

## Abnormalities of the corpus callosum: Magnetic resonance imaging analysis in children

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### ABSTRACT

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**Purpose:** This study reports the clinical profile of children with abnormalities of the corpus callosum in magnetic resonance imaging (MRI).

**Materials and methods:** Children with agenesis of the corpus callosum (ACC), hypoplasia, and dysgenesis were identified in a database of patients at the Department of Pediatric Radiology. Medical records were then systematically reviewed. Twenty brain MRI scans of children with abnormalities of the corpus callosum were chosen randomly and retrospectively analyzed. We also analyzed age, gender, motor development, mental development, epilepsy, and concomitant disorders.

**Results:** The study group was composed of 20 children with various disorders (11 girls, 9 boys). The ages of the children ranged from 4 months to 17 years, with a mean age of 9.8 years. Almost all children were born at term. More than half of

patients 11(55%) had ACC, 6 children had hypoplasia of the corpus callosum hypoplasia and 3 patients had an absence of genu of the corpus callosum or splenium. Nine children had mental retardation. Four patients had hydrocephalus and two had meningomyelocele, while two patients had Dandy-Walker syndrome and one had holoprosencephaly. Three patients had headache. One patient had tics syndrome and one Attention deficit-hyperactivity disorder. Fifteen children had normal motor development, with three using a wheelchair, and two unable to sit and walk. Three patients had epilepsy.

**Conclusion:** A spectrum of clinical presentations is apparent in children with abnormalities of the corpus callosum.

**Key words:** corpus callosum, abnormalities, children

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## **INTRODUCTION**

Brain malformations, particularly related to early brain development, are a clinically and genetically heterogeneous group of fetal neurological disorders [1]. In some cases, exposure to certain medicines, infections or radiation during pregnancy interferes with brain development. Fetal cerebral malformation, predominantly of impaired prosencephalic development namely agenesis of the corpus callosum and septo-optic dysplasia, is the main pathological feature in fetus, and causes prominent neurodevelopmental retardation, and associated with congenital facial anomalies and visual disorders [1-3].

The corpus callosum is the largest commissure connecting the cerebral hemispheres. It develops from the lamina reunions of His between 8 and 20 weeks [4] New insights into the formation of the corpus callosum have identified molecules secreted by midline glial populations that are involved in attracting and repelling axons so that they cross the midline and form the corpus callosum [5,6]. Thus, formation of the corpus callosum is complex; this characteristic may explain why most cases of callosal agenesis (ACC) are not isolated [7].

Although the corpus callosum is not the only path connecting the hemispheres, it is by far the largest and most important [1,7]. Other interhemispheric connections include the anterior commissure which is about 50,000 fibers, as well as the posterior commissure and the hippocampal commissure, both of which are smaller even than the anterior commissure [7,8].

Often individuals with ACC have some other much smaller interhemispheric connections (i.e., the anterior commissure). While this may allow for some information transfer between the hemispheres, no other commissure has the same functionality as the corpus callosum. If the corpus callosum does not form prior to birth, it will never form. If there are some corpus callosum nerves crossing between the hemispheres at birth, these may continue to develop but new fibers or nerves won't develop. Since ACC is congenital (occurs before birth), all the rests of the brain connections are organized accordingly [1]. ACC is one of the most prevalent brain malformations with an incidence of 0.5-70 in 10,000 [9], and it is seen in many syndromes of various etiologies [5]. Although ACC is predominantly genetic, few genes have as yet been identified. Data regarding the epidemiology of callosal anomalies are contradictory. ACC incidence varies as a function of both diagnostic techniques and sample populations: in the general population, its estimated prevalence is 3-7 per 1000 birth, while in children with developmental disabilities it is 2-3 per 100 [10]. The significant and continuous development

of the various neuroimaging techniques (especially of MR imaging) has revolutionized the analysis and understanding of multiple congenital brain anomalies over the last decade. The diagnosis of callosal agenesis depends on neuroimaging [11-13].

In the newborn, before closure of the anterior fontanelle occurs, screening ultrasonography may clearly show ACC; it may also show parallel lateral ventricles, interhemispheric cysts, hydrocephalus, and other related anomalies. Ultrasonography was the first imaging modality to allow direct sagittal imaging of callosal dysgenesis [12,14] and can identify ACC in the second trimester of pregnancy (18-20 weeks gestation).

ACC is often associated with other anomalies such as Chiari II malformation with abnormal development of cerebellar vermis and medulla oblongata, which tend to descend into the foramen magnum, usually accompanied by myelomeningocele, basilar type encephalocele and disorders of neural migration (which occurs concurrently in human brain development) such as schizencephaly, lissencephaly, pachygyria, marked neuronal heterotopias [1-3, 7,15].

MRI is currently the imaging procedure of choice in infants and children with ACC, even in patients who have previously undergone CT and ultrasonography examinations. The multiplanar capability and high soft-tissue contrast that are possible with MRI permit confident diagnosis of ACC and its associated anomalies, especially neuronal migration anomalies or atypical forms of holoprosencephaly [7,16,17].

ACC may occur as an isolated malformation or as a component of more complex malformation syndromes [18]. It has been associated with several consistent chromosomal rearrangements in more than 20 autosomal and X-linked malformation syndromes. A growing body of literature reporting that structural changes in the corpus callosum may correlate with cognitive and behavioral deficits in neurodevelopmental disorders including autism [19], dyslexia [20], cerebral palsy [3] and attention-deficit disorder [21].

Neurodevelopmental impairments in infants born preterm appear to be related to corpus callosum [22], as well as regionally specific microstructural callosal abnormalities. Specifically, reductions in callosal area are most evident in the posterior body of preterm infants.

The purpose of this study was to estimate the clinical profile of children with the corpus callosum abnormalities in MRIs.

## **MATERIALS AND METHODS**

This was a retrospective case-control study carried out in 2011. All MRI scans were obtained

using a 0.25 -T magnetic resonance scanner (MAGNETOM C, Siemens) with the use of a standard circularly polarized head coil. The MRIs were performed at the Department of Pediatric Radiology. Twenty brain MRI scans of children with ACC, hypoplasia, hypogenesis or dysgenesis were retrospectively analyzed. The MR images' abnormalities were assessed. The following structures were analyzed: size of lateral ventricles, loss of white matter, corpus callosum, thinning of corpus callosum, agenesis of corpus callosum, cerebellum, brain stem, and abnormalities of cortical gray matter. Images from the 20 MRI studies were evaluated by a neuroradiologist and a pediatric neurologist. We analyzed also age, gender, motor development, mental development, epilepsy and concomitant disorders.

### Definitions

*Complete Agenesis of the Corpus Callosum.* There is a complete or partial absence of the corpus callosum. *Partial Agenesis of the Corpus Callosum.* Partial ACC includes the entire range of partial absence, from absence of only a small portion of callosal fibers to absence of most of the corpus callosum. In partial ACC, the other smaller commissures usually are present. *Hypoplasia of the Corpus Callosum.* Hypoplasia refers to a thin corpus callosum. *Dysgenesis of the Corpus Callosum.* Dysgenesis means that the corpus callosum developed, but developed in some incomplete or malformed way, e.g., absent splenium or genu absent.

Exclusion criteria included the following: intraxial or extra-axial tumors other than small prechiasmatic and chiasmatic optic nerve gliomas, history of previous or ongoing radiation or chemotherapy, the presence of other disorders that have previously been described as possible factors that alter the size of the corpus callosum, and T2 signal abnormalities in the corpus callosum. Additional reasons for exclusion were identification of a normal corpus callosum on MRI and presence of a normal corpus callosum other than a nonvisualized rostrum. The study was approved by the Ethical Committee at Medical University of Bialystok, Poland.

### RESULTS

The study group was composed of 20 children with various disorders (11 girls, 9 boys), (details are summarized in table 1). The ages of the children ranged from 4 months to 17 years, with a mean age of 9.8 years. Nine patients (45%) were born from the first pregnancy. Nine patients (45%) were born from the second pregnancy and two from the third gestation. Almost all (90%) children were born at term and only two subjects were born prematurity. The average gestational age of the infants was 38.1 weeks  $\pm$  2.75 (27-40). Most children were born at 38 weeks. Nine children were born from the first gestation, nine were from the second gestation and only two from the third pregnancy.

**Table 1.** Clinical data of patients with corpus callosum abnormalities

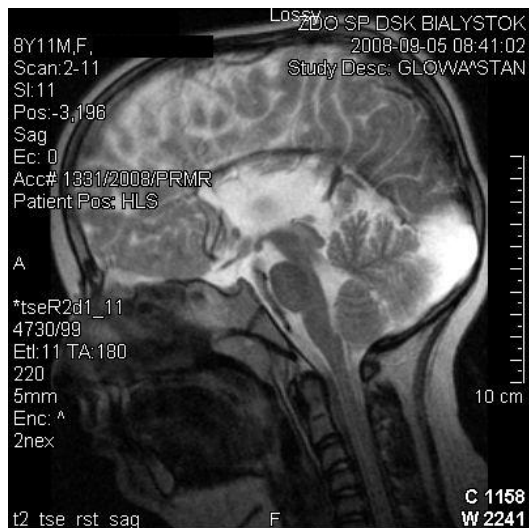
Patients	Age	Gender	Pre-gnancy	Birth	Childbirth wk.	Diagnosis	Motor function
1.MM	6	Girl	I	I	38	MMC	Wheelchair
2.WR	9	Girl	I	II	39	MR, Epi	Normal
3.KA	18	Girl	II	II	40	HP, MR	Wheelchair
4.MM	6	Girl	I	I	39	MR, Epi	Normal
5.GK	10	Girl	II	II	38	ADHD, Tics	Unable walking
6.NK	13	Girl	II	III	40	Headache	Normal
7.LK	12	Girl	I	I	36	Headache	Normal
8.FJ	6	Boy	III	III	39	PDD	Normal
9.KM	6	Girl	II	III	38	PDD, MR	Unable walking
10.ChJ	1	Girl	II	II	37	PDD, Epi	Normal
11.DM	16	Boy	II	II	40	MR	Normal
12.AR	9	Boy	I	II	40	HC	Normal
13.LA	2	Girl	II	III	39	PDD, DWS	Normal
14.LA	15	Girl	I	I	38	MR	Normal
15.BR	17	Girl	II	II	40	MR	Normal
16.RE	10	Girl	I	I	38	MR	Normal
17.FM	14	Boy	II	II	39	Headache	Normal
18.ZK	13	Boy	I	I	27	HC, MR	Normal
19.PB	12	Boy	III	III	38	HC, MMC	Wheelchair
20.PM	4	Boy	I	I	39	PDD	Normal

ADHD- Attention Deficit Hiperactivity Disorder, DWS- Dandy Walker syndrome, Epi- Epilepsy, HC- Hydrocephalus, HP- Holoprosencephaly, PDD -psychomotor development delay, MR- Mental retardation, wk-week



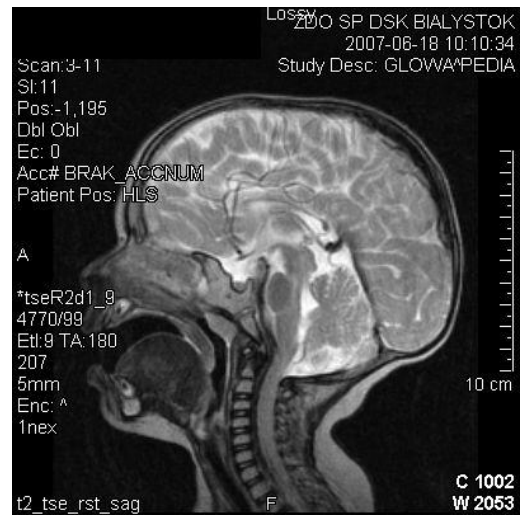
**Figure 1.** Sagittal T2-weighted MRI in 6-year-old girl a Chiari II malformation shows hypoplasia of the corpus callosum

Nine children had mental retardation, 6 girls and 3 boys. Four patients had hydrocephalus and two patients had MMC. Cerebral malformations were present in 3 children, two patients had Dandy-Walker syndrome and one holoprosencephaly. Three patients had headache. One patient had tics syndrome and one ADHD. Fifteen children had normal motor development, with three using a wheelchair, and two were unable to sit and walk. Three patients had epilepsy.



**Figure 2.** Sagittal T2-weighted MRI in 9-year-old girl shows ACC

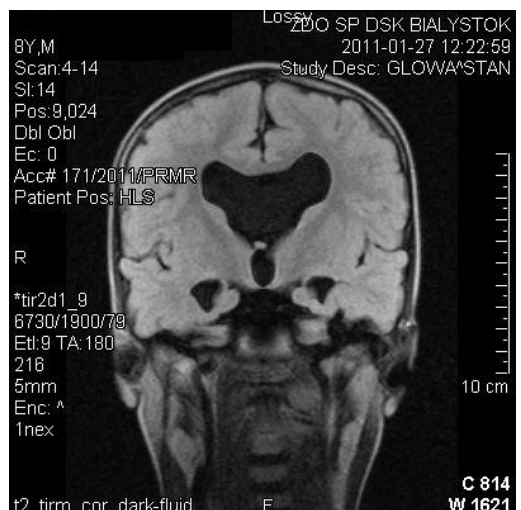
More than half of patients 11 (55%) had ACC (Figure 2), 6 children had hypoplasia (Figure 1) of the corpus callosum hypoplasia and 3 patients had an absent of genu of the corpus callosum or splenium (Figure 3). For children had also brain malformations: (2) Dandy- Walker syndrome (1) Chiari II malformation and (1) holoprosencephaly (Figure 4a,b).



**Figure 3.** Sagittal T2-weighted MR image in 1-year-old girl shows dysgenesis of the corpus callosum. The rostrum and genu are absent.



**Figure 4a.** Sagittal T2 weighted MRI in 9-year-old boy shows dysgenesis of the corpus callosum. The hypoplasia of genu and splenium, thin brain stem.



**Figure 4b.** Frontal T2 weighted MRI in 9-year-old boy shows enlarged lateral ventricles; the Evans ratio about 0.46; the enlarged III ventricle (12mm); no septum pellucidum

## **DISCUSSION**

In the present study, we found various abnormalities of the corpus callosum in children and adolescents in different disorders. ACC and hypoplasia of the corpus callosum were noted in similar proportion in girls and boys. In contrast in the literature the incidence of corpus callosum anomalies is higher in boys than girls [2,7,23]. We did not find correction between week gestation and abnormalities of the corpus callosum. About half of patients had mental retardation and one quarter had motor delay. Only three patients had epilepsy. Our findings are in accordance with previous results [2,24,25].

This study includes a small number of MRI of patients with callosal anomalies. There was considerable heterogeneity in our patients.

ACC or hypoplasia of the corpus callosum is present in more than 50 different human congenital syndromes, with clinical manifestations ranging from mild to devastating [10,22,26]. Complete and partial ACC can result from genetic, infectious, vascular, or toxic causes. Current evidence suggests that a combination of genetic mechanisms, including single-gene Mendelian, single-gene sporadic mutations and complex genetics (which may have a mixture of inherited and sporadic mutations) may be involved in the etiology of ACC. For approximately 30–45% of individuals with ACC, the cause is identifiable (about 10% have chromosomal anomalies and the remaining 20–35% have recognizable genetic syndromes [27].

Nosarti et al. [22] demonstrated differences in the absolute size of callosal subregions between preterm and full-term adolescents: a 14.7% decrease in the posterior and an 11.6% decrease in the midposterior corpus callosum quarters. Rademaker et al. [27] determined the relation between the size of the corpus callosum and motor performance in a population-based cohort of preterm children (<32 weeks). The preterm children with cerebral palsy had significantly smaller mean corpus callosum areas compared with the preterm children who did not develop cerebral palsy. However, the preterm children born without cerebral palsy also had significantly smaller body, posterior, and total corpus callosum areas compared with term-born controls. There was a strong association between the size of the corpus callosum and motor function in preterm children, investigated at school age. In the present study, we did not have patients with cerebral palsy and more children were born at term.

Shevell [28] identified children with ACC in a comprehensive computerized database of all patients seen in a single pediatric neurology practice over an 11-year interval. Twenty-four children with agenesis of the corpus callosum were

identified from 6911 children in the database (0.35%). Eight were microcephalic, 12 were dysmorphic, 11 had coexisting epilepsy, and 9 had a cerebral palsy variant. Investigations revealed an etiology in 11: 3 with chromosomal abnormality, 3 with metabolic disorder, 3 with cerebral dysgenesis, and 2 with genetic syndromes (Aicardi, Andermann). Normal or mild developmental delay was noted in 7 children, and moderate-severe developmental delay was noted in the remaining 17. These findings are partially in agreement with our results.

Corpus callosum is sensitive to viral infection. Iype et al. [29] reported two cases of encephalopathy following a short febrile illness. Case one was a 5 year old child whose MRI of the brain showed a reversible discrete lesion in the splenium of the corpus callosum and a 10 year old boy who had extensive hyperintensity of the splenium of the corpus callosum. As these children have presented while there was an outbreak of influenza in our locality and since the second child tested positive for H1N1 antigen on PCR test. The authors concluded that case one showed signs of a splenial syndrome.

Neuropsychologic testing of patients with callosal agenesis has previously revealed subtle deficits of higher cognitive function not evident on routine clinical examinations [30,31]. Another study reported that the only individuals with normal neurodevelopment were those with isolated callosal hypogenesis [32]. Only a large population-based MRI screening study could sort this out, and that task is beyond the scope of our current study.

Studies of cross-sectional callosal morphology and area have revealed developmental, gender, and hemispheric differences in healthy populations and callosal deficits associated with neurodegenerative disease and brain injury. The quantitative morphological analysis of the midsagittal corpus callosum is complicated by the interindividual variability of its size and shape [33]. However, in the current study, we did not determine volume of the corpus callosum.

Classic lissencephaly, cobblestone lissencephalies, polymicrogyria, schizencephaly, and heterotopia have all been described previously in conjunction with anomalies of the corpus callosum [33-35]. In the present study, we had patients with Dandy-Walker syndrome and holoprosencephaly.

## **CONCLUSIONS**

A spectrum of clinical presentations is apparent in children with abnormalities of the corpus callosum. More than half of patients had ACC. No correlation between gestation and the corpus callosum anomalies was found. The vast majority of patients had normal motor development and about half of patients had mental retardation.

### Conflicts of interest

The authors have declared no conflicts of interest.

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