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Morphometric changes of white matter structures in the pediatric age group

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Abstract

The corpus callosum (CC) and capsula interna (CI), which are among the white matter structures of the brain, provide the connection between the hemispheres. The development of the CC in childhood, its relationship with age and sex, and its relationship with the development of cognitive functions in adolescence are among the issues of interest. Our study aimed to evaluate the CC and CI measurements with magnetic resonance imaging (MRI) to assess age-related normal growth and development from childhood to young adulthood. Three hundred thirty cases (170 males and 160 females) between the ages of 0-15 whose brain MRI examinations were performed and whose images were considered normal by expert radiologists were evaluated in our study. The participants were divided into four groups according to their age. For the CI measurements, the thickness of the crus anterior, crus posterior, and genu parts and the genu angle were evaluated. In the measurements on the CC, the total length of the CC (CC VI), which indicates the distance between the endpoint of the genu and splenium part, was taken with measurements number CC I, II, III, IV, and V, in which the thicknesses of the CC genu, truncus, and splenium parts were measured on the midsagittal section. In the evaluation of the CC sections between the 1st groups and the other groups (p<0.001), and the anterior and middle parts of the truncus were the earliest developing parts. All parameters increased with age. Except for the thickness conther groups in males, no difference was revealed between the sexes in any parameter (p>0.05). No difference was observed between the right and left sides in the CI measurements (p>0.05). The angle formed in the genu part was found to be 119°. In the literature review, we observed that there were few studies on the healthy pediatric population in Turkish society. We hope that the parameters we obtained may contribute to evaluating potential clinical conditions.

Keywords: Corpus callosum, internal capsule, morphometry, MRI, pediatrics

Introduction

The corpus callosum (CC) and capsula interna (CI) are among the white matter structures of the brain and are stated to have quite a lot of fibers passing through them [1]. The CC is approximately 10 cm long and is anatomically divided into four parts the rostrum, genu, truncus, and splenium [2-4]. The CI is an important pathway

and has three parts defined as the crus anterior, genu, and crus posterior [2].

The development of the CC is quite evident during the first 1-4 years after birth, and this increase continues throughout adolescence and lasts until the age of 30s [1,4]. It has been indicated that the thickness of the CC, one of the important regions especially due to its role in the interhemispheric connection, is associated with higher intelligence, problem-solving, and analysis abilities in children [4,5]. Furthermore, morphological abnormalities in the CC are associated with abnormalities in cognitive processes and behavioral development [6,7].

The thickening or thinning of the CC originates from inherited or

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acquired neurodegenerative conditions that affect its development [8]. Morphological abnormalities of the CC may be a cause of diseases such as speech disorder and dyslexia, neurofibromatosis, and multiple sclerosis [9,10]. The shape and size of the CC may also differ between sexes. Thus, it was indicated that there was thickening in certain parts in males in some studies and females in other studies, while some studies stated no difference [4,11].

It is considered that an analysis of age-related changes in the size and characteristics of the CC can provide information about the processes related to normal or abnormal development [4,12]. Likewise, the CI is an important indicator region to identify neurological diseases at every stage of life and is vital in diagnosing diseases with axonal damage [13]. Considering that neurodegenerative diseases and neurological disorders may also contribute to the diagnostic stage, we conducted the present study to evaluate the normal growth and development of the CC and CI from childhood to young adulthood with magnetic resonance imaging (MRI). In our study, it was aimed to give morphometric data on normal growth and development, which we have identified in relatively few studies and which we think may lead to later studies, especially in normal populations without any developmental pathology.

Materials and Methods

Our retrospective study was conducted on archival data of the patients who applied to Afyonkarahisar Faculty of Medicine and had brain MRIs in the Department of Radiology. The procedures followed for our retrospective study were carried out following the 1975 Declaration of Helsinki, which was revised in 2000, and with the ethical approval of the institutional 'Clinical Research Ethics Committee (decision dated 04.02.2022 and numbered 2022/107).

Our study is a retrospective study, and cases with a diagnosis of congenital brain malformations, intracranial trauma or tumor cases or suspected cases, known epilepsy, migraine, and autism were excluded from the study. Patients between the ages of 0-15 who applied to the pediatric clinic between 01 January 2019 and 31 October 2021 with complaints such as headache, dizziness, vertigo, and neuromotor developmental delay or were followed up, who underwent brain MRI examinations for diagnostic purposes in the department of radiology and whose radiological images were considered normal by expert radiologists as a result of the examination were included in the study. Three hundred thirty cases (170 males and 160 females) whose radiological follow-ups were considered normal were evaluated in the study. The participants were divided into 4 groups according to their age Group 1 (1-2 years), Group 2 (3-6 years), Group 3 (7-11 years), and Group 4 (12-15 years).

According to the information obtained from the archival research, cases with diffuse gliotic foci on radiological images, encephalomalacia of any size, congenital brain malformations, findings suggestive of infection in the central nervous system, pathologies that may affect the thickness of the CC and CI, and poor MR image quality were excluded from the study.

Radiological images were obtained from the 1.5T MRI (Philips Medical Systems, Netherlands) device. The MR protocol was as follows: TR=500ms; TE=15 ms; FOV =23cm, slice thickness

5mm; output number=2; matrix size=256×256. Anatomical measurements were performed using the Aquarius NET program (TeraRecon Inc., USA) on Aquarius Workstation.

The CI measurements were based on images with TSE/T1weighted white matter hyperintensity at the level where the nucleus caudatus, nucleus lentiformis, and thalamus were seen on the same transverse section. The thickness of the CI parts (crus anterior CIA, crus posterior CIP, and genu CIG) was evaluated. The widest parts of the CI between the thalamus and the nucleus lentiformis were measured bilaterally. The lateral opening angle (genu angle CIAC) of the line passing through the middle of the crus anterior and posterior and intersecting at the genu was evaluated (Figure 1).



Figure 1. Capsula interna (CI) measurements on the transverse sections. A: CI crus anterior thickness (CIA), B: CI genu thickness (CIG); C: CI crus posterior thickness (CIP); D: CI genu angle, the outward-facing angle between the lines passing between the crus anterior and crus posterior (CIAC)

The measurements related to the CC were obtained on images with TSE/T1-weighted white matter hyperintensity and the midsagittal section. The morphometric measurements were performed by applying some modifications according to the methods reported in previous studies [1,14]. First, a transverse line (AP line) drawn parallel to the long axis of the CC was determined. The vertical lines shown in Figure 2 were taken to the AP line to determine the standard regions at the measurement points. Then, the number of the measurement CCI, CCII, CCIII, CCIV, and CCV passing through the genu, truncus, and splenium parts of the CC were taken. Finally, the total length of the CC (CCVI) was measured with the transverse line connecting the endpoint of the genu part and the endpoint of the splenium part on the sagittal plane (Figure 2).

Statistical analysis of the study data was performed with the IBM Statistical Package for Social Sciences (SPSS) Statistics 25.0 program. The normal distribution of data was analyzed with the Shapiro Wilk test. After it was determined that the data were not normally distributed, the Kruskal-Wallis H test was used to determine the differences between multiple independent continuous variables, and the Mann-Whitney U test was used to compare the paired groups with Bonferroni correction. P <0.05 were considered statistically significant.



Figure 2. Brain MRI image of a 4-year-old male patient admitted with the complaint of headache. Mid-sagittal T1-weighted corpus callosum (CC) sections are seen. First, the transverse line (AP line) and the lines perpendicularly intersecting this line were drawn as the leading lines. The measure passing through the genu part of the CC was indicated as Corpus callosum I (CCI), and the measure passing through the splenium part was indicated as Corpus callosum V (CCV). Corpus callosum II, III, and IV (CCII, CCIII, and CCIV) measurements were taken according to the lines perpendicularly intersecting the AP line from the truncus part. Then, the measure passing through the extreme points of the rostrum and genu parts was measured as the CC anteroposterior length (CCVI)

Results

All groups were compared between the sexes. The mean and standard deviations and minimum and maximum values of the thickness of the CC parts according to age groups are presented in Table 1. Accordingly, in the measurement number CCI showing the genu part of the CC and in the measurement number CCIV showing the thickness of the isthmus, a difference was found between the 1st group and the other groups, and between the 2nd group and the 4th group. In the measurement number CCII showing the thickness of the anterior part of the truncus part of the CC and in the measurement number CCIII showing the thickness of the middle part, it was determined that there was a difference between the 1st group and the other groups, but there was no difference between the other groups. In the CCV measurement showing the total length of the CC, a difference was found between the 1st group and the 2nd group, and the other groups (Table 1).

In the comparison of the thicknesses of the CC parts according to sex, in the CCIV measurement showing the thickness of the isthmus part, it was determined that there was a difference between sexes and it was bigger in males compared to females and that there was no difference between the other groups (Table 2).

When the mean and standard deviation of the lateral angulation in the crus anterior, genu, and crus posterior and genu parts of the CI were evaluated across all age groups, no statistical difference was observed between the sides (Table 3).

In the correlation table, there was a relationship indicating a weak and moderate but statistically positive correlation with age in the CC measurements [15]. There was a weak and highly varying relationship showing a statistically positive correlation between the crus anterior, genu, crus posterior, and lateral angle of the CI (Table 4).

Table 1. Mean and standard deviation (sd) of the corpus callosum (CC) parts according to age groups

Age	Number of cases	CCI Mean±sd (mm) Min-max	CCII Mean±sd (mm) Min-max	CCIII Mean±sd (mm) Min-max	CCIV Mean±sd (mm) Min-max	CCV Mean±sd (mm) Min-max	CCVI Mean±sd (mm) Min-max	
1 st group	44	7.9±1.5	5.1±1.5	4.4±1.0	5.5±4	6.6±1.4	52.8±4.4	
(1-2 years)		(4.6-10.3)	(2.9-8.5)	(2.3-6.3)	(2.5-8.2)	(3.4-9.2)	(41.5-59.1)	
2 nd group (3-6 years)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		5.8±0.9ª (4-7.7)	$\begin{array}{c} 6.4{\pm}1.05^{\rm a} \\ (4{\text{-}}8.4) \end{array}$	9.3±1.2a (7.8-11.5)	60.65±4.2a (45-70.7)		
3 rd group	110	11.1±0.9ª	7.0±1.1ª	6±1ª	6.9±0.9ª	10.1±1 ^{ab}	63.9±3.1 ^{ab}	
(7-11 years)		(8.8-13.9)	(5.2-8.7)	(4.4-7.9)	(5.2-9.4)	(8.1-13)	(54.4-72.5)	
4 th group	88	11.6 ±1.1 ^{ab}	7±1.1ª	6.1±0.8ª	7.2 ± 0.8^{ab}	10.4±0.9 ^{ab}	64.4±2.6 ^{ab}	
(12-15 years)		(8.5-13.5)	(5.2-10.1)	(4.4-8.7)	(4.6-9.4)	(8.1-13)	(56.6-72.5)	

^a: There is a statistical difference between the 1st group and the other groups p<0.001

⁽CCI: Corpus callosum I, CCII: Corpus callosum II, CCIII: Corpus callosum III, CCIV: Corpus callosum IV, CCV: Corpus callosum V)

Table 2 Mean and standard deviation (sď) of the corn	us callosum ((CC)	narts according to sex
Table 2. Weath and Standard deviation	and a	, or the corpt	us cunosum ($(\mathcal{O}\mathcal{O})$	puits according to sex

Age	Number of cases	CCI Mean±sd (mm)	CCII Mean±sd (mm)	CCIII Mean±sd (mm)	CCIV Mean±sd (mm)*	CCV Mean±sd (mm)	CCVI Mean±sd (mm)
Female	170	10.6±1.8	6.5±1.2	5.7±1	6.4±1.1	9.5±1.7	61.4±5.9
Male	160	10.7±1.6	6.8±1.2	5.8±1.1	6.9±1.4	9.5±1.6	61.9±4.9
Total	330	10.6±1.7	6.7±1.2	5.7±1	6.6±1.3	9.5±1.6	61.6±5.4
P-value		P=0.503	P=0.103	P=0.588	P=0.01 *	P=0.817	P=0.606

*: There is a statistical difference between the two groups p<0.001

(CCI: Corpus callosum I, CCII: Corpus callosum II, CCIII: Corpus callosum III, CCIV: Corpus callosum IV, CCV: Corpus callosum V, CCVI: Corpus callosum VI)

^b: There is a statistical difference between the 2nd group and the other groups p<0.001

Table 3. Mean and standard deviation (sd) of the parts of the capsula interna (CI) and lateral angulation

	Right side Mean±sd (mm) / Min-max (mm)	Left side Mean±sd (mm) / Min-max (mm)	P-value					
Crus anterior (CIA) (330)	3.6±2.2/1.7-29.4	3.4±0.9/1.6-5.7	0.354					
Genu (CIG) (330)	6.5±1.3/2.8-9.1	6.5±1.3/3.2-9.1	0.694					
Crus posterior (CIP) (330)	4.5±0.9/1.9-9.1	4.4±1/1.1-6.6	0.689					
Genu angle (CIAC) (330) 119.80±4.26/107.6-130.5		119.180±4.4/107.4-129	0.226					
There is no statistical difference be	tween the two groups p>0.05							
Table 4. Correlation table between the corpus callosum (CC) and capsula interna (CI) measurements and age								

	CCI	CCII	CCIII	CCIV	CCV	CCVI	CIA	CIG	CIP	CIAC
Correlation coefficient	0.57	0.36	0.37	0.41	0.6	0.6	0.3	0.73	0.6	0.114
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.038

The correlation coefficient can be interpreted according to the specified criteria:

0-0.25 Very weak correlation; 0.26-0.49 Weak correlation; 0.5-0.69 Moderate correlation; 0.7-0.89 High correlation; 0.9-1 Very high correlation; (CCI: Corpus callosum I, CCII: Corpus callosum II, CCII: Corpus callosum II, CCIV: Corpus callosum IV, CCV: Corpus callosum V, CCVI: Corpus callosum VI)

Discussion

Different pathological conditions affect the morphological structure of the CC, there are also demographic differences such as sex, age, right or left-hand use, and genetic differences [1,3,7,16-18]. Concerning the CI, another white matter structure affected by different pathological conditions, studies have been conducted with different methods such as diffusion tensor tractography, functional MRI, and cadaver studies [13].

The thinning of the CC can be observed locally or widely in conditions that cause myelin damage such as leukoencephalopathy, myelination disorder, metabolic diseases affecting white matter, hypoxic-ischemic encephalopathy, diffuse axonal injury due to trauma, and hydrocephalus [8]. While the thickening of the CC was reported as a finding that was considered by some researchers as a sign of poor prognosis in the fetal period, it was reported by other researchers as a finding with an asymptomatic course and a low incidence [16]. The study by Schupper et al. [16] indicated that children with the thickened CC did not face any obstacles in their lives and also identified that the increased callosal thickness was associated with higher intelligence, problem-solving, and processing skills [16,19].

While the studies that contribute to the morphometric evaluation of the CC have been mostly conducted on adults, there are also studies on children. In these studies, the measures of the CC and the relationships between age and sex were evaluated. In their study on 190 children aged between 5-18 years, Luders et al. [20] indicated that the most prominent thickening and the least prominent thickening in the CC were in the splenium region and the genu region, respectively [20] In their study comparing preschool children and adults, Giedd et al. [21] found that the rostrum and genu parts of the CC completed their development in the early period [21]. In their study on a large series of 622 cases, Garel et al. [11] found that the thickness of the genu and splenium parts of the CC increased rapidly until 3 years of age and that there was a progressive increase in the length of the CC during childhood [11]. Some researchers have also revealed that the thickness of

all segments, except for the rostral part, increases with age [4,12]. Likewise, in the present study, in the comparison of all parts of the CC between the groups, we found a difference between the 1st group and the other groups and no difference between the 3rd and 4th groups. In our study, it draws attention that the 2nd group, namely, 3-6 years old, was the age group showing growth together with the 1st group in all parts of the CC. Similar to previous studies, we can think in our study that the development of the CC parts was shaped in the 3-6 age group, the anterior and middle parts of the truncus were the earliest developing parts since there was no difference between the groups from the age of 3 in these two parts. We observed that the splenium part and the total length continued to develop after the anterior and middle parts of the truncus and the genu and isthmus parts statistically significantly increased again in the 11-15 age group. In this way, our study is consistent with the result showing that some parts of the CC were shaped in the early period, as indicated by Garel et al. [11]; however, it differs in that the part shaped in the early period was the anterior and middle part of the truncus, and the last shaped part was the genu.

When the sex differences in CC development were evaluated, some studies indicated a difference in certain regions in males and females, while other studies indicated no difference between sexes [4,17]. Guz et al. [3] stated in their study that the thickness of the isthmus was more common in males in the 15-20 age group, but this difference was not statistically significant [3]. When Kapıcı et al. [4] compared the relationship between the CC parts and sex, they determined that the genu thickness was greater in the 7-11 age group, and the isthmus thickness was greater in males in the 0-2 age group (p<0.05). In their study on 200 children aged 6-18 years in the pediatric population, Akın et al. [22] could not reveal a difference between the sexes [22]. Other studies that evaluated the thickness of the CC parts, the length of the CC, and the total callosal area reported no significant difference between the sexes [5,11]. In our study, in the evaluation of the thickness of the CCIV, which corresponds to the isthmus region from the CC parts, between sexes, it was observed to be higher in males.

When the total length of the CC was examined, Guz et al. [3] stated

that there was no difference between sexes in the 0-10 age group. However, although the CC length was greater in males between the ages of 11-70, this difference was not statistically significant. Kapıcı et al. [4] found that the total length of the CC increased significantly between the groups of both sexes, but there was no difference between the sexes. Our study revealed that the CCVI parameter, which shows the total length of the CC, did not differ between sexes, it increased with age between the groups, and this increase was significant between the 1st and 2nd groups and between the 3rd and 4th groups. It was found that the length of the CC increased in the first two groups, namely, until the age of 6, and it was observed that the increase in the growth curve with age was not statistically significant.

The development of the CC consisting of myelinated nerve fibers has always been a matter of concern from the fetal period to adulthood [3,4,17]. The studies indicated that the CC continued to grow until adolescence, and then, its size decreased slightly [20]. It is stated that there are many factors in the size of the CC, such as the number and size of the axons that form it, the thinness or thickness of the fibers passing through its parts, and perivascular fluid, that the most likely reason for the age-related increase in myelination, and that myelination continues from the fourth month after birth to young adulthood [11,17,23,24]. In our study, a significant difference between the 1-2 age and 3-6 age groups and other age groups in all regions of the CC supports the idea that myelination is more prominent in the first four age groups.

In studies on adults, parameters such as the length and distribution of fibers forming the CI, which is an important region in terms of functional and clinical features, were evaluated, and a study determined that the lateral angulation in the genu region was 120 degrees [13]. There are few studies evaluating the capsula interna morphometry with imaging methods such as diffusion tensor imaging, fMRI, and cadaver dissection, and they are very few [13]. In our study, compared with the morphometric measurements reported in adults, it was found that the measurements were greater in the 0-15 age group and that the lateral angle was 120 degrees, just like in adults [13]. Data are indicating that the crus anterior part of the CI and the genu part of the CC were myelinated almost simultaneously as the structures containing axons originating from the same brain region [25]. In addition to the opinions stating that most changes in white matter structures occur in the first four years of life and that there is no significant difference in the maturation rate in adolescence, there are also opinions stating that they continue to increase in volume and become more myelinated during adolescence [26]. Therefore, it is also stated that the importance of quantitative measurements to detect brain maturation in this "late" period of brain development is greater [26].

In the literature, different techniques were used to estimate the size and growth of the CC. The CC, which has four parts in classical sources, was divided into 3, 4, 6, or 7 subsections on the midsagittal sections, and thickness, area, or circumference measurements were performed [1,11,17,23,24]. To identify the thinning or thickening of the CC, it is necessary to consider that the location of the measurement points and the person who performs the measurement may differ, as is stated in the studies [11,16,27]. The difference in the individual appearance of the CC is also one of the possible problems in determining the thickness of the CC parts [1,11]. Different and advanced imaging techniques mentioned in previous studies are very useful for a better understanding of CC growth and its variations. However, their use in daily practice is not considered more ergonomic [11]. Therefore, we conducted our study with this method by believing that its easy accessibility and easy evaluation in daily practice can be an advantage, although widespread use of magnetic imaging and measurements taken on a single section are a handicap.

In the present study, we aimed to determine the mean morphometric values by measuring the thickness of the CC and CI parts and the length of the CC with MR imaging in the pediatric population. Larger scale and comprehensive studies are still needed to obtain accurate measurements of these important neural structures. In the study by Ng et al. [5], one of the studies in which the CC morphology was evaluated together with clinical findings, they showed that the academic and language learning performance of 100 primary school children was associated with the thickness of the posterior CC. On the other hand, Chavarria et al. [28] showed that children with a thicker CC had higher puberty scores [1,28]. To understand the effect of different morphological structures on individuals, it will be more efficient to monitor the studies in which the psychosomatic development of individuals is evaluated in the longer term and the effects of behavioral patterns can be observed until adulthood.

Conclusion

CIn the literature review, we found that there are few studies on the development process of CC and CI in the healthy pediatric population, including infancy, in Turkish society [1,4,22]. Our study determined the mean morphometric values by measuring the thickness of the CC and CI parts and the length of the CC with MR imaging in the pediatric population. In the future, we hope that the use of these data can contribute to evaluating possible clinical conditions of the CC and CI morphometric evaluation.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

The procedures followed for our retrospective study were carried out following the 1975 Declaration of Helsinki, which was revised in 2000, and with the ethical approval of the institutional 'Clinical Research Ethics Committee (decision dated 04.02.2022 and numbered 2022/107).

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