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The Impact of Multiple Sclerosis on the Size and Morphology of Corpus Callosum: An MRI-Based Retrospective Study

Impacto de la Esclerosis Múltiple en el Tamaño y la Morfología del Cuerpo Calloso: Un Estudio Retrospectivo Basado en Resonancia Magnética

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SUMMARY: The corpus callosum (CC) includes the majority of fibers linking the two brain hemispheres. Several cross sectional studies showed an association between callosal atrophy and malfunction and neurodegenerative diseases, which may play a role in their pathological manifestations. As a result, the accurate quantification of the corpus callosum is important to have normative values according to sex, age and ethnicity. The purpose of this study is to determine the size of CC in patients suffering from multiple sclerosis, and compare it to CC size in healthyindividuals. Midsagittal size of CC were recorded prospectively from 404 routine MR brain examinations in normal individuals. The internal skull surface was measured to calculate CC/ internal skull surface ratio. Two groups of patients were studied: 200 (100 male /100 female) healthy individuals and 204 (101 males/103 females) with multiple sclerosis (MS). Mean surface area of CC in controls was 6.58±1.04 cm^2 and there was no significant difference between males and females ($P< 0.627$). CC/ internal skull surface ratio was 4.44±0.77 %. MS patients showed a significant decrease in CC size compared to normal controls. Using MR imaging, we measured the mean sizes of the various portions of the CC in normal individuals, in addition to MS patients; these values may provide a useful basis to determine changes occurring in CC structures.

KEY WORDS: Corpus callosum; Morphology; Magnetic resonance image; Multiple sclerosis.

INTRODUCTION

The corpus callosum (CC) is the largest white matter tract in the nervous system connecting the two brain hemispheres. A combination of sensory, motor and cognitive information is constantly being transferred between hemispheres via this neural highway (Sidtis *et al*., 1981). The midsagittal CC area (CCA) is used as an estimator of the number of small diameter fibers involved in higher-order cognitive functions (Aboitiz, 1992) and a larger CCA has been hypothesized to reflect improved interhemispheric communication (Luders *et al*., 2007).

The CC has four parts: (1) the anterior part called the rostrum, (2) the second part located behind the anterior CC called the genu (3) the long central section that lies between the genu and splenium, which forms the body, and (4) the posterior rounded end called the splenium.

Several neurodegenerative pathologies were found to lead to alterations in the CC morphometry, including bipolar disorder (Sarrazin *et al*., 2015), leukoaraiosis (Yamauchi *et al*., 2000), Alzheimer's disease (Khasawneh *et al*., 2022), and Williams's syndrome (Schmitt *et al*., 2001). In case of severe injury, the brain's hemispheres are not able to communicate properly, and the loss of a range of functions can occur, such as visual perception, speech and memory.

Multiple sclerosis (MS) is a neurodegenerative disorder affecting the central nervous system (Doshi & Chataway, 2016). In MS, the immune system attacks myelin sheath that covers nerve cells in the brain and spinal cord, which leads to communication problems between the brain and other parts of the body, causing a wide range of potential symptoms, including impaired vision, arm or leg movement, sensation or balance (Doshi & Chataway, 2016).

The CC is of peculiar interest in MS. Lesions of the CC were found in up to 53 % of MS patients (Caligiuri *et al*., 2015). Moreover, it is well known that CC damage progresses along the course of MS.

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The introduction of magnetic resonance imaging (MRI) has permitted the evaluation of CC abnormalities *in vivo* in both healthy subjects and patients with diseases that affect the white matter like MS. MS diagnosis is mainly based on MRI, which is also useful for prognostic purposes (Sotgiu *et al*., 2022). The main advantage of this method is that it is a noninvasive imaging technology that produces detailed three-dimensional anatomical images. Congenital CC deformities such as agenesis, dysgenesis, and hypoplasia are the most frequent callosal anomalies, and these malformations have been reported extensively using MRI technology (Barkovich & Norman, 1988).

In the present study, we investigated the CC size in healthy participants and in patients suffering from MS, and we evaluated the possible atrophy of the CC by comparing the mean surfaces of CC and the CC/ internal skull surface ratios measured on the midsagittal MR plane. This method was chosen because individuals with a small skull may show a small corpus callosum (Krupa & Bekiesinska-Figatowska, 2013). To control variations in skull size, we measured the areas of the midline internal skull surface by manually tracing the line through the inner table, as these measurements are easier to obtain.

MATERIAL AND METHOD

Sample study

This retrospective study was approved by the Institutional Research Board at the Jordan University of Science and Technology (IRB #6/133/2021).

The study participants included patients from King Abdallah Hospital who have been referred for brain MRI in the past 10 years. Individuals with a history of fractures in the skull, surgeries in the brain or skull, mass or head injury were excluded from the study. Moreover, patients with space-occupying diseases involving corpus callosum or not, such as tumors, aneurysms, and arteriovenous malformations, were also excluded from the study.

The total study sample size is 404 individuals with ages ranging between 50 and 83 years. The study participants were divided into the following groups: 200 healthy control (100 males and 100 females), and 204 patients with multiple sclerosis (101 males and 103 females). the enrolled MS patients had a disease duration of 10 or more years.

Allocation of the enrolled patients in the healthy control group or in the MS group was based solely on clinical findings and diagnoses reported in the patients' files.

For the healthy individuals, the MRI examinations were performed to find the possible association with cerebral pathology like facial palsy, balance disorders, and scalp midline cyst or mass without any cerebral abnormality.

MS patients had a positive cerebrospinal fluid examination, and no risk factors for other diseases. All MS patients underwent a complete neurological examination, with rating of the Expanded Disability Status Scale (EDSS) score of 1.37±1.2 (range 0–4.5). Subjects with significant depression measured by the Beck Depression Inventory (score 14 or higher) were excluded from the study. All patients were out of clinical relapse and were steroid-free for at least three months prior to MRI examination.

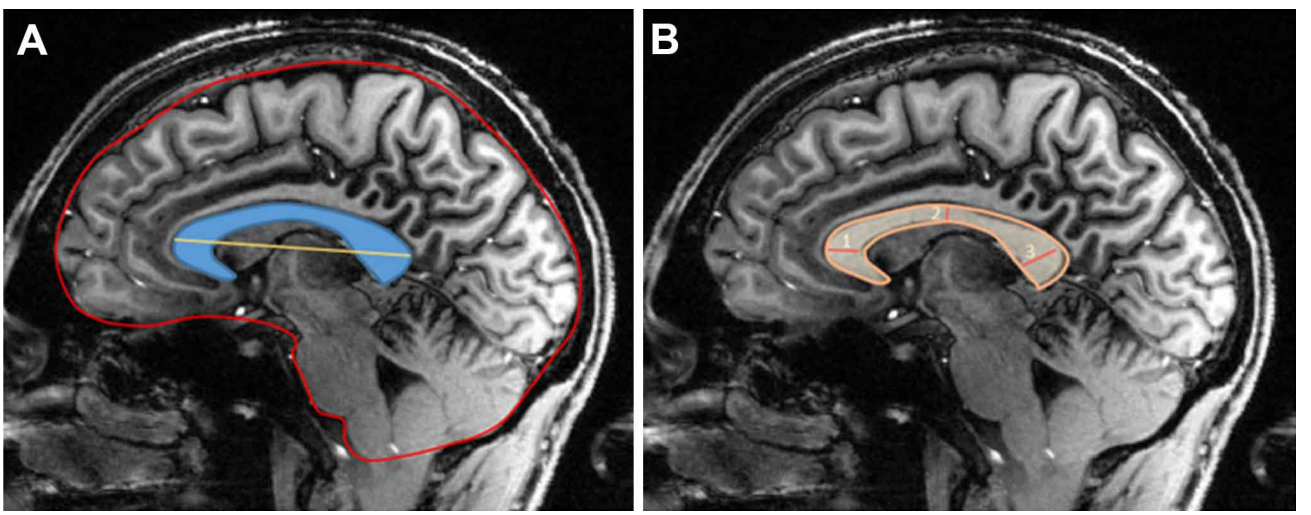

Fig. 1. Illustration of midsagittal measurements in T1-weighted MR images. The corpus callosum was traced in the three most medial brain slices. A, CC area presented in blue, whole skull surface presented in red and CC length in yellow; B, the thickness at genu (1), body (2), and splenium (3).

MRI imaging measurements

T1 weight images on the sagittal plane were acquired for all studied individuals using a Siemens 3.0T MRI machine scanner. The scanning protocol parameters were: repetition time = 3200 ms, echo time = 499 ms, slice thickness = 1 mm, field of view = 256 mm, 256 X 160 matrix.

Observations were recorded on the DICOM files using the manufacture's software. The CC size was evaluated by two radiology specialists, who were blinded to the study design and sample groups. The CC measurements were made on the midsagittal T1-weighted sections in each participant, through areas within irregular regions of interest or with a cursor to determine four major diameters (Fig. 1); 1) the surface area of the CC, 2) the midline internal skull surface, which includes the inner table, foramen magnum, clivus, sellar diaphragm, jugum sphenoidale, 3) the length of CC from the anterior-most part of the genu to the posterior-most part of the splenium, and 4) the thickness of genu, corpus, and splenium. Hyperostosis frontalis interna measurements were not reported because it spares the midline and has a negligible effect on the midline of the internal skull surface measurements.

Statistical analysis

The Student's t-test for unpaired samples was used to determine significant differences between healthy and diseased subsets. Each subgroup proved to be homogeneous for sex and age ratios, respectively, by x2 and Student's t-tests. 1) Average values for CC normal surface, diameters, and CC/internal skull surface ratio were calculated for normal subjects and patients with normal clinical and MRI evaluations; for each sex and age group. A preliminary validation that normal subjects and volunteers offered similar values had to be obtained before further investigations. 2) Overall determination of significant differences between normal females and males, and for sex and age groups (Student's t-test), were performed. 3) Comparison between normal and pathologic subsets was conducted: I) For an available comparison, a subset of normal participants statistically identical for age and sex to each pathologic group was preselected by the following criteria: mean age (one-way and two-way ANOVA tests followed by Bonferoni's); sex ratio (one-way and two- way ANOVA tests followed by Bonferroni's); II) From these data, significant differences were calculated for CC surface and CC/internal surface skull ratio. Statistical significance was tested at the level of P =0.05. The data are presented as mean ± standard error of the mean (SEM).

RESULTS

Corpus callosum size in normal participants

We studied 200 healthy individuals, divided according to sex as follows: male (n=100) and female (n=100) groups. The CC was insignificantly larger in females than in male participants (Table I). The CC midsagittal surface area in females was 6.59±1.01cm^2, while in males it was 6.57±1.07 cm^2. To check the reason for this insignificant difference, we investigated the parts of CC in both sexes (Table I). The results did not show any significant difference in the mean thickness of the genu and body (Table I), but the mean thickness of splenium was nonsignificantly larger in females, while the mean internal skull surface was nonsignificantly larger in males. On the other hand, the results did not show any significant difference in the CC/internal skull surface ratio between males and females (Table I).

No significant difference in mean age or sex was detected between the normal participants and no statistical differences were seen in the measurements. As a results, we could validate the appropriateness to combine these subgroups, and we can also exclude the age and sex as factors that might affect the CC surface measurement or the CC/internal skull surface ratio in healthy participants. Differences between males and females are summarized in Table I, which included the mean surface of the CC, mean body thickness of the CC, the mean internal skull surface, and the CC/internal skull surface ratio.

Table I. Average CC mean values normal healthy individuals.

	Total subjects N= 200	Males N=100	Females N=100	Significant
Mean age ± SE	66.145±10.05	66.14±10.04	66.15±10.06	Non sig
Mean CC surface ± SE (cm^2)	6.58±1.04	6.57±1.07	6.59±1.01	Non Sig
Mean genu thickness ± SE (mm)	9.65±1.17	9.77±1.11	9.53±1.23	Non Sig
Mean Body thickness ± SE(mm)	6.26±1.24	6.30±1.39	6.22±1.1	Non Sig
Mean splenium thickness ± SE (mm)	11.07±1.43	10.97±1.24	11.17±1.62	Non Sig
Length of CC ±SE (cm)	7.31±0.31	7.33±0.27	7.3±0.35	Non Sig
Mean internal skull surface ±SE (cm^2)	147.965±12.01	149.26±12.1	146.67±11.92	Non Sig
CC/internal skull surface ratio ± SE (%)	4.44±0.77	4.4±0.29	4.49±0.67	Non Sig

Nonsignificant (P > 0.05). Determination of control subset homogeneity for age and sex by x2 test.

Comparing the corpus callosum between the normal multiple sclerosis patients

The study group of MS patients included 101 males and 103 females with an age range between 60 and 84 years. The MS group was homogenous with the control group by age and sex. The measurements showed a significant reduction in the CC size between the MS group (5.67±1.815 cm^2) and the control group (6.58±1.04 cm^2) (Table II).

The mean CC surface appears to be significantly smaller in females with MS than males with MS. To investigate this further, the mean diameters for the genu, body, and splenium in both male and female patients were measured. The results did not show any significant difference in the mean value of both genu and splenium between males and females with MS. However, the measurements showed that the mean value of the body thickness was significantly thinner in females (4.69±1.6mm) than in males (5.25±1.9mm) with MS. Moreover, the CC/internal skull surface ratio was larger in MS males (4.01±0.15 %) compared to MS females (3.75±0.09 %), but this increase was not significant (Table III).

Table II. Average values of CC in multiple sclerosis individuals: comparison with normal values.

	Control	Multip sclerosis	Significant
Mean age ± SE	66.155±10.05	65.76±3.6	Non Sig
Mean CC surface ± SE (cm^2)	6.58±1.04	5.67±1.815	$P \leq 0.05$
Mean genu thickness ± SE(mm)	9.66±1.175	8.0±1.58	$P \leq 0.05$
Mean Body thickness ± SE (mm)	6.06±2.51	4.95±1.75	$P \leq 0.05$
Mean splenium thickness ± SE (mm)	11.01±1.35	9.49±.37	$P \leq 0.05$
Length of CC ± SE (cm)	7.3±0.31	7.05±.28	Non Sig
Mean internal skull surface ± SE (cm^2)	148.06±12.325	145.785±11.4	Non Sig
CC/internal skull surface ratio ± SE (%)	4.44±0.77	3.89±0.18	$P \leq 0.05$

Nonsignificant ($P > 0.05$). Determination of control subset homogeneity for age and sex by x^2 test.

Table III. Average CC values in multiple sclerosis patients.

	Total subjects N= 204	Males N=101	Females N=103	Significant
Mean age ± SE	65.76±3.6	65.83±2.5	65.69±4.7	Non Sig
Mean CC surface ± SE (cm^2)	5.65±1.815	5.91±2.11	5.4±1.52	$P \leq 0.05$
Mean genu thickness ± SE (mm)	8.0±1.58	8.09±1.58	7.91±1.29	Non Sig
Mean Body thickness ± SE (mm)	4.95±1.75	5.25±1.9	4.69±1.6	$P \leq 0.05$
Mean splenium thickness ± SE (mm)	9.49±.37	9.35±0.42	9.63±.32	Non Sig
Length of CC ± SE (cm)	7.05±.28	7.12±.15	6.98±.41	Non Sig
Mean internal skull surface ± SE (cm^2)	145.785	147.2±11.6	144.37±10.89	Non Sig
CC/internal skull surface ratio ± SE (%)	3.9±0.18	4.01±0.15	3.75±0.09	Non Sig

Nonsignificant ($P > 0.05$). Determination of control subset homogeneity for age and sex by x^2 test.

DISCUSSION

In recent years, many studies worldwide have used MRI scans to assess the size and morphology differences of CC in normal individuals. In the present study, we analyzed the corpus callosum size in healthy individuals and patients with MS using midsagittal MRI images.

According to our findings, there is no significant sexual dimorphism in human CC dimensions in healthy individuals, which is consistent with previous literature (Weis *et al*., 1989; Allen *et al*., 1991; Bishop & Wahlsten, 1997; Takeda *et al*., 2003; Mohammadi *et al*., 2011). In addition, the results showed insignificant increase in CC in females compared to males as they have a larger splenium. Ardekani *et al*. (2013) showed that the average CC was significantly larger in females (Ardekani *et al*., 2013).

Many studies compared the CC size with the whole brain, but recent studies confirmed that males have a larger average brain size than females (Bermudez & Zatorre, 2001). To overcome this, we compared the CC measurement with skull size.

With regard to the MS patients, we found a significant decrease in CC morphometry compared to the normal control group. Dietemann *et al*. (1989) subjectively evaluated the size and morphology of CC in MS patients and their

correlation with the duration and severity of the disease. They reported that MS symptoms were more pronounced in patients with severe CC atrophy and that CC atrophy appeared earlier than brain atrophy in MS patients (Dietemann *et al*., 1989). Moreover, CC atrophy manifested mainly in long-standing MS cases of at least 10 years disease duration (Dietemann *et al*., 1989). Simon *et al*. (1986) found significant differences between controls and MS patients, in both the mean thickness of CC and area (Simon *et al*., 1987). The association between MS and callosal atrophy has been described with a prevalence ranging from 2 % to more than 50 % (Simon *et al*., 1986, 1987; Hasan *et al*., 2012).

Notably, in our study, we examined the thickness of CC in different parts (genu, body, and splenium). Our results have shown a considerable reduction in thickness of all parts of the CC area in patients with MS compared to healthy controls. For the first time, the results showed that the reduction in total CC area in MS patients is not particular to a specific CC subregion, but could be a result of the collective involvement of all CC subregions despite the difference in the degree of atrophy between the different subregions. The most prominent reduction was observed in the body (27.8 %), followed by the genu (17.18 %), while the least observed reduction was in splenium (13.81 %).

The significant correlation between the reduction in the overall CC area thickness and the progression of MS disease is in agreement with previous studies, which reported that the thickness profile of CC is considered an important indicator for the progression of many neurodegenerative pathologies (Walterfang *et al*., 2009; Khasawneh *et al*., 2022). Our findings set a clinically important platform by illustrating the importance of continuous observation and examination of CC thickness as a prognostic tool in patients with MS and other related neurodegenerative disorders. Furthermore, the CC thickness changes can be used to monitor the effectiveness of prescribed medications for MS patients.

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RESUMEN: El cuerpo calloso (CC) incluye la mayoría de las fibras que unen los dos hemisferios cerebrales. Varios estudios transversales mostraron una asociación entre la atrofia y el mal funcionamiento calloso y las enfermedades neurodegenerativas, lo que puede desempeñar un papel en sus manifestaciones patológicas. En consecuencia, la cuantificación precisa del cuerpo calloso es importante para tener valores normativos según sexo, edad y etnia. El propósito de este estudio fue determinar el tamaño de CC en pacientes que padecen esclerosis múltiple y compararlo con el tamaño de CC en individuos sanos. El tamaño sagital medio del CC se registró prospectivamente a partir de 404 exámenes cerebrales de RM de rutina en individuos normales. Se midió la superficie interna del cráneo para calcular la relación CC/superficie interna del cráneo. Se estudiaron dos grupos de pacientes: 200 (100 hombres/100 mujeres) sanos y 204 (101 hombres/103 mujeres) con esclerosis múltiple (EM). El área superficial media de CC en los controles fue de 6,58±1,04 cm^2 y no hubo diferencia significativa entre hombres y mujeres (P< 0,627). La relación CC/superficie interna del cráneo fue de 4,44±0,77 %. Los pacientes con EM mostraron una disminución significativa en el tamaño de CC en comparación con los controles normales. Usando imágenes de RM, medimos los tamaños medios de las diversas porciones del CC en individuos normales, además de pacientes con EM; estos valores pueden proporcionar una base útil para determinar los cambios que ocurren en las estructuras CC.

PALABRAS CLAVE: Cuerpo calloso; Morfología; Imagen de resonancia magnética; Esclerosis múltiple.

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