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Normative Data of the Corpus Callosum Index and Discriminant Validity in Patients with Multiple Sclerosis

María Yaiza Pérez-Martín[1*], Montserrat González-Platas[1], Alejandro Jiménez-Sosa[2], Julio Plata-Bello[3,4], Arelys López-Segura[1] and Elisa Lucas-Hernández[1]

[1]Department of Neurology, Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain

[2]Unit of Research, Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain

[3]Department of Physiology, Faculty of Medicine, University of La Laguna, San Cristóbal de La Laguna, Spain

[4]Department of Neurosurgery, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

[*]**Corresponding author:** Pérez-Martín MY, Department of Neurology, Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain, Tel: +34616464403; E-mail: yaizaneuro@hotmail.com

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Abstract

Background: The corpus callosum (CC) plays an important role in many cognitive and behavior functions and can be easily identified by conventional Magnetic Resonance Imaging (MRI). For these reasons, its integrity has been used as predictor of symptoms in different pathologies.

Methods and findings: to provide standardized data of the corpus callosum index (CCI) and obtain a cut-off point as a possible early marker of cognitive impairment in multiple sclerosis (MS), 209 healthy subjects and 96 patients were consecutively evaluated with a brain MRI scanning protocol. CCI was measured by two blinded raters. ROC curves were obtained for the total of sample and subgroups and the Youden Index was calculated to indentify the best cut-off points.

Results: Normative data of CCI are presented by age. No sex differences were found. Cut-off points were established for subjects in different age groups.

Conclusion: CCI cut-off values could be useful to identify alarm points below which we could think of inquiring about deficits that are not currently "visible". Longitudinal evaluations will enable us to know if CCI is an early marker of cognitive damage in MS.

Keywords: Corpus callosum; Multiple sclerosis; MRI; Corpus callosum index; Autism spectrum disorders

Introduction

The corpus callosum (CC) is the largest interhemispheric commisure connecting cortical and subcortical areas of the two cerebral hemispheres. Histologically, the CC contains approximately 200 million myelinated nerve fibers. The composition of these fibers is variable, with thinner (or less myelinated) and slower conducting fibers and larger (or more myelinated) and faster conducting fibers or unmyelinated fibers that reach up to 31% in the monkey brain [1]. The macrostructure of the CC is made up of variable degrees of axonal myelination, redirection and shortening in normal and pathological conditions [2].

Topographically, the CC is organized in different parts which interconnect homotopic cortical regions. The genu is the anterior region and connects the anterior cerebral hemispheres and the prefrontal cortical areas. The CC midbody connects the motor, somatosensory and auditory cortices. The posterior region connects the temporal, parietal and occipital lobes [3]. More specifically, the splenium is involved in interhemispheric communications along with auditory, visual information and language processes [4].

The number of callosal fibers is already fixed around birth, but structural changes of the CC continue to occur during postnatal development due to fiber myelination, redirection and pruning [5]. During childhood, the CC expands quickly due to the increase in the number of axons, their diameter and myelination and continues growing until the second decade of life at a much slower rate. Adolescence is an important period for brain development and, in particular, for the CC. Many studies have found that dramatic changes occur in the callosal micro and macro anatomy throughout the hormone-laden period of adolescence [6].

Sex may be an important biological factor in the development of the CC, in relation to the presence or absence of the Y chromosome and the production of gonadal hormones that affect differences between the sexes. Some studies have shown that the total area of the CC is greater in women than in men, which seems to be related to fetal testosterone levels. However, the link with its size is still unclear [7]. Some researchers have argued that the splenic area of the CC is greater in women than in men, while others

report a sex difference for the isthmus area [8]. Theoretically speaking, these differences suggest that women may be protected from cognitive aging by a greater capacity to compensate through bilateral activation.

The CC has a special influence on affective behavior, non-literal language and bilateral functional connection in both motor and sensory cortices. Several studies have reported that the size of the CC changes in bipolar disorders, Alzheimer's disease, Down´s syndrome or Williams syndrome among others [9].

A brief summary is provided below of the involvement of the CC in some of the pathologies in which it has been studied.

Corpus callosum and neurological and psychiatric pathology

Multiple Sclerosis (MS): MS is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination of white matter and early axonal damage that commonly leads to inflammation, atrophy and cognitive decline. Chronic neurological disability in young people develops when the cumulative threshold for axonal loss is reached and the compensatory resources of the CNS area are exhausted. In MS, the CC is extensively affected by local and Wallerian degeneration determining a disconnection syndrome in large-scale networks [10]. Due to its periventricular location and the close relationship with the subependymal veins, the CC is susceptible to early inflammation and demyelination.

Because of the CC's functional relevance to inter-hemispheric information transfer, it might be one of the components of the complex pathological processes that lead to cognitive changes in MS. Due to this fact, studies have aimed to find a relationship between functional and clinical disability and CC measures in MS [11-13].

Alzheimer´s Disease (AD): AD has been described as an irreversible neurodegenerative pathology that normally affects gray matter, but a significant callosal atrophy in Alzheimer´s patients has been found. It has been postulated that there are two different mechanisms that could contribute to this fact: cell death in the gray matter, especially the large pyramidal cells in cortical layer III and the direct decomposition of myelin in callosal fibers [14].

Parkinson´s Disease (PD): PD is one of the most common age-related brain disorders. PD is defined primarily as a movement disorder but cognitive impairment (whose anatomical substrate is not yet well defined) is common and leads to substantial disability.

Macrostructural differences in the CC have been associated with PD cognitive impairment with greater volume loss in patients with PD and dementia compared to patients with PD and mild cognitive impairment or who are cognitively normal [15,16].

Schizophrenia: Schizophrenia has been characterized as a disorder of disconnectivity [17]. There is a considerable evidence demonstrating changes in the white matter tracts connecting brain regions in people with schizophrenia compared to healthy controls.

Structural MRI in schizophrenia studies have noted smaller white matter volumes in several brain regions. These abnormalities may be present early in the course of the disease. Overall, disruptions of white matter integrity have been found in cortical and subcortical brain regions as well as in associative white matter and commissural tracts, suggesting that changes of cortical-subcortical white matter integrity are found at an early stage of the disorder. These changes in white matter integrity have been correlated with specific cognitive deficits as well as psychopathology (positive more than negative symptoms) [18].

Specifically, the CC has been a region of much interest in schizophrenia. It has been found that patients with schizophrenia have a smaller anterior genu, anterior body, isthmus, and anterior splenium, consistent with observed reductions in the size of the structures that are connected by these CC regions (the prefrontal, temporal, and inferior parietal cortex) [19].

Histopathological studies have failed to find differences in the density of axonal fibers in the CC [20] but recent diffusion tensor and magnetization transfer imaging studies of the CC in schizophrenia have indicated reduced fractional anisotropy of the diffusion of water in the splenium [21] and reductions in the magnetisation transfer ratio in the genu [22] in schizophrenia, indicating focally abnormal white matter in the CC.

Corpus callosum and developmental disorders

Autism Spectrum Disorders (ASD): Current theories concerning autism include the consideration of this disorder as being due to a poor connectivity between different cortical regions resulting in impaired integrative processing and deficient higher order cognitive abilities [23]. This poor connectivity can be observed in the CC as many studies hypothesize [24].

Among the most replicated brain imaging findings in ASD is that of a disproportionally small corpus callosum relative to overall brain size. Several magnetic resonance imaging (MRI) studies of autism have found significant reductions in the CC, particularly among posterior regions, in children and adults with autistic disorder relative to control subjects [25].

Data indicate that CC size associated with ASD is observed in terms of total CC area as well as most subdivisions [26]. In addition to area and volume, differences have also been observed in CC thickness, with the splenium and genu being particularly 'thinner' in school-age children with the disorder [27].

Dyslexia: Dyslexia is a persistent and specific reading and writing disorder that occurs in children who do not have any physical, mental or sociocultural handicap. Despite numerous neuroimaging studies of both children and adults with dyslexia, the underlying neural substrates remain uncertain.

Given that the CC plays a major role in interhemispheric communications, the bilateral brain activations observed in dyslexics suggests possible changes in CC connectivity. Thus far, the CC literature on dyslexia is inconsistent and contains numerous contradictions.

A study carried out in 2012 shows an increase in CC5 (posterior midbody of the CC) myelination suggesting that the dyslexic brain is " wired for increased inter-hemispheric communication. Increases in axonal caliber in this CC segment could be an indication of re-wiring due to recruitment of additional brain regions during processing of written language [28].

Attention-Deficit hyperactivity Disorder (ADHD): Neuroimaging studies of patients with ADHD have revealed deviations of the CC in children and adolescents [29]. In adults, negative correlations have been found in males with respect to inattention and hyperactivity in various callosal regions, including the anterior third, anterior and posterior midbody, isthmus, and splenium. In females, callosal thickness has been positively related to hyperactivity in a small area within the rostral body, suggesting a sexually dimorphic neurobiology of ADHD symptoms [30].

Corpus callosum and ischemia

Infarcts of the corpus callosum are generally a part of large vessel ischemia. Hence, diabetes mellitus and hypertension are the major risk factors as they predispose sufferers to atherosclerosis. Focal infarct patterns are uncommon as the blood supply is by small perforating vessels running perpendicular to the parent vessel, making it difficult for the emboli to enter and lodge in them. The splenium is the most vulnerable, followed by the body and genu [31].

Toxic pathology

Alcoholism: Specific white matter structures of the brain, like the CC, are particularly affected by alcoholism and could be useful in the study of its progression. Excessive drinking can lead to impairment of motor and cognitive function (such as abstract problem solving, visuospatial and verbal learning or selective memory processes) [32] and structural brain changes. Chronic alcoholics with callosal atrophy present a significant impairment in neurocognitive functions compared with subjects with normal CC size. In addition, frontal lobe atrophy and tests evaluating frontal function have been associated with the thickness of the genu of the CC [33].

The CC is also affected by Marchiava-Bignami (MB) disease. MB is a rare encephalopathy observed in malnourished chronic alcoholics which is associated to demyelination or necrosis of the CC and its adjacent subcortical white matter whose clinical presentation includes spasticity, dysarthria, dementia and inability to walk which may progress to coma and death. Nevertheless, reductions in the thickness of the CC have been reported in a dose-dependent manner in chronic alcoholics regardless of their nutritional status [33].

This fact could be associated to the permanent effect of chronic alcohol consumption in different brain regions producing axonal loss associated with Wallerian degeneration (as opposed to changes related to deficient consumption of thiamine that would lead to reversible white matter shrinkage) [34].

Other drugs: As regards the consumption of other drugs, frequent use of high-potency cannabis is associated with disturbed callosal microstructural organization in individuals with and without psychosis [35]. Changes in the CC are also associated to cocaine consumption [36].

CC interhemispheric communication plays an important role in language, executive, volitional and working memory functions and contributes to motricity. Furthermore, the CC is one of the few white matter tracts that can be discretely identified by conventional MRI. For these anatomic and functional properties, it is reasonable to assume that CC morphometrics might be a possible marker for the integrity of these associative fibers [37] in different pathologies and might be a useful predictor of symptoms.

Therefore, many different measures of the CC have been used including volumetric measures, morphometry or inter-hemispheric connectivity [2,24,38-42]. Despite the fact that the volumetric analyzes are of choice in the follow-up of certain pathologies, they are currently confined to the field of research or pre-surgical planning of functional and structural surgery of the CNS.

The aim of the present study is to provide standardized data of the corpus callosum index (CCI), a simple measure (a possible alternative to the methods based on brain segmentation) that does not require specific software or highly qualified personnel and that can be used in routine clinical practice to monitor certain pathologies. Furthermore, taking into account the relationship that has been demonstrated between CC atrophy and cognitive integrity in general [43], and in MS patients in particular [44,45], a group of MS patients has been included in the study to assess the ability of the CCI to identify CC atrophy that could be used as an early marker of cognitive decline.

Research Methodology

The study was conducted in accordance with the principles of the Declaration of Helsinki [46] and good clinical practice standards and was approved by the local ethics committee for clinical research on March 04, 2016 (Code 2015_91). All participants provided written informed consent to participate.

Subjects

A total of two hundred and nine healthy subjects were included in the study. This group of participants was recruited from the waiting room of the Department of Neurology in the Hospital Universitario de Canarias through informative brochures about the study.

Inclusion for the healthy group was based on the following criteria:

- Being over 18 years of age
- Willing and able to sign written informed consent

The exclusion criteria for the healthy group were as follows:

- Personal history of severe neurological and/or psychiatric pathology
- Having contraindication/s to an MRI study
- Personal history of severe traumatic brain injury
- Personal history of alcohol or drug abuse
- Personal history of any serious medical illness
- Having received chemotherapy or immunomodulator treatment.
- Having received radiotherapy treatment in the skull region.

Ninety-six MS patients were included in the study. Patients were recruited from the Section of Demyelinating diseases of the Department of Neurology in the Hospital Universitario de Canarias.

Inclusion for the patient group was based on the following criteria:

- Willing and able to sign written informed consent
- Remitting-relapsing MS (RRMS) diagnosed according to the McDonald criteria 2010 [47]
- Being over 18 years of age

The exclusion criteria for the patient group were as follows:

- Diagnosis of demyelinating disease other than MS
- Subtypes of MS other than remitting-relapsing forms
- Evidence of relapse of steroid treatment in the four weeks preceding the enrollment
- Have no subjective cognitive complaints

Procedure

Data for the experiment were collected at the Magnetic Resonance for Biomedical Research Service of the University of La Laguna.

All the participants were consecutively evaluated with a brain MRI scanning protocol. Structural images were obtained on a 3 T General Electric (Milwaukee, WI, USA) scanner using an echo-planar imaging gradient-echo sequence and an 8 channel head coil (TR= 3000 ms, TE= 21 ms, flip angle =90°, matrix size =64 × 64 pixels, 57 slices/volume, spacing between slices= 1 mm, slice thickness= 3 mm). The slices were aligned to the anterior commissure – posterior commissure line and covered the whole cranium.

Identification criteria of CC were the clearest visualization of the CC and the septum pellucidum, cerebellum and patency of the aqueduct in a midsagittal slice T1W image. Quantification of the CCI was obtained following Figueira et al., [37] by drawing a straight line across the greatest anteroposterior diameter of the CC (from the most anterior point of the genu to most posterior point of the splenium (A-C line) and a perpendicular at its midline **(Figure 1)**. All segments (aa´, bb´ and cc´) were measured and normalized to their greatest anteroposterior diameter (A-C).

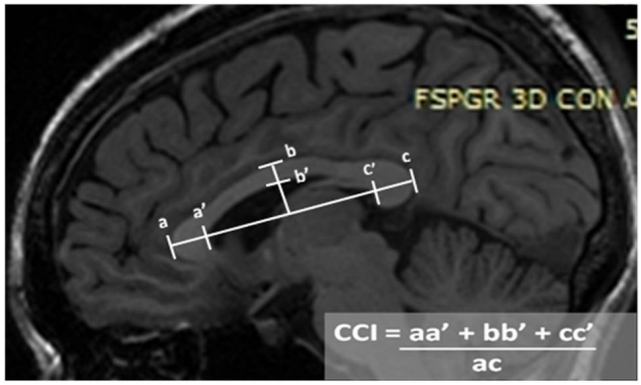

Figure 1: Identification criteria of CC.

A second measure of the CCI was taken by a second rater blinded to the assessment of the first rater in order to evaluate the inter-observer reliability.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean ± SD, median and range (min-max). Normality was tested with the Kolmogorov-Smirnov test.

The comparison between groups for continuous variables was performed using the Student's t-test. The Chi-square tests were used for the comparison of categorical variables.

Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were calculated and used to determine the ability of CCI to discriminate between patients and healthy subjects. The Youden index, which maximizes a combination of sensitivity and specificity, was calculated and used to determine the optimal cut-off point of CCI. The optimal cut-off point was defined as the maximum vertical distance between the ROC curve and the diagonal.

The Lin's concordance correlation coefficient (CCC) was calculated to test the inter-observer reliability.

Statistical analysis was performed with SPSS v20.0 software (IBM Corporation, Armonk, NY, USA). The P values< 0.05 were considered statistically significant.

Results

Healthy participants were divided into age groups as follows: 30 years of age or younger, between 31 and 40 years of age, between 41 and 50, between 51 and 60 and subjects

older than 60. **Table 1** shows the distribution of the sample in age and sex.

Table 1: Characteristics of healthy subjects.

Age group -n (%)	Females n=137	Male n=72	Total n=209	P value
Younger than 30	66 (31.6)	34 (16.3)	100 (47.8)	0.2
31-40	29 (13.8)	9 (4.31)	38 (18.2)	
41-50	24 (11.5)	11 (5.3)	35 (16.7)	
51-60	9 (4.31)	9 (4.31)	18 (8.6)	
Older than 60	9 (4.31)	9 (4.31)	18 (8.6)	

Total CCI was 0.396 0.412. The Lin's CCC between the first and the second blinded rater was 0.90 (CI: 0.84-0.94) indicating moderate agreement. The normalized measurements of each of the three portions of the CC were the following: anterior segment or genu 0.156 0.021, middle region or midbody 0.088 0.013 and posterior segment or splenium 0.152 0.186. The average length of the CC was 73.133 4.772 millimeters (mm). No significant differences were found in the CCI, midbody and splenium, between males and females. Females had a thicker genu (t = -2.015; P<0.045). **Table 2** shows CCI and the normalized size of the three portions of the CC in the different age groups.

The patient group consisted of 96 participants with RRMs with a mild neurological disability measured with the Expanded Disability Status Scale (EDSS) [48] with a median value of 1.5 and 8.91 (6.04) years of disease duration. A total of 71 participants (74%) were females. The mean age was 39.76 (9.09).

The area under the curve (AUC) was calculated in order to determine the ability of the CCI to discriminate between patients with MS and healthy subjects. The Youden index was calculated to determine the value of the optimal cut-off point which combines the highest sensitivity and specificity together. AUC were calculated for the total sample and for each age group.

Table 2: Normalized measures of CC and CCI.

Age group	Genus			Midbody			Splenium			CCI		
	M	F	Tot	M	F	Tot	M	F	Tot	M	F	Tot
Up to 30	0.164 ± 0.019	0.162 ± 0.022	0.163 ± 0.021	0.091 ± 0.009	0.091 ± 0.013	0.091 ± 0.012	0.157 ± 0.019	0.155 ± 0.019	0.156 ± 0.019	0.412 ± 0.035	0.409 ± 0.039	0.409 ± 0.037
31-40	0.155 ± 0.134	0.158 ± 0.018	0.157 ± 0.167	0.086 0.006	0.089 ± 0.013	0.089 ± 0.021	0.156 ± 0.013	0.152 ± 0.021	0.153 ± 0.019	0.397 ± 0.024	0.399 0.042	0.398 ± 0.038
41-50	0.138 ± 0.133	0.156 ± 0.019	0.150 ± 0.194	0.086 ± 0.010	0.089 ± 0.012	0.088 ± 0.011	0.146 ± 0.166	0.152 ± 0.014	0.149 ± 0.015	0.369 ± 0.033	0.396 ± 0.037	0.388 ± 0.038
51-60	0.137 ± 0.019	0.146 ± 0.018	0.142 ± 0.189	0.081 ± 0.012	0.085 ± 0.013	0.083 ± 0.013	0.146 ± 0.027	0.144 ± 0.011	0.145 ± 0.019	0.364 ± 0.055	0.375 ± 0.033	0.369 ± 0.044
Older than 60	0.133 ± 0.007	0.140 ± 0.016	0.134 ± 0.127	0.078 ± 0.009	0.084 ± 0.024	0.081 ± 0.018	0.144 ± 0.027	0.142 ± 0.019	0.143 ± 0.017	0.355 ± 0.024	0.367 ± 0.049	0.362 ± 0.038
Total Sample	0.152 ± 0.021	0.158 ± 0.021	0.156 ± 0.021	0.087 ± 0.011	0.089 ± 0.138	0.088 ± 0.013	0.152 ± 0.019	0.153 ± 0.018	0.152 ± 0.186	0.391 ± 0.042	0.399 ± 0.041	0.396 ± 0.412

Abbreviations: M, Males; F, Females

The AUC for the total sample was 0.79. The value of the CCI with the better ability to discriminate between patients and healthy subjects was 0.34 with a sensitivity of 54% and a specificity of 93% **(Figure 2)**.

A different discriminatory capacity of the CCI was observed depending on the age group of the subjects. The ROC curve for the different groups is shown in **Figure 3**. The AUC was 0.85 for subjects younger than 30 years of age. For this group, the cut-off was 0.35 with a sensitivity of 62% and a specificity of 97%. The AUC for subjects between 31-40 and 41-50 was 0.74 and 0.81 respectively and the cut-offs for these groups were 0.34 and 0.33. The other subjects included in the final group corresponding to subjects older than 50 years of age (subjects between 51 and 60 and older were included together due to the low number of subjects). In this last group, the AUC was 0.70 and it was not significant.

Discussion

The CC is a bridge of white matter bundles and a critical brain structure for inter hemispheric information implicated in the transfer of important functions. The CC plays a significant role in cognitive and behavior functions [43]. In addition, the CC can easily be identified by conventional MRI sequences. For these reasons different measures of CC integrity have been used as a useful predictor of symptoms in many pathologies.

The present study provides standardized data of CCI, which is a normalized linear measure that can be taken without image analysis software or highly qualified personnel and that

can be used in routine clinical practice to monitor different pathologies. These data could improve the applicability of the CCI in clinical monitoring and research use.

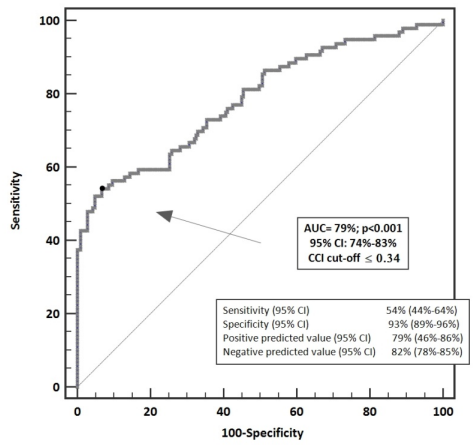

Figure 2: Value of the CCI.

For obvious reasons, the use of three-dimensional quantitative measures over two-dimensional ones will always be more accurate but there are still no defined and standardized protocols with respect to the assessment of brain atrophy and these 3D measures require specialized software and training in some of the more complex volumetric tools.

The mean average of CCI for the total sample was 0.39 and this value was in reasonable agreement with inter-observer values of around 0.90. The results are presented in age groups and data of normalized size of the three segments of CC are presented independently in order to identify possible regional differences.

When sex comparisons were made, no differences between males and females were found in the CCI. In regional terms, only the genu was thicker in females while the midbody and splenium size did not show significant differences.

These data contribute and serve to increase the uncertainty of the effect of sex in the size of the CC and contradict data about a larger size of the CC in females reported in other studies [8] and its possible protecting role of the age effect.

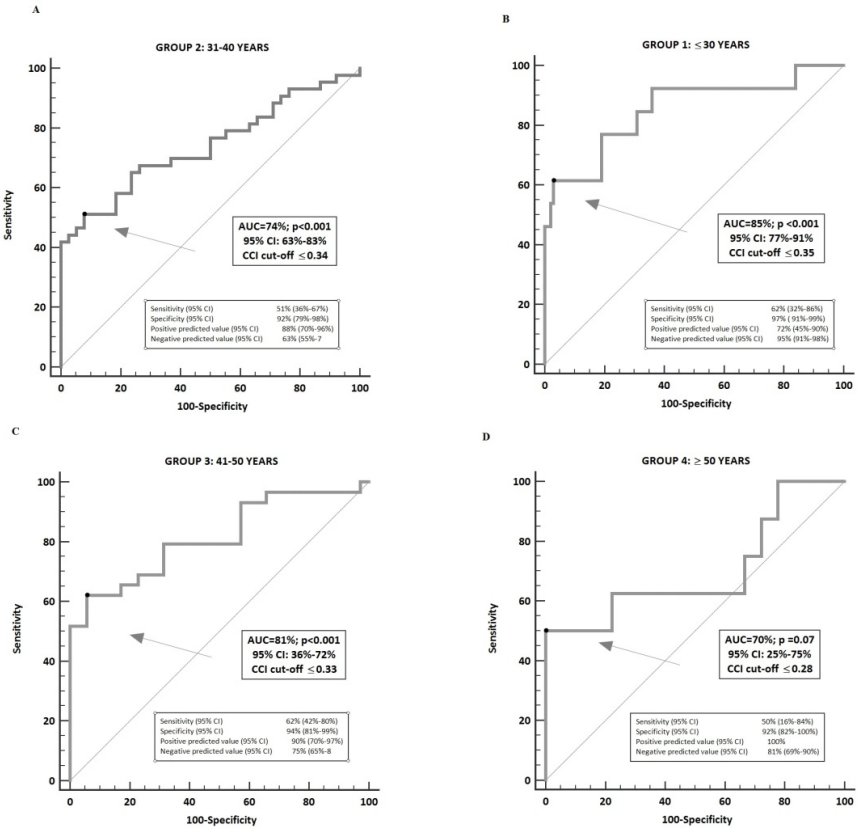

Figure 3: ROC curve for the different groups.

In MS, CC atrophy could be the result of focal demyelination and axonal damage and associated to Wallerian degeneration after inflammation and axonal transaction. CC atrophy in MS might be a marker of disease progression as a reflection of the irreversible process of pathological damage.

The CCI has been used in monitoring MS patients and a correlation has been found with whole brain volume [49] and long-term disability [45]. CCI decrease has been associated with fatigue independent of disability, disease duration, gender and age [12,37] and cognitive impairment [45].

Ninety-six patients with clinically stable RRMS and without subjective cognitive complaints were included and compared with a healthy subject group. ROC curves were performed for the total sample revealing that the best cut-off point to identify early susceptible to cognitive damage subjects was 0.34.

Only patients with RR forms of the disease were included so as not to interfere with the results with other subtypes (progressive forms) that are characterized by increased and early brain atrophy [50].

The incidence in MS is not the same in all ages. MS is often diagnosed in the second or third decade of life [51]. For this reason, ROC curves were built for different age groups in the present study. Thus, the CCI cut-off point was 0.35, 0.34 and 0.33 for subjects younger than 30, between 31 and 40, and between 41-50 respectively (due to the low size of the sample of older than 50 among healthy subjects and among patients, it was not possible to identify an optimal cut-off in the older than 50 group (p=0.07). These values could be identified as the alarm points below which deficits that are not currently "visible" could be investigated.

The participating subjects were not cognitively evaluated in the study. Even those subjects who were older than 60, an age when a certain level of deterioration associated with age may begin to be present. It should be pointed out that this is a limitation of the present study.

Conclusion

The longitudinal evaluation of the participating patients will provide information for future use about whether those subjects with values below the cut-off point will actually develop cognitive symptoms. If this is the case, the CCI could be used as an early marker of cognitive damage and early strategies could be initiated to reduce or alleviate its important effects on the quality of life of affected people.

References

1. Reuter-Lorenz PA, Stanczak L (2000) Differential effects of aging on the functions of the corpus callosum. Dev Neuropsychol 18: 113-137.
2. Zito G, Luders E, Tomasevic L, Lupoi D, Toga AW, et al. (2014) Inter-hemispheric functional connectivity changes with corpus callosum morphology in multiple sclerosis. Neuroscience 266: 47-55.
3. Anstey KJ, Mack HA, Christensen H, Li SC, Reglade-Meslin C, et al. (2007) Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. Neuropsychologia 45: 1911-1920.
4. De Guise E, Lassonde M (2001) Callosal contribution to procedural learning in children. Dev Neuropsychol 19: 253-272.
5. Luders E, Thompson PM, Toga AW (2010) The development of the corpus callosum in the healthy human brain. J Neurosci Off J Soc Neurosci 30: 10985-10990.
6. Chavarria MC, Sánchez FJ, Chou YY, Thompson PM, Luders E (2014) Puberty in the corpus callosum. Neuroscience 265: 1-8.
7. Tanaka-Arakawa MM, Matsui M, Tanaka C, Uematsu A, Uda S, et al. (2015) Developmental changes in the corpus callosum from infancy to early adulthood: a structural magnetic resonance imaging study. PloS One 10: 3.
8. Prendergast DM, Ardekani B, Ikuta T, John M, Peters B, et al. (2015) Age and sex effects on corpus callosum morphology across the lifespan. Hum. Brain Mapp 36: 2691-2702.
9. Mohammadi MR, Zhand P, Mortazavi Moghadam B, Golalipour MJ (2011) Measurement of the corpus callosum using magnetic resonance imaging in the north of iran. Iran J Radiol QJ Publ Iran Radiol Soc 8: 218-223.
10. Bester M, Lazar M, Petracca M, Babb JS, Herbert J, et al. (2013) Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis. J Neurol Sci 330: 61-66.
11. Rimkus CdeM, Junqueira TdeF, Callegaro D, Otaduy MCG, Leite CdaC (2013) Segmented corpus callosum diffusivity correlates with the Expanded Disability Status Scale score in the early stages of relapsing-remitting multiple sclerosis. Clin São Paulo Braz 68: 1115-1120.
12. Yaldizli Ö, Atefy R, Gass A, Sturm D, Glassl S, et al. (2010) Corpus callosum index and long-term disability in multiple sclerosis patients. J Neurol 257: 1256-1264.
13. Yaldizli Ö, Glassl S, Sturm D, Papadopoulou A, Gass A, et al. (2011) Fatigue and progression of corpus callosum atrophy in multiple sclerosis. J Neurol 258: 2199-2205.
14. Ardekani BA, Bachman AH, Figarsky K, Sidtis JJ (2014) Corpus callosum shape changes in early Alzheimer's disease: an MRI study using the OASIS brain database. Brain Struct Funct 219: 343-352.
15. Bledsoe IO, Stebbins GT, Merkitch D, Goldman JG (2018) White matter abnormalities in the corpus callosum with cognitive impairment in Parkinson disease. Neurology 91: 24.
16. Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, et al. (2017) Cognitive decline in Parkinson disease. Nat Rev Neurol 13: 217-231.
17. Friston KJ (1999) Schizophrenia and the disconnection hypothesis. Acta Psychiatr Scand Suppl 395: 68-79.
18. Kuswanto CS, The I, LeeTS, Sim K (2012) Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. Clin. Psychopharmacol. Neurosci Off Sci J Korean Coll Neuropsychopharmacol 10: 13-24.
19. Keshavan KS, Anderson S, Pettegrew JW (1994) Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res 28: 239-265.
20. Casanova MF, Zito M, Bigelow LB, Berthot B, Sanders RD, et al. (1989) Axonal counts of the corpus callosum of schizophrenic patients. J Neuropsychiatry Clin Neurosci 1: 391-393.

21. Foong J, Maier M, Clark CA, Barker GJ, Miller DH, et al. (2000) Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry 68: 242-244.

22. Foong J, Symms MR, Barker GJ, Maier M, Woermann FG, et al. (2001) Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging. Brain J Neurol 124: 882-892.

23. Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004) Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain J Neurol 127: 1811-1821.

24. Keary CJ, Minshew NJ, Bansal R, Goradia D, Fedorov S, et al. (2009) Corpus callosum volume and neurocognition in autism. J Autism Dev Disord 39: 834-841.

25. Wolff JJ, Gerig G, Lewis JD, Soda T, Styner MA, et al. (2015) Altered corpus callosum morphology associated with autism over the first 2 years of life. Brain J Neurol 138: 2046-2058.

26. Frazier TW, Hardan AY (2009) A meta-analysis of the corpus callosum in autism. Biol Psychiatry 66: 935-941.

27. Vidal CN, Nicolson R, DeVito TJ, Hayashi KM, Geaga JA, et al. (2006) Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. Biol Psychiatry 60: 218-225.

28. Hasan KM, Molfese DL, Walimuni IS, Stuebing KK, Papanicolaou AC, et al. (2012) Diffusion tensor quantification and cognitive correlates of the macrostructure and microstructure of the corpus callosum in typically developing and dyslexic children. NMR Biomed 25: 1263-1270.

29. Valera EM, Faraone SV, Murray KE, Seidman LJ (2007) Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 61: 1361-1369.

30. Luders E, Kurth F, Das D, Oyarce DE, Shaw ME, et al. (2016) Associations between corpus callosum size and ADHD symptoms in older adults: The PATH through life study. Psychiatry Res Neuroimaging 256: 8-14.

31. Chrysikopoulos H, Andreou J, Roussakis A, Pappas J (1997) Infarction of the corpus callosum: computed tomography and magnetic resonance imaging. Eur J Radiol 25: 2-8.

32. He X, Sullivan EV, Stankovic RK, Harper CG, Pfefferbaum A (2007) Interaction of thiamine deficiency and voluntary alcohol consumption disrupts rat corpus callosum ultrastructure. Neuropsychopharmacol 32: 2207-2216.

33. Estruch Nicolás JM, Salamero M, Aragón C, Sacanella E, et al. (1997) Atrophy of the corpus callosum in chronic alcoholism. J Neurol Sci 146: 145-151.

34. Carlen PL, Wilkinson DA, Wortzman G, Holgate R (1984) Partially reversible cerebral atrophy and functional improvement in recently abstinent alcoholics. J Can Sci Neurol 11: 441-446.

35. Rigucci S, Marques TR, Di Forti MT, Taylor H, Dell'Acqua F, et al. (2016) Effect of high-potency cannabis on corpus callosum microstructure. Psychol Med 46: 841-854.

36. Ma L, Hasan KM, Steinberg JL, Narayana PA, Lane SD, et al. (2009) ' Diffusion tensor imaging in cocaine dependence: regional effects of cocaine on corpus callosum and effect of cocaine administration route. Drug Alcohol Depend 104: 262-267.

37. Figueira FFA, dos Santos VS, Figueira GMA, da Silva ACM (2007) Corpus callosum index: a practical method for long-term follow-up in multiple sclerosis. Arq Neuropsiquiatr 65: 931-935.

38. Keshavan MS, Diwadkar VA, Harenski K, Rosenberg DR, Sweeney JA, et al. (2002) Abnormalities of the corpus callosum in first episode, treatment naive schizophrenia. J Neurol Neurosurg Psychiatry 72: 757-760.

39. Erdoğan N, Ulger H, Tuna I, Okur A (2005) A novel index to estimate the corpus callosum morphometry in adults: callosal/supratentorial-supracallosal area ratio. Diagn Interv Radiol Ank Turk 11: 179-181.

40. Hasan KM, Kamali A, Iftikhar A, Kramer LA, Papanicolaou AC, et al. (2009) Diffusion tensor tractography quantification of the human corpus callosum fiber pathways across the lifespan. Brain Res 1249: 91-100.

41. Choo AL, Kraft SJ, Olivero W, Ambrose NG, Sharma H, et al. (2011) Corpus callosum differences associated with persistent stuttering in adults. J Commun Disord 44: 470-477.

42. Van Schependom J, Jain S, Cambron M, Vanbinst AM, De Mey J, et al. (2016) Reliability of measuring regional callosal atrophy in neurodegenerative diseases. NeuroImage Clin 12: 825-831.

43. Doron KW, Gazzaniga MS (2008) Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication. Cortex J Devoted Study Nerv Syst Behav 44: 1023-1029.

44. Papathanasiou A, Messinis L, Zampakis P, Papathanasopoulos P (2017) Corpus callosum atrophy as a marker of clinically meaningful cognitive decline in secondary progressive multiple sclerosis. Impact on employment status. J Clin Neurosci Off J Neurosurg Soc Australas 43: 170-175.

45. Yaldizli Ö, Penner IK, Frontzek K, Naegelin Y, Amann M, et al. (2014) The relationship between total and regional corpus callosum atrophy, cognitive impairment an d fatigue in multiple sclerosis patients. Mult Scler Houndmills Basingstoke Engl 20: 356-364.

46. http://www.wma.net/es/30publications/10policies/b3/

47. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria'. Ann Neurol 69: 292-302.

48. Kurtzke, JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33: 1444-1452.

49. Perez-Alvarez AI, García-Rúa A, Suárez-Santos P, Castanon-Apilanez M, Ameijide-San Luis E, et al. (2018) Appraisal of cerebral atrophy in multiple sclerosis by means of the corpus callosum index. Rev Neurol 67: 417-424.

50. Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T (2012) Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity?, Acta Neuropathol 123: 627-638.

51. Markowitz CE (2013) Multiple sclerosis update (2013). Am J Manag Care 19: 294-300.