGH — array comparative genomic hybridisation; ASP — agenesis of septum pellucidum; CSP — cavum septi pellucidi; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; DWS — Dandy-Walker syndrome; F — female; fMRI — foetal MRI, GA — gestational age, HCC — hypoplasia of corpus callosum; HLHS — hypoplastic left heart syndrome; HPE — holoprosencephaly; IACC — isolated agenesis of corpus callosum; M — male; MRI — magnetic resonance imaging; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; OH — occipital horn; pACC — partial agenesis of corpus callosum; TAC — truncus arteriosus communis; TOP — termination of pregnancy; VD — vaginal delivery; VM — ventriculomegaly; VSD — ventricular septal defect

**Table 5.** Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations; additional brain anomalies found on MRI

| Sex, GA at birth/ /weeks | Mode of delivery; Neonatal care | GA at diagnosis (weeks); Antenatal diagnosis AD | Postnatal findings | | Age at last exam | Epilepsy | Neurodevelopmental outcome |
|---|---|---|---|---|---|---|---|
| | | | Brain anomalies | Other organ anomalies; Genetic tests results | | | Development; Death |
| M 36 | CD elect; NIMCU admission | AD: GA 23; Hydrocephalus | ACC; hydrocephalus, Chiari syndrome | (–) | 17 years | Yes | Mild developmental delay: mild intellectual deficit, learning difficulties, social problems |
| M 38 | CD emerg; Normal | AD: GA 38; Hydrocephalus | ACC; midline cyst, gyration abnormalities | (–) | 11 years | Yes | First year of life — hypotonia; normal development |
| F 35 | VD; NIMCU admission | (–) | ACC; microcephaly, heterotopy | Dysmorphism, cleft lip, musculoskeletal defects, ToF, 46,XX | 2 years | No | Severe developmental delay |
| M 41 | CD emerg; NIMCU admission | (–) | ACC; microcephaly, heterotopy | Cleft lip, genitourinary anomalies, 46,XY | 3 years | Yes | Severe developmental delay |
| M 35 | VD; NICU admission | AD: GA 24; Hydrocephalus 25 mm | HCC; ASP, Cortical dysplasia | (–) | 3 years | Yes | First year of life — hypotonia, mild developmental delay, speech delay |
| F 29 | CD elect; NICU admission | AD: GA 20; VM ventricle width 15 mm | HCC; hydrocephalus, midline cyst, cerebellum hypoplasia, ASP, focal cortical dysplasia | 46,XX | 8 years | Yes | First year of life — hypotonia, mild developmental delay, learning difficulties |
| F 38 | VD; NIMCU admission | AD: GA 24; DWS, CoA | HCC; widening of Sylvian fissures | Dysmorphism, musculoskeletal defects, renal anomalies, 46,XX | 7 years | Yes | Severe encephalopathy, severe developmental delay. Able to stand up with a walker, special needs school |
| M 39 | CD elect; Normal | AD: GA 25; Colpocephaly OH: 12 mm, IACC | pACC; ASP, colpocephaly, midline cyst, cortical dysplasia, heterotopy, gyration abnormality | Dysmorphism, ASD | 18 years | Yes | Mild global developmental delay: able to walk, selfdependent, learning difficulties, choreoathetosis |
| M 38 | CD emerg; NIMCU admission | AD: GA 22; fMRI excluded ACC,Dextrocardia | pACC; ASP, septo-optic dysplasia | (–) | 5 years | No | Normal development; visual impairment, strabismus |
| N = 9 | N = 9 | | | (–) | | | |

ACC — agenesis of corpus callosum; ASD — atrial septal defect; ASP — agenesis of septum pellucidum; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; CoA — coarctation of aorta; DWS — Dandy-Walker syndrome; F — female; fMRI — foetal magnetic resonance imaging; GA — gestational age; HCC — hypoplasia of corpus callosum; IACC — isolated agenesis of corpus callosum; M — male; MRI — magnetic resonance imaging; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; OH — occipital horn; pACC — partial agenesis of corpus callosum; ToF — tetralogy of Fallot; VD — vaginal delivery; VM — ventriculomegaly

**Table 6.** Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations; patients with a determined underlying cause

| Sex, GA at birth/ /weeks | Mode of delivery; Neonatal care | GA at diagnosis (weeks); Antenatal diagnosis AD | Postnatal findings | | Age at last exam | Neurodevelopmental outcome | |
|---|---|---|---|---|---|---|---|
| | | | Associated brain and other organ anomalies | Chromosomal diagnoses and known genetic syndromes | | Epilepsy | Development; Death |
| F32 | VD; palliative care | AD: GA 29; hydrocephalus | ACC, hydrocephalus | Dysmorphism, DSD, eyeballs hypoplasia, renal anomalies, 46, XY | (–) | (–) | Neonatal death |
| M38 | CD elect; NIMCU admission | AD: GA 32; Hydrocephalus, ventriculoam niotic shunt | ACC, hydrocephalus, absence of fornix and anterior commissure | Rubinstein-Taybi syndrome; 46, XY, aCGH — no abnormalities | 3 years | Yes | Severe developmental delay |
| M39 | CD elect; NIMCU admission | AD: GA 30; Strawberry shaped skull, CSP absence, bilateral anophtalmos, nose bone agenesis, 46, XY, complex ACC | ACC, hydrocephalus, midline cyst, cerebellum agenesis; bilateral anophtalmos, cleft lip/palate, genitourinary anomalies | Clinically suspected Fraser syndrome, 46, XY | 2 years | Yes | Severe global developmental delay, drug-resistant epilepsy, GTDeath aged 2 years |
| F31 | CD elect; NICU admission | AD: GA 28; choroid plexus cyst, colpocephaly OH: 10 mm; isolated ACC | ACC, cerebellum hypoplasia, PA, TAC type IV | DiGeorge syndrome:46, XX, ish22q11.2 | 1 year | No | Severe developmental delay Death: first year |
| F38 | CD emerg; NIMCU admission | AD: GA 27; Ebstein anomaly | ACC, Ebstein anomaly | Vici syndrome,EPG5 gene mutation | (–) | Yes | Severe encephalopathy, Severe global developmental delay; ventilation at night, GT, Neurogenic bladder |
| M39 | CD elect; Normal | AD: GA 13; hydrocephalus | ACC, renal and genitourinary anomalies | Trisomy 8 mosaicism: 47, XY, +8 [22] 46, XY [1] | 12 years | No | Mild developmental delay: 1st year of life — hypotonia, mild intellectual deficit |
| F37 | VD; NIMCU admission | AD: GA 13; 47,XX,+18 | pACC, cleft lip/palate, renal anomalies, ASD | Trisomy 13/trisomy 18 mosaicism | 12 years | No | Severe developmental delay Death: 12 years |
| M40 | VD; NIMCU admission | (–) | pACC; | 5p deletion syndrome: 46, XY del(5)(p14,2)(11) | 3 years | No | Severe developmental delay |
| M38 | CD elect; NICU admission | AD: GA 25; dolichocephaly, HPE, HCC, unilateral renal agenesis, TAC, 46, XY | pACC, renal and genitourinary anomalies, AVSD | SLOS, 46, XY | (–) | (–) | Neonatal death |
| M36 | CD elect; NICU admission | AD: GA 23; legs, arms and facial abnormalities | pACC | Apert syndrome | 1 year | No | Mild psychomotor delay |
| F39 | VD; NIMCU admission | AD: GA 23; legs, arms and facial abnormalities | HCC | Apert syndrome | 9 years | No | Mild intellectual delay |
| M39 | CD emerg; NIMCU admission | AD: GA 31; hydrocephalus, DWS, HPE semilobaris | ASP, DWS, hydrocephalus, stenosis of aqueduct of Sylvius | 47, XYY | 6 months | Yes | Severe developmental delay |
| N = 12 | | | | (–) | | | |

ACC — agenesis of corpus callosum; aCGH — array comparative genomic hybridisation; ASD — atrial septal defect; ASP — agenesis of septum pellucidum; AVSD — atrioventricular septal defect; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; DSD — disorders of sex development; DWS — Dandy-Walker syndrome; F — female; GA — gestational age; GT — gastrostomy tube; HCC — hypoplasia of corpus callosum; HPE — holoprosencephaly; M — male; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; PA — pulmonary atresia; pACC — partial agenesis of corpus callosum; SLOS — Smith Lemli Opitz syndrome; ToF — tetralogy of Fallot; TAC — truncus arteriosus communis; VD — vaginal delivery; VSD — ventricular septal defect

**Table 7.** Neurodevelopmental outcomes in all patients with corpus callosum anomalies: isolated callosal anomalies versus callosal anomalies associated with other abnormalities

| Group | Development | | | Sum |
|---|---|---|---|---|
| | Normal | Mild delay | Severe delay | |
| Isolated ACC | 9 (64.3%) | 4 (28.6%) | 1 (7.1%) | 14 (100%) |
| ACC + other brain defects + other organ defects | 4 (14.3%) | 9 (32.1%) | 15 (53.6%) | 28 (100%) |
| Sum | 13 (31%) | 13 (31%) | 16 (38%) | 42 (100%) |
| p = 0.001 | | | (–) | |

ACC — agenesis of corpus callosum

postdelivery ACC diagnosis. In more than three-quarters of patients from our series, a neonatal head ultrasound and a subsequent diagnosis of ACC resulted from a prenatal suspicion of CNS defects [1].

Neonatal head ultrasound is usually the first step in the diagnosis of ACC; however, it has some limitations; it does not provide enough information to determine whether the lesion is isolated or not. Including MRI in the diagnostic pathway helps to confirm the diagnosis and to identify associated brain anomalies, especially cortical malformations previously undiagnosed during the prenatal and postnatal ultrasound [10, 21, 22].

Some clinicians value the reliability and reproducibility of a neonatal ultrasound in an accurate diagnosis of callosal anomalies, and this can lead them to abstain from performing MRI. MRI is typically undertaken in the context of evaluation for either developmental delay or epilepsy, and is not considered to be a standard procedure for a detailed diagnosis of callosal abnormalities. We noticed a similar trend in our study. MRI was performed most often in the group of patients presenting with additional defects and displaying neurological symptoms. In those cases in which an MRI was carried out, previously undiagnosed brain defects were revealed.

Like most previous series, we confirmed that callosal defects are frequently accompanied by a large number of brain and somatic anomalies [11, 13, 21, 23]. Isolated cases comprised only one-third of our cohort, while the remaining cases were accompanied by other defects. Most of these associated defects were found after birth, as has been shown in previous studies [24, 25]. Malformations of cortical development and heterotopia have been identified as the most common concomitant brain abnormalities, and their presence dramatically alters the prognosis [11, 13, 21, 22, 24, 25].

Chromosomal aberrations or gene mutations have been reported as common underlying factors of ACC. However, due to the presence of unknown causative genes and technical problems, approximately half of all ACC cases cannot be identified [3–5, 8, 13].

Although trisomy 18 and trisomy 13 have been previously shown as the genetic basis of ACC, the rare reported cases of their mosaicism did not include callosal defects [26].

To the best of our knowledge, this is the first study to describe a patient presenting with trisomy 13/trisomy 18 mosaicism accompanied by pACC. Other chromosomal disorders may impact upon CC morphogenesis [27–29]. Our study found DiGeorge and 5p deletion syndromes as an underlying aetiology of ACC. ACC accompanied by these syndromes has been previously presented in case reports [30, 31].

The challenge of identifying the underlying disorder of patients with ACC is significant. Patients should be offered paediatric genetic testing following a diagnosis of ACC. Genetic investigation usually starts with karyotyping. Molecular diagnostics with aCGH may be a valuable method, allowing re-investigation of cases in which conventional cytogenetic techniques reached no conclusion. Although the implementation and availability of molecular gene analysis is increasing, it is still not performed as a routine diagnostic protocol. It is more often undertaken in children with developmental delay, epilepsy or multiorgan manifestations, than in patients with normal or slightly delayed neurodevelopment. We observed a similar trend in our survey.

There are numerous conditions in which ACC may be a feature, as in Vici or Fraser syndromes. All previously reported cases of Vici syndrome featured ACC. In our patient suffering from this condition, ACC was also found. Vici syndrome is caused by mutations in the EPG5 (ectopic P granules protein 5) gene, while Fraser syndrome is caused by mutations in the FRAS1 and FREM2 gens. Fraser syndrome is rare, without clear genotype-phenotype correlations, and FRAS1 gene has many exons, which impedes the investigation of mutations in affected patients. For Vici syndrome, almost 40 EPG mutations have been already detected, making it difficult to identify the mutation in some patients [9, 32, 33]. Two of our patients were screened for FRAS1 and EPG5 mutations. Unfortunately, in a patient who met the clinical diagnostic criteria for Fraser syndrome, genetic testing did not prove this diagnosis. Patients with Fraser syndrome described so far have presented with several brain abnormalities, but, callosal anomalies have not been among those reported [32].

The differential diagnosis of ACC is wide. Subsets of callosal anomalies, dysmorphic features, other anatomical malformations and neurological impairment can be encountered in different syndromes, which can result in difficulties in choosing the relevant molecular screening test.

Apert, Aicardi, Smith-Lemli-Opitz, and Rubinstein-Taybi syndromes are among the known genetic syndromes that

could manifest with ACC [3, 8, 10]. Our results are in line with these findings, although we did not include any patients with Aicardi syndrome.

Defects of the CC, neurodevelopmental delay, epilepsy, and dysmorphism are frequently reported in patients presenting with various types of dystonia and other hereditary movement disorders with childhood onset. Results of the latest gene analyses have revealed varied molecular bases of these disorders [34, 35]. In neurodegenerative diseases with onset in the 4$^{th}$ and 5$^{th}$ decades of life, in which brain macrophages known as microglia play an important role in their formation, defects of the CC may also be present. Microglia proliferation and development requires the activation of a Colony Stimulating Factor 1 Receptor (CSF1R), the gene previously associated with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). However, the role played by brain microglia in nervous system development has been recently noted. Individuals with homozygous CSF1R mutations who presented paediatric phenotypes distinct from ALSP have been described. This mutation has been found in infants with ACC and in adolescents with severe developmental regression, epilepsy and leukodystrophy [36, 37]. It has also been described in paediatric patients as BANDDOS, a syndrome consisting of brain abnormalities including ACC, neurodegeneration and dysosteosclerosis [34, 35].

A CSF1R mutation was identified in a Polish patient with a diagnosis of ALSP accompanied by thin CC [38]. The clinical features of CSF1R-related leukoencephalopathy occupy a broad spectrum, encompassing seizures, movement disorders and psychiatric features, seen also in individuals with ACC [39].

Therefore, in patients with callosal abnormalities, genetic testing should also include this gene mutation.

The clinical course in children with callosal anomalies is unpredictable and varies from asymptomatic cases to a wide range of neurodevelopmental impairments [21–23]. Establishing the prognosis for further neurodevelopment of affected individuals remains difficult, as these infants may not show symptoms during the neonatal period, especially if they have no other associated malformations. Poor outcomes have often been reported when ACC has been associated with extracallosal anomalies, while patients without other associated malformations or chromosomal abnormalities have been shown to be more likely to obtain better neurological outcomes [6, 19, 25, 40–42]. Our results are consistent with these findings. The majority of children with normal development in our study were patients with isolated ACC. However, even in isolated cases, the prognosis remains unclear, and the neurodevelopmental outcome can range from normal development in 75% of patients, to differing levels of intellectual disability. Some clinical features may become more apparent during infancy and childhood, including seizures, abnormal muscle tone, poor coordination, cognitive impairment, and language developmental delay [24, 40, 41]. Similarly to previous works, a third of our isolated ACC cases showed (mostly mild) developmental disabilities. Hypotonia and slight motor delay occurred in the first six months of life, while cognitive disabilities manifested at school age.

The presence of extracallosal CNS and extra-CNS malformation, together with the detection of a genetic aetiology, have been linked to abnormal developmental outcomes [3, 6, 19].

Our study confirmed these findings: delayed neurodevelopment and intellectual disability were evident in all patients displaying chromosomal disorders and known genetic syndromes. Unfavourable neurological findings were also seen in the majority of children with additional serious CNS and non-CNS abnormalities.

Like most earlier studies, the present paper confirms that the coexistence of other defects significantly increases the risk of epilepsy [42].

### Limitations of study

Firstly, as this was a retrospective study, some data may be missing or not fully reported (e.g. genetic testing reported for 43%, MRI imaging available for 55% of patients). MRI data was reported mostly in patients with poor neurological outcomes. It remains unknown how many patients with normal intelligence, mild behavioural problems, or assessed as having isolated ACC, actually had additional brain abnormalities. Secondly, intellectual disability, social problems, and speech delay were defined by hospital psychologists without providing the type of tools used for the diagnosis. Moreover, the assessment of neurological impairments relied on our review of medical records. However, our diverse cohort was a strength of this study; based on our hospital database, we obtained a diverse sample of ACC cases which were not limited to patients with neurodevelopmental delays. With respect to developmental outcomes, the results in our cohort may reflect those to be expected for the overall population of children with callosal defects.

## Conclusions

Callosal defects are frequently accompanied by a large number of brain and somatic anomalies. Therefore, both children with additional malformations, and those with apparently isolated callosal anomalies, should undergo a detailed brain and cardiac examination. Thorough neuroimaging should also be carefully planned at a later date to confirm partial or complete agenesis and other accompanying abnormalities.

Since several chromosomal aberrations may be an underlying cause of callosal anomalies, genetic testing should be offered to all ACC patients. Patients presenting with ACC may exhibit different degrees of neurodevelopmental impairment. The coexistence of extracallosal abnormalities significantly worsens the neurological prognosis and increases the risk of epilepsy. Individuals with isolated ACC show better neurodevelopmental outcomes.

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## References

1. Paul LK, Brown WS, Adolphs R, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci. 2007; 8(4): 287–299, doi: 10.1038/nrn2107, indexed in Pubmed: 17375041.
2. Raybaud C. The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. Neuroradiology. 2010; 52(6): 447–477, doi: 10.1007/s00234-010-0696-3, indexed in Pubmed: 20422408.
3. Edwards TJ, Sherr EH, Barkovich AJ, et al. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. Brain. 2014; 137(Pt 6): 1579–1613, doi: 10.1093/brain/awt358, indexed in Pubmed: 24477430.
4. Stoll C, Dott B, Roth MP. Associated anomalies in cases with agenesis of the corpus callosum. Am J Med Genet A. 2019; 179(10): 2101–2111, doi: 10.1002/ajmg.a.61330, indexed in Pubmed: 31444900.
5. Bedeschi MF, Bonaglia MC, Grasso R, et al. Agenesis of the corpus callosum: clinical and genetic study in 63 young patients. Pediatr Neurol. 2006; 34(3): 186–193, doi: 10.1016/j.pediatrneurol.2005.08.008, indexed in Pubmed: 16504787.
6. Jeret JS, Serur D, Wisniewski KE, et al. Clinicopathological findings associated with agenesis of the corpus callosum. Brain Dev. 1987; 9(3): 255–264, doi: 10.1016/s0387-7604(87)80042-6, indexed in Pubmed: 3310713.
7. Hetts SW, Sherr EH, Chao S, et al. Anomalies of the corpus callosum: an MR analysis of the phenotypic spectrum of associated malformations. AJR Am J Roentgenol. 2006; 187(5): 1343–1348, doi: 10.2214/AJR.05.0146, indexed in Pubmed: 17056927.
8. Schell-Apacik CC, Wagner K, Bihler M, et al. Agenesis and dysgenesis of the corpus callosum: clinical, genetic and neuroimaging findings in a series of 41 patients. Am J Med Genet A. 2008; 146A(19): 2501–2511, doi: 10.1002/ajmg.a.32476, indexed in Pubmed: 18792984.
9. Hofman J, Hutny M, Sztuba K, et al. Corpus Callosum Agenesis: An Insight into the Etiology and Spectrum of Symptoms. Brain Sci. 2020; 10(9), doi: 10.3390/brainsci10090625, indexed in Pubmed: 32916978.
10. 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): 184–197, doi: 10.1002/ajmg.c.31405, indexed in Pubmed: 24866859.
11. Ballardini E, Marino P, Maietti E, et al. Prevalence and associated factors for agenesis of corpus callosum in Emilia Romagna (1981-2015). Eur J Med Genet. 2018; 61(9): 524–530, doi: 10.1016/j.ejmg.2018.06.004, indexed in Pubmed: 29902589.
12. Szabó N, Gergev G, Kóbor J, et al. Corpus callosum anomalies: birth prevalence and clinical spectrum in Hungary. Pediatr Neurol. 2011; 44(6): 420–426, doi: 10.1016/j.pediatrneurol.2011.01.002, indexed in Pubmed: 21555052.
13. Glass HC, Shaw GM, Ma C, et al. Agenesis of the corpus callosum in California 1983-2003: a population-based study. Am J Med Genet A. 2008; 146A(19): 2495–2500, doi: 10.1002/ajmg.a.32418, indexed in Pubmed: 18642362.
14. Ghi T, Carletti A, Contro E, et al. Prenatal diagnosis and outcome of partial agenesis and hypoplasia of the corpus callosum. Ultrasound Obstet Gynecol. 2010; 35(1): 35–41, doi: 10.1002/uog.7489, indexed in Pubmed: 20020466.
15. Janiak K, Respondek-Liberska M, Liberski PP, et al. Agenesis of corpus callosum — significance of prenatal diagnosis. Current Neurology. 2009; 9: 194–202.
16. Santo S, D'Antonio F, Homfray T, et al. Counseling in fetal medicine: agenesis of the corpus callosum. Ultrasound Obstet Gynecol. 2012; 40(5): 513–521, doi: 10.1002/uog.12315, indexed in Pubmed: 23024003.
17. Volpe P, Votino C, Fanelli T, et al. Corpus Callosum and Septum Pellucidum Anomalies. Obstetric Imaging: Fetal Diagnosis and Care. 2018: 162–172.e1, doi: 10.1016/b978-0-323-44548-1.00034-6.
18. Rüland AM, Berg C, Gembruch U, et al. Prenatal Diagnosis of Anomalies of the Corpus Callosum over a 13-Year Period. Ultraschall Med. 2016; 37(6): 598–603, doi: 10.1055/s-0034-1399699, indexed in Pubmed: 26114344.
19. Francesco P, Maria-Edgarda B, Giovanni P, et al. Prenatal diagnosis of agenesis of corpus callosum: what is the neurodevelopmental outcome? Pediatr Int. 2006; 48(3): 298–304, doi: 10.1111/j.1442-200X.2006.02208.x, indexed in Pubmed: 16732799.
20. Ballardini E, Tarocco A, Rosignoli C, et al. Universal Head Ultrasound Screening in Full-term Neonates: A Retrospective Analysis of 6771 Infants. Pediatr Neurol. 2017; 71: 14–17, doi: 10.1016/j.pediatrneurol.2017.03.012, indexed in Pubmed: 28449983.
21. Al-Hashim AH, Blaser S, Raybaud C, et al. Corpus callosum abnormalities: neuroradiological and clinical correlations. Dev Med Child Neurol. 2016; 58(5): 475–484, doi: 10.1111/dmcn.12978, indexed in Pubmed: 26661037.
22. Sztriha L. Spectrum of corpus callosum agenesis. Pediatr Neurol. 2005; 32(2): 94–101, doi: 10.1016/j.pediatrneurol.2004.09.007, indexed in Pubmed: 15664768.
23. Margari L, Palumbi R, Campa MG, et al. Clinical manifestations in children and adolescents with corpus callosum abnormalities. J Neurol. 2016; 263(10): 1939–1945, doi: 10.1007/s00415-016-8225-x, indexed in Pubmed: 27383641.
24. Folliot-Le Doussal L, Chadie A, Brasseur-Daudruy M, et al. Perinatal Network of Haute-Normandie. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. Early Hum Dev. 2018; 116: 9–16, doi: 10.1016/j.earlhumdev.2017.10.004, indexed in Pubmed: 29091783.
25. Yeh HR, Park HK, Kim HJ, et al. Neurodevelopmental outcomes in children with prenatally diagnosed corpus callosal abnormalities. Brain Dev. 2018; 40(8): 634–641, doi: 10.1016/j.braindev.2018.04.012, indexed in Pubmed: 29801921.
26. Abe K, Harada N, Itoh T, et al. Trisomy 13/trisomy 18 mosaicism in an infant. Clin Genet. 1996; 50(5): 300–303, doi: 10.1111/j.1399-0004.1996.tb02378.x, indexed in Pubmed: 9007314.
27. Rüland AM, Gloning KP, Albig M, et al. The Incidence of Chromosomal Aberrations in Prenatally Diagnosed Isolated Agenesis of the Corpus Callosum. Ultraschall Med. 2017; 38(6): 626–632, doi: 10.1055/s-0043-113818, indexed in Pubmed: 28946151.
28. Serur D, Jeret JS, Wisniewski K. Agenesis of the corpus callosum: clinical, neuroradiological and cytogenetic studies. Neuropediatrics. 1988; 19(2): 87–91, doi: 10.1055/s-2008-1052407, indexed in Pubmed: 2453812.
29. Chen CP, Hsu CY, Chern SR, et al. Prenatal diagnosis of mosaic trisomy 8 by amniocentesis in a fetus with ventriculomegaly and dysgenesis of the corpus callosum. Taiwan J Obstet Gynecol. 2020; 59(1): 127–129, doi: 10.1016/j.tjog.2019.11.020, indexed in Pubmed: 32039780.

30. Kraynack NC, Hostoffer RW, Robin NH. Agenesis of the corpus callosum associated with DiGeorge-velocardiofacial syndrome: a case report and review of the literature. J Child Neurol. 1999; 14(11): 754–756, doi: 10.1177/088307389901401115, indexed in Pubmed: 10593557.
31. Vialard F, Robyr R, Hillion Y, et al. Dandy-Walker syndrome and corpus callosum agenesis in 5p deletion. Prenat Diagn. 2005; 25(4): 311–313, doi: 10.1002/pd.1130, indexed in Pubmed: 15849798.
32. Slavotinek A, Li C, Sherr EH, et al. Mutation analysis of the FRAS1 gene demonstrates new mutations in a propositus with Fraser syndrome. Am J Med Genet A. 2006; 140(18): 1909–1914, doi: 10.1002/ajmg.a.31399, indexed in Pubmed: 16894541.
33. Byrne S, Dionisi-Vici C, Smith L, et al. Vici syndrome: a review. Orphanet J Rare Dis. 2016; 11: 21, doi: 10.1186/s13023-016-0399-x, indexed in Pubmed: 26927810.
34. Figura M, Geremek M, Milanowski ŁM, et al. Movement disorders associated with chromosomal aberrations diagnosed in adult patients. Neurol Neurochir Pol. 2021; 55(3): 300–305, doi: 10.5603/PJNNS.a2021.0038, indexed in Pubmed: 34037980.
35. Akçakaya NH, Özeş Ak B, Gonzalez MA, et al. Clinical and genetic aspects of hereditary spastic paraplegia in patients from Turkey. Neurol Neurochir Pol. 2020; 54(2): 176–184, doi: 10.5603/PJNNS.a2020.0026, indexed in Pubmed: 32242913.
36. Oosterhof N, Chang IJ, Karimiani EG, et al. Homozygous Mutations in CSF1R Cause a Pediatric-Onset Leukoencephalopathy and Can Result in Congenital Absence of Microglia. Am J Hum Genet. 2019; 104(5): 936–947, doi: 10.1016/j.ajhg.2019.03.010, indexed in Pubmed: 30982608.
37. Daghagh H, Kafshboran HR, Daneshmandpour Y, et al. Homozygous mutation in CSF1R causes brain abnormalities, neurodegeneration, and dysosteosclerosis (BANDDOS). BioImpacts; 2022: 12.
38. Żur-Wyrozumska K, Kaczmarska P, Mensah-Glanowska P. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia associated with an A792D mutation in the CSF1R gene in a Polish patient. Neurol Neurochir Pol. 2021; 55(3): 322–324, doi: 10.5603/PJNNS.a2021.0012, indexed in Pubmed: 33528831.
39. Wszolek ZK. First Polish case of CSF1R-related leukoencephalopathy. Neurol Neurochir Pol. 2021; 55(3): 239–240, doi: 10.5603/PJNNS.a2021.0022, indexed in Pubmed: 34096015.
40. des Portes V, Rolland A, Velazquez-Dominguez J, et al. Outcome of isolated agenesis of the corpus callosum: A population-based prospective study. Eur J Paediatr Neurol. 2018; 22(1): 82–92, doi: 10.1016/j.ejpn.2017.08.003, indexed in Pubmed: 28947381.
41. Sotiriadis A, Makrydimas G, Sotiriadis A, et al. Neurodevelopment after prenatal diagnosis of isolated agenesis of the corpus callosum: an integrative review. Am J Obstet Gynecol. 2012; 206(4): 337.e1–337.e5, doi: 10.1016/j.ajog.2011.12.024, indexed in Pubmed: 22284958.
42. Kim YU, Park ES, Jung S, et al. Clinical features and associated abnormalities in children and adolescents with corpus callosal anomalies. Ann Rehabil Med. 2014; 38(1): 138–143, doi: 10.5535/arm.2014.38.1.138, indexed in Pubmed: 2463993