J Neurol (2016) 263:1939–1945
DOI 10.1007/s00415-016-8225-x

ORIGINAL COMMUNICATION

Clinical manifestations in children and adolescents with corpus callosum abnormalities

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Received: 18 May 2016 / Revised: 29 June 2016 / Accepted: 30 June 2016 / Published online: 6 July 2016
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Abstract Corpus callosum abnormality (CCA) outcomes are quite unpredictable and variable, from asymptomatic forms to mild or severe neurodevelopment disorders. The aim of this study was to examine clinical outcomes in CCA patients. The study included 61 children and adolescents in whom brain magnetic resonance imaging (MRI) scans showed CCA, isolated or associated to other central nervous system lesions. All patients underwent anamnesis, physical and neurological examination, routine laboratory tests, electroencephalogram (EEG), and MRI scans. In all participants, the intelligence quotient (IQ) was determined. We divided the participants into two subgroups: the first subgroup included patients with an isolated CCA, and the second subgroup included patients with CCA associated with extra-callosal brain lesions (complex CCA). We found that CCA were associated with elevated frequency to intellectual disability (ID), other neurodevelopment disorders, epilepsy, and isolated EEG anomalies. Mild ID ($p = 0.003$) was more frequent in the isolated subgroup, while epilepsy ($p = 0.036$) and pre-perinatal risk factors ($p = 0.023$) were more frequent in the complex CCA subgroup. Although the role of the CC in the interhemispheric communication is known, neurological and neurodevelopment outcomes of CCA are extremely variable and unpredictable. The presence of extra-callosal brain anomalies is one of the major prognostic factor, and probably, they have an important impact on the clinical outcome.

Keywords Corpus callosum abnormalities · Clinical outcome · Neurodevelopment disorders · Intellectual disability · Autism · Epilepsy

Abbreviations

ACC	Agenesis of the corpus callosum
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorders
CC	Corpus callosum
CCA	Corpus callosum abnormalities
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
HCC	Hypoplasia of the corpus callosum
ID	Intellectual disability
IQ	Intelligence quotient
MRI	Magnetic resonance imaging
pACC	Partial agenesis of the corpus callosum
PCA	Post-conceptional age
tACC	Total agenesis of the corpus callosum
WISC-IV	Wechsler intelligence scale for children–fourth edition, Italian version

Introduction

The corpus callosum (CC) is a unique placental mammal structure. It is the largest of the interhemispheric white matter tracts in the brain, connecting neocortex areas between the two cerebral hemispheres [1–3].

The CC is divided into four anatomically defined regions: the rostrum, the genu, the body, and the splenium.

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It consists of approximately 200 million axons (2–3 % of all cortical fibers) topographically organized, establishing homotopic and heterotopic connections between several neocortex areas [4, 5]. The anterior sections of the CC connect more anterior regions of the cortex (prefrontal association areas, premotor, supplementary areas, and anterior inferior parietal regions); the more posterior sections connect areas of the parietal, temporal and occipital lobes [6]. Callosal connections are both excitatory and inhibitory, but the majority of fibers are excitatory [7].

In humans, CC development begins by week 8 of fetal life [8]. The number of callosal fibers is more or less determined at birth, but structural changes continue throughout post-natal development, most of all during childhood and adolescence. The CC fibers originate from neurons of layers II/III, V, and VI of the neocortex [9], while pioneering axons originate from the cingulate cortex [10]. Recent neuroimaging and neuroembryology studies show that at 13–14 weeks of post-conceptional age (PCA), callosal fibers begin to cross the midline, and then, they grow bidirectionally during weeks 18 and 19. By 20 weeks of PCA, CC shows its final shape, although exuberant axonal growth continues until 2 months after birth. Usually, post-natal maturation of the splenium precedes the genu one [3, 11, 12].

CC development is influenced by a series of complex and highly regulated events (cellular proliferation, migration, post-migrational maturation, myelinization, and axons pruning). Corpus callosum abnormalities (CCA) are the result of an anomaly of these events caused by intrauterine exposure to teratogens, metabolic disorders, genetic aberrations and several syndromes [13–16]. About 20 % of CCA are caused by single or multiple genes mutations or chromosomal aberrations [3, 15]. Autosomal dominant, autosomal recessive, and X-linked causes of CCA have been described. Many cases are apparently sporadic, so it is possible that a significant proportion of CCA cases are caused by de novo mutation [17]. New genetic microarray analysis improved the possibility to detect specific loci associated with agenesis of the CC, and recently about 30 new genomic loci have been described [18]. Because of phenotypic variability, the identification of a specific genetic cause of CCA is quite difficult.

CCA have an estimated prevalence of 0.3–0.7 % in patients undergoing neuroimaging in the general population [19–21].

Structural CCA can be classified by the images of magnetic resonance imaging (MRI) scans and include the agenesis of the CC and the hypoplasia of the CC. The total agenesis of the CC (tACC) is a complete absence from birth of all the anatomically regions of the CC; the partial agenesis of the CC (pACC) is the partial absence from birth of at least one region of the CC; the hypoplasia of the CC (HCC) is a CC thinner but with a normal extent; hypoplasia may interest one or all regions of the CC (respectively, partial or harmonic hypoplasia) [22, 23]. Other CCA include hyperplasia and dysgenesis. Hyperplasia refers to a CC thicker than normal and it results from reduced post-natal axonal pruning; dysgenesis refers to a CC developed but malformed in one or more regions [24].

CCA may be isolated or occur in association with additional cerebral lesions and/or congenital anomalies (cortical dysplasia, neuronal migration disorders, and brainstem anomalies) [16, 21, 25, 26].

Although prenatal imaging (ultrasound) may help with a CCA diagnosis, clinical outcomes in patients with CCA are quite unpredictable and variable, from asymptomatic forms to mild or severe neurodevelopment disorders [6, 27, 28]. The aim of this study was to examine clinical outcomes in CCA patients.

Methods

Population

In this observational study, we retrospectively analyzed a sample of 61 children and adolescents admitted to the Child and Adolescent Neuropsychiatric Unit of Bari and the Department of Pediatrics of the University Chieti and of the University of L'Aquila, during the period between 2009 and 2016, because of neuropsychiatric symptoms and in whom magnetic resonance imaging (MRI) scans showed CCA, isolated or associated to other SNC lesions.

We divided the participants into two subgroups: the first subgroup included patients with an isolated CCA and the second subgroup included patients with CCA associated with extra-callosal brain lesions (complex CCA). This study was approved by the Local Ethic Committee of Azienda Ospedaliero-Universitaria Policlinico di Bari, all children were recruited after obtaining written informed consent by their parents; in addition, informed consent was also obtained from the patients who could understand the content and aim of study.

Assessment

All patients underwent anamnesis (familiar, physiological, pre-perinatal, pathological, and academic), physical and neurological examination, routine laboratory tests, including blood count, liver, and renal functions, metabolic laboratory tests (ammonemia, aminoacidemia and aminoaciduria), sleep and awake electroencephalogram (EEG). MRI study was performed with a 1.5 T magnet and 8 channels coil for brain. In all participants, the intelligence quotient (IQ) was determined by Wechsler Intelligence

Scale for Children–Fourth Edition (WISC-IV) [29]; Leiter International Performances Scale Revised-Visualization and Reasoning battery (Leiter-R) [30] was administered, as an alternative to WISC-IV, to subjects with verbal disorders.

Statistical analysis

The demographical and clinical variables underwent statistical analysis. We calculated proportions and differences between the subgroup of patients with isolated CCA and the subgroup including patients with complex CCA using a Fisher's exact test and Mann–Whitney *U* test (e.g., age) to calculate *p* values. Results having $p < 0.05$ were considered significant. Calculations were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Inc., NY, USA).

Results

The patients involved in this study were 61 (male 47.5 %; female 52.5 %). The mean age was 8.8 ± 4.3 years (range 1–17 years). Three patients (4.9 %) showed a complete agenesis of the CC (tACC), seven patients (13 %) showed a partial agenesis (pACC), and 49 patients (82 %) showed a hypoplasia interesting uniformly its portions (HCC). Table 1 are summarized clinical and demographical data about all the participants. Intellectual disability (ID) was evident in 44 patients (72 %): a mild ID was found in 16 patients (26.2 %), a moderate ID was revealed in 15 patients (24.6 %), and a severe ID was found in 13 patients (21.3 %). A single neurodevelopment disorder was present in 28 patients (47.5 %): language disorders were present in seven patients (11.5 %), autism spectrum disorders (ASD) were found in four patients (6.6 %), attention deficit hyperactivity disorder (ADHD) was present in two patients (3.3 %), and developmental coordination disorder was present in one patient (1.6 %). More than one neurodevelopment disorder was found in 21 patients (35.6 %). Epilepsy was present in 22 patients (36 %): a partial epilepsy in 10 patients (45.4 %), a partial with secondary generalization epilepsy in 6 patients (27.3 %), and a generalized epilepsy in 6 patients (27.3 %). Pre/perinatal risk factors were present in 26 patients (42.6 %). Isolated EEG anomalies were present in 14 patients (23 %), with variable patterns. Cerebral palsy was detected in two patients (3.3 %). A syndromic diagnosis was found in ten patients (16.4 %): a Noonan syndrome in one patient, a Sotos syndrome in one patient, an Arnold–Chiari malformation in one patient, a Dandy–Walker malformation in one patient, an incontinentia pigmenti in two patients, a Smith–Lemli–Opitz syndrome in two patients, and an unknown plurimalformative syndrome in two patients.

Table 1 Characteristics of the participants (n = 61)

	M ± Ds
Age	8.8 ± 4.3
	%
Gender	
M	47.5
F	52.5
tACC	4.9
pACC	13.1
HCC	82
Intellectual disability	72.1
Mild	26.2
Moderate	24.6
Severe	21.3
Other neurodevelopment disorders	47.5
Language disorders	11.5
Autism spectrum disorders	6.6
ADHD	3.3
Developmental coordination disorder	1.6
>Than one	35.6
Epilepsy	36
Isolated EEG anomalies	23
Pre-perinatal risk factors	42.6

CC corpus callosum, *ACC* agenesis of the CC, *tACC* total ACC, *pACC* partial ACC, *HCC* hypoplasia CC

Isolated CCA vs. complex CCA

In 16 patients (26.2 %), the CCA was isolated; in 45 patients (73.8 %), the CCA was associated with other SNC lesions, including cerebral cortex malformations (cortical dysplasia, neuronal migration disorders, Arnold–Chiari malformation, and Dandy–Walker malformation), cerebellum hypoplasia, and perinatal hypoxic-ischemic damages. The two subgroups were homogeneous by age ($p = 0.266$) and sex ($p = 0.524$). Clinical characteristics of each subgroup are summarized in Table 2. The isolated CCA was found only in the hypoplasia of the CC. ID was present in the 81.3 % of the isolated CCA subgroup (mild ID was present in the 56.6 %, moderate ID was present in the 18.8 %, and severe ID was present in the 12.5 %) and in the 68.9 % of the complex CCA subgroup (mild ID was present in the 15.6 %, moderate ID in the 26.7 %, and severe ID in the 24.4 %). The isolated CCA subgroup was more characterized by mild ID level ($p = 0.003$) compared with complex CCA subgroup. We found also a statistical significant difference in presence of epilepsy ($p = 0.036$) and pre-perinatal risk factors ($p = 0.023$) between subgroups. Epilepsy and pre-perinatal risk factors were more frequent in the complex CCA compared with isolated CCA

Table 2 Characteristics and differences between isolated CCA and complex CCA subgroups

	Isolated CCA ($N = 16$), M ± Ds	Complex CCA ($N = 45$), M ± Ds	p value
Age	7.8 ± 4.5	9.26 ± 4.2	NS
	%	%	p value
Gender			
M	50	46.7	NS
F	50	53.3	NS
tACC	–	6.7	NS
pACC	–	17.8	NS
HCC	100	75.6	NS
Intellectual disability	81.3	68.9	NS
Mild	56.6	15.6	0.003*
Moderate	18.8	26.7	NS
Severe	12.5	24.4	NS
Other neurodevelopment disorders	37.5	51.2	NS
>Than one	43.8	32.6	NS
Epilepsy	12.5	42.2	0.036*
Isolated EEG anomalies	37.5	17.8	NS
Pre-perinatal risk factors	18.8	51.1	0.023*

tACC total agenesis, *pACC* partial agenesis, *CC* corpus callosum, *NS* not significant; * $p < 0.005$

subgroup. No statistical significant difference was found for the other emerged data including isolated EEG anomalies, moderate and severe ID and other neurodevelopment disorders. Table 2 shows comparison and differences between the two subgroups.

Discussion

CCA are frequently associated with neurological conditions (epilepsy, cerebral palsy, and movement disorders) and neurodevelopment disorders (ID, ASD, developmental coordination disorder, language disorders, learning disorders, and ADHD) [6, 24, 31]. Clinical consequences of CCA are quite unpredictable and wide ranging. The co-presence of other brain anomalies and the etiology may influence the clinical outcome [27, 28]. Even when the neuroradiological and neuroanatomical findings are similar, the clinical consequences of CCA are variable [21]. Therefore, this variability could be influenced by differences in neuronal compensatory plasticity, precise anatomy, presence of other clinical comorbidities, genetic background, or by environmental factors.

In our sample, we found that CCA were associated in high frequency to intellectual disability, other neurodevelopment disorders, epilepsy, and isolated EEG anomalies.

The role of the CC in the cognitive functions is well documented in literature. Recent studies show that the absence of a complete development of the CC interferes with the intra-interhemispheric functional interactions between brain areas involved in some cognitive processes (executive functions, processing speed and problem solving abilities) [31]. However, CCA do not seem to have actually a dramatic or direct impact on general cognitive abilities. Recently, some authors [27] report that neurodevelopment outcome of individuals diagnosed antenatally with an ACC (with no additional postnatal MRI anomalies) can range in a normal development in about 75 % of cases to different levels of intellectual disability; in this series, about 12 % of individuals had severe intellectual disability. Moreover, the neuropsychological outcome is not clearly linked to the severity of the CCA; individuals with CCA have more consistently deficits in complex information processing abilities, such as "cognitive information processing" (the ability to automatically perform previously learnt cognitive tasks), complex attention and memory skills, and specific academic skills, especially mathematics [24]. However, the patients with CCA, even with a normal IQ, have subtle behavioral and social problem [31–33]. In this study, the intellectual disability was present in 72.1 % of all participants. Mild ID prevailed in the isolated CCA subgroup with a statistical significant difference; moderate and severe ID prevailed in the subgroup of the complex CCA, with no statistical significant difference. Therefore, the associated brain lesions may be responsible of the severity of ID. Other neurodevelopment disorders were frequent in our cohort (47.5 % of patients had at least one disorder), with a higher incidence in the complex CCA subgroup. The more frequent disorders were language disorders, ASD, ADHD, developmental coordination disorder, and cerebral palsy. The association of CCA and neurodevelopment disorders is well described in literature. First, studies focused on inter-hemispheric transfer suggested a relationship between CC malformations, language disorders, and motor coordination disorder. This hypothesis was based on the observation that several children with CCA showed also language impairment and motor coordination deficits [34]. More recent functional neuroimaging studies support the hypothesis that, in patients with CCA, there is a correlation between the alterations of the integration of sensorial and motor processes realized by the interhemispheric transmission of the CC and the development of both language disorders and developmental coordination disorders [6]. The involvement of the CC in autism is supported by several literature data. Many studies show that in ASD, there is a reduction of the total or partial volume of the CC. Structural meta-analysis studies [35] and diffusion tensor imaging (DTI) with tractographic reconstruction meta-analysis studies [36, 37] in autistic patients support the hypothesis of a CC structural

connectivity dysfunction [6, 38]. First, children with ADHD and dyslexia were detected a significant reduction of genu and splenium of the CC [39]. Successive studies confirmed also these findings in children and adolescent with isolated ADHD [40, 41]. These alterations of the splenium of the CC in ADHD patients were also reported in recent studies of functional neuroimaging based on MRI with DTI technique [42, 43].

Structural alterations of the CC are well reported in epilepsy syndromes with childhood onset [41, 44–46], such as temporal lobe [47] and neocortical epilepsy [48]. In our study, epilepsy was present in the 36 % of the participants and it was more frequent in the complex CCA subgroup than in the isolated CCA subgroup with a statistical significant difference. As reported in a recent review, CCA are not indicative for seizure disorders; in fact, seizures generally hint to an additional pathology. Since white matter structures include no firing neurons they cannot act as epileptic foci [26]. Therefore, the extra-callosal lesions, such as the cortical dysplasia, may be the origin of the epileptic focus and the CC may be involved only in the diffusion of the abnormal electrical activity from one hemisphere to the contralateral hemisphere [26, 49]. A recent study confirmed the genu of the CC as the major pathway for seizure generalization [50]. We found isolated EEG anomalies not associated to epilepsy in the 22 % of our patients and these findings may confirm the role of the CC in the diffusion of interhemispheric abnormal electrical activity. On the other hand, in both subgroups, these EEG anomalies did not present specific patterns as already reported in the literature [49]. Furthermore, pre-perinatal risk factors were present in the 42.6 % of the participants and they were more frequent in the complex CCA subgroup than in the isolated CCA subgroup, with a statistical significant difference. According to literature data, children born pre-term and with a low birth weight have frequently widespread damages of white matter, including a reduction of the total volume of the CC and microstructural alterations of the CC [51–54].

Bias of our data may be linked to small sample sizes, short follow-up time, lack of consistency in neuropsychological measures, heterogeneity of sampled individuals, and lack of appropriate control subgroups.

Conclusions

The development of the CC is the result of sophisticated processes and regulated events, from the proliferation of the precursor cells to migration and post-migration maturation pathways. These complex mechanisms may be interrupted in different stages of the CC development by several factors (genetic anomalies or environmental factors), resulting in different kind of CCA. However, it remains unclear whether the CCA follow an initial failure of connections to establish correct organization, or a later loss of successfully formed brain connections. Even if the role of the CC in the interhemispheric communication is known, neurological and neurodevelopment outcomes of CCA are extremely variable and unpredictable. The presence of extra-callosal brain anomalies is one of the major prognostic factor, and probably, they have an important impact on the clinical outcome. Future clinical, genetic, and neuroimaging studies may be helpful to better understand CCA clinical outcomes.

Acknowledgments We thank the families for their contribution to this study.

Compliance with ethical standards

This study was approved by the Local Ethic Committee of Azienda Ospedaliero-Universitaria Policlinico of Bari, all children were recruited after obtaining written informed consent by their parents; in addition, informed consent was also obtained from the patients who could understand the content and aim of study.

Conflicts of interest The authors declare that they have no conflict of interests.

Funding No fundings were provided for this study. The authors declare that they have no financial relationship with any sponsoring organization.

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