Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.14.031

Anatomical Evaluation of The Corpus Callosum in Multiple Sclerosis Patients Using MRI

Hussam Alabdullah[1*], Mennan Ece Pirzirenli[2], Aslı Tanrıvermiş Sayıt[3], Aymen Warille[4]

[1] Ph.D. student, Department of Anatomy, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

[2] Associate Professor, Department of Anatomy, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

[3] Associate Professor, Department of Radiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

[4] Professor, Department of Anatomy, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

***Corresponding author:** Hussam Alabdullah, Ph.D. student, Department of Anatomy, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey, Email: dr.surgeon2@gmail.com

Submitted: 12 March 2023; Accepted: 19 April 2023; Published: 06 May 2023

ABSTRACT

Background: Multiple sclerosis MS is a chronic, complicated disease of still unknown exact etiology that impacts the whole central nervous system (CNS). Corpus callosum atrophy in MS patients may serve as a disease-progression biomarker because it is a representation of the permanent process of degenerative injury. We designed this study with the aim of addressing the anatomical changes of the corpus callosum in multiple sclerosis patients using easy linear MRI measurements and comparing the results with those in the normal population.

Methods: MRI images for 50 participants (25 MS patients and 25 healthy controls) were collected. The chosen MRI scans were carried out between 2017 and 2021. Five anatomical parameters of the corpus callosum were measured in the best MRI mid-sagittal plane.

Results: In the patient group, the mean thickness of genu G, body B, splenium S, anterior-posterior diameter AP, and corpus callosum index CCI were 9.75 ±1.85mm, 4.83±1.17 mm, 9.96±2.1 mm, 66.24 ±4.33 mm, and 0.37 ±0.06 respectively. In the control group, the mean G, B, S, AP, and CCI were 12.9 ±1.86mm, 7.54 ±1.19mm, 13.01±1.53mm, 69.72±4.47mm, and 0.48±0.04 respectively. The results of the t-test revealed that there is a statistically significant difference between the two groups for G (P=0.000), B (P=0.000), S (P=0.000), AP (P=0.008), and CCI (P=0.000). All dimensions were smaller in the patients group than in the control group.

Conclusion: Morphometric evaluation revealed that patients with MS had significantly thinner CC segments than their neurologically normal counterparts. We believe that these findings may serve as a baseline to guide subsequent analyses with other groups, as well as studies of forensic and MS-related alterations in the CC in Turkish young adults.

Keywords: *corpus callosum, multiple sclerosis, MRI, brain atrophy*

J Popul Ther Clin Pharmacol Vol 30(14):e235–e241; 06 May 2023.

INTRODUCTION

The corpus callosum (CC) is the largest bundle of commissural connections in the human brain. It is made up of a minimum of 200–300 million fibers that link the right and left lobes of the cerebrum (Sakai et al., 2017). It is a white matter structure and is critical in transmitting sensory, motor, and even cognitive signals between both cerebral hemispheres (Lamantia & Haven, 1990). The rostrum, genu, body, and splenium are morphologically distinct components of the CC. The genu is located close to the frontal lobe, whereas the splenium is located close to the occipital lobe. The inferior backward elongation from the genu is called the rostrum, while the body is the CC's largest region, positioned between the genu and splenium (Allouh et al., 2020).

Multiple sclerosis (MS) is a chronic, complicated disease of still unknown exact etiology that impacts the whole central nervous system (CNS) (Vasileiadis et al., 2018). It is the most common disorder that causes non-traumatic neurological impairment in young people (Dobson & Giovannoni, 2019). The occurrence of MS and its associated socioeconomic impact are both growing worldwide (Browne P et al., 2014).

Brain atrophy, or the slow decrease of brain volume, is highly common in MS, averaging about 0.5–1.35% each year, well above the limits of normal aging (Giovannoni et al., 2016). It starts early in the disease process and increases throughout progression but is mitigated by disease-modifying medicines (Heliopoulos et al., 2015). Severe axonal transection and demyelination are believed to cause MS atrophy (Amiri et al., 2018).

The use of magnetic resonance imaging (MRI) for the diagnosis, monitoring, and prognosis of multiple sclerosis (MS) is essential in the field of clinical neurology. In particular, MRI's predictive significance has attracted substantial interest (Granberg et al., 2015). Despite the increasing interest in MS-related brain atrophy research and the fact that MRI linear measurements have been widely applied in monitoring the disease, Most studies have tended to focus on a few parameters of the CC, like the corpus callosum index CCI and the corpus callosum area CCA, with less concentration on anatomic measurements and dimensions of this structure.

For a more comprehensive evaluation, we designed this study aiming to address the anatomical changes of the corpus callosum in multiple sclerosis patients using easy linear MRI measurements and compare the results with those in the normal population.

METHODS

The Medical Research Ethics Committee at Ondokuz Mayıs University granted approval for this study on August 4th, 2020, with document number: B.30.2.ODM.0.20.08/496-569. A retrospective monocenter case-control study was conducted. and only utilize the essential information that has been extracted from the anonymized data. Participants were not involved beyond what was permitted in this study.

From the radiology department database at Ondokuz Mayıs University Hospital, MRI images for 50 participants (25 MS patients and 25 healthy controls) were collected. The chosen MRI scans were carried out between 2017 and 2021.

All patients had to fulfill the MS diagnostic criteria and be enrolled in a management program in order to be considered for inclusion.

Exclusion criteria included any neurological condition other than MS that might impact the physical structure of the brain, prior brain surgery, and current or previous mental disorder. To reduce the impact of normal brain atrophy in children and the elderly, age limitations were imposed. The participants in the control group had brain MRIs for various reasons, such as headaches, and were found to be normal by a neuroradiologist. The control group was matched to the patients' group for gender and race.

The patients’ group and the control group constitute a subset of the larger sample drawn from the radiology department at our institution. Participants were chosen sequentially from the list after the eligibility criteria were examined.

We used MRI for direct visualization of the corpus callosum. A routine brain MRI protocol using a 1.5-T MRI machine (Philips, Achieva) was performed with the following parameters: TR/TE: 600/10, slice thickness: 5mm, and gap: 1 mm for sagittal T2-weighted images. The Radiant DICOM 2020.1.1 software was used to produce measurements because it is the same program used at our institution, and the

sequential MRI data sets were analyzed on a desktop computer using the trial version obtained from radiantviewr.com. To reduce measurement errors, the observer took the measures under the supervision of an experienced neuroradiologist; for intra-rater variability, all measurements were assessed twice at a four-week interval. The final value of each variable was calculated by taking the average of the two measurements. All measurements in this investigation were taken in millimeters.

We used the best T2-weighted mid-sagittal plane where the cerebral aqueduct that connects the third ventricle to the fourth ventricle can be visualized, separating the midbrain into tectum and tegmentum, as well as a clear identification of the septum pellucidum,inter-thalamic adhesion with the anterior and posterior commissures. On the mid-sagittal plane, the corpus callosum can easily be demarcated. For corpus callosum segmentation, we used the method described by Figueira (Figueira et al., 2007) but we used T2 images, not T1 images, since they have the best quality in our data. We considered five parameters of the corpus callosum in this study.

1.Anteroposterior diameter (AP):

We identified the most anterior and the most posterior points of the corpus callosum, and then we connected between these points by drawing a line that resembles the greatest anteroposterior diameter (AP) of the corpus callosum.

2.Anterior segment (G):

It is the segment that results from the intersection of the anteroposterior diameter with the genu of the corpus callosum, as shown in (fig1).

3.The posterior segment (S):

It is the segment that results from the intersection of the anteroposterior diameter with the splenium of the corpus callosum, as shown in (fig1).

4.The middle segment (B):

We drew a line perpendicular to the anteroposterior diameter at its midpoint, this line will

intersect the body of the corpus callosum. The middle segment (B) is the segment that results from this intersection (fig1).

5. Corpus callosum index (CCI):

Corpus callosum index CCI has been proposed as a possible biomarker of brain atrophy in MS patients. It can be easily and reliably obtained from conventional MRI. CCI is calculated by dividing the sum of the three segments G, B, and S by the anteroposterior diameter, as in the following formula: CCI = (G+B+S)/AP.

The study participants' basic clinical and demographical characteristics were analyzed using SPSS version 25. Statistical indicators were calculated, such as the mean, standard deviation (SD), and percentage. Non-numerical variables, such as gender, were translated into analyzable forms during SPSS data analysis. As a result, males were denoted by (1) and females by (2). We performed the Shapiro-Wilk normality test to determine the statistical tests that would be used.

A simple independent t-test was used to compare differences between two groups, pathological and control groups in the case of parametric data, and the Mann-Whitney U-test in the case of non-parametric data. The level of confidence is 95%, and the significance level for all statistical tests was determined to be significant at $p<0.05$.

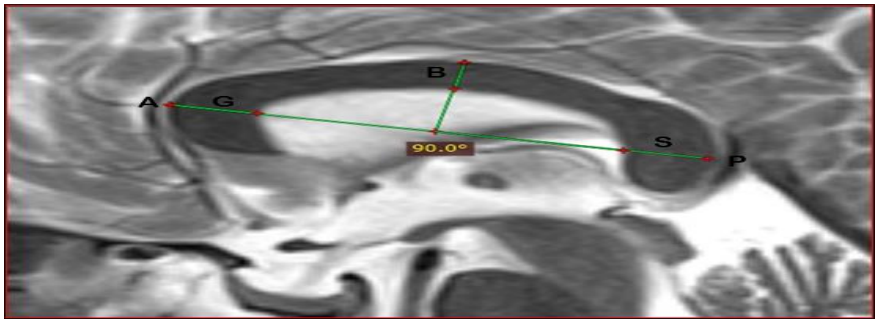

FIGURE 1: T2 midsagittal plane showing the segmentation of corpus callosum , AP the maximum anterior posterior diameter of the corpus callosum, G the thickness of genu, B the thikness of the body, S the thickness of splenium

J Popul Ther Clin Pharmacol Vol 30(14):e235–e241; 06 May 2023.

RESULTS

The demographic and basic characteristics of patients and controls are summarized in Table 1.

TABLE 1: Demographic and basic characteristics of the study population

Variables	control group	patient group	P- value
Number	25	25	
Age			
Mean	33.2	37	0.04*
(SD)	7.51	4.08	
Gender			
Male	5	6	0.73
Female	20	19	

(SD) standard deviation, * statistically significant

The study involved 50 individuals who matched the inclusion criteria, ranging in age from 23 to 48 years. The participants were separated into two groups: patients and controls. The patients' group included 25 participants, with 6 (24%) males and 19 (76%) females, with a mean age of 37±4.08 years. The control group consisted of 25 participants, with 5 (20%) males and 20 (80%) females. The mean age in the control group was 33.2±7.51 years, less than that of the patients' group. There was a statistically significant difference between the two groups' age (p=0.04). Regarding gender, there was no statistically significant difference (p=0.73).

In the pathological group the mean G, B, S, AP, and CCI were 9.75 ±1.85mm, 4.83±1.17 mm, 9.96±2.1 mm, 66.24 ± 4.33 mm, and 0.37 ±0.06 respectively. In the control group the mean G, B, S, AP, and CCI were 12.9 ±1.86mm, 7.54 ±1.19mm, 13.01±1.53mm, 69.72± 4.47mm, and 0.48± 0.04 respectively.

We aimed to explore the differences between patient and control groups using a t-test in the case of normal distribution. The results of the t-test shown in Table 2. revealed that there is a statistically significant difference between the two groups for G (p=0.000), B (p=0.000), S (p=0.000), AP (p=0.008), and CCI (p=0.000). All dimensions were smaller in the patient group than in dimensions in the control group.

TABLE 2: Measurements of corpus callosum in millimeters

variables	Controls (n=25)	patients (n=25)	p-value
G			
Min	9.38	6.06	
Max	16.7	12.9	
Mean	12.90	9.75	0.000*
(SD)	1.86	1.85	
B			
Min	5.23	2.17	
Max	9.81	7.51	
Mean	7.54	4.83	0.000*
(SD)	1.19	1.17	
S			
Min	9.29	4.82	
Max	15.40	14.4	
Mean	13.01	9.96	0.000*
(SD)	1.53	2.1	
AP			
Min	62.5	55.6	
Max	78.60	75	
Mean	69.72	66.24	0.008*
(SD)	4.47	4.33	

J Popul Ther Clin Pharmacol Vol 30(14):e235–e241; 06 May 2023.

CCI			
Min	0.40	0.26	
Max	0.58	0.47	
Mean	0.48	0.37	0.000*
(SD)	0.04	0.06	

SD standard deviation, G thickness of the genu, B thickness of the body, S thickness of the splenium, AP maximum anterior-posterior diameter of the corpus callosum, CCI corpus callosum index, * statistically significant

DISCUSSION

As mentioned in the introduction, the core objective of this study is to use straightforward, doable linear MRI measures to characterize the possible structural abnormalities in the corpus callosum in multiple sclerosis patients. Because it can accurately represent the pathologic features of this disease, conventional magnetic resonance imaging (MRI) has established itself as a tool for diagnosing and monitoring MS.

Although there are several techniques to monitor brain atrophy, manual measures have the advantage of being simple and quick to use when the MRI exam is over. Earlier studies that claimed manual 2D measurements lacked accuracy were refuted by the finding that the planimetric measuring approach is equally accurate as semiautomatic volume measurements (Lutz et al., 2017). Linear measurements can be quantified on a single picture segment with a distance tool on a computer workstation. The 2D atrophy assessments have demonstrated continuous sensitivity to disease development (Bermel & Bakshi, 2006), considerable relationships with clinical outcomes (Bermel et al., 2002), and significant correlations with 3D brain atrophy measures (Sharma et al., 2004).

The corpus callosum is the biggest commissure in the brain, linking similar parts of the cerebral hemispheres and allowing communication between cortical and subcortical neurons (Bloom & Hynd, 2005). In MS, localized demyelination, axonal injury, and Wallerian degeneration following inflammation may result in CC atrophy. Because it is a representation of the permanent process of degenerative injury, CC atrophy in MS patients may serve as a disease-progression biomarker (Pérez-Martín et al., 2020).

Numerous methods have been devised to partition the CC in order to facilitate measurement and guarantee reproducibility. Inconsistent findings when evaluating the CC have been put down, at least in part, to the employment of many techniques with varying scopes (Constant & Ruther, 1996).

In our study, we used the corpus callosum index (CCI) for corpus callosum segmentation. Figueira reported that the CCI was easy to use, required no complicated software, and was sensitive to callosal thinning. Because of this, it showed promise for use in MS patients' long-term monitoring (Figueira et al., 2007). Accordingly, we measured the thickness of the genu G, body B, splenium S, and anteroposterior diameter AP, and the results were 9.75 ±1.85mm, 4.83±1.17 mm, 9.96±2.1 mm, and 66.24 ± 4.33 mm in the MS group respectively, and the result of the CCI was 0.37 ±0.06. In a Spanish study Perez-Alvarez et al. studied 109 MS patients and calculated the CCI, which was also 0.377 as in our study (Perez-Alvarez et al., 2018). Unfortunately, as in most clinical trials,the anatomical measures of CC segments in the Spanish study were not mentioned to be compared with ours.

On the other hand,in the control group, the mean G, B, S, AP, and CCI were 12.9 ±1.86mm, 7.54 ±1.19mm, 13.01±1.53mm, 69.72± 4.47mm, and 0.48± 0.04 respectively. Allouh et al. measured the CC segments in Middle Eastern young adult Araps in 100 participants with an age mean of 32 years; the results of G,B, S, and AP were as follows: 10.9±1.4, 6.2±0.8, 16.6±2.3 and 68.4±4.0 (Allouh et al., 2020). In comprison we see that all the varibles are smaller than ours except for the thickness of the splenium which was apparently wider in the Arap population. Allouh himself reported the same observations when he compared the results with another Turkish study (Karakaş et al., 2011). It is worthy to say that Allouh et al. used a different technique in CC segmentation (Suganthy et al., 2003). However, due to different restrictions, it is challenging to draw strong inferences on racial differences in CC from our comparative research. This is because of the differences in

methodology, sample size, and male/female ratio in each study.

We believe that these findings may serve as a baseline to guide subsequent analyses with other groups, as well as studies of forensic and MS-related alterations in the CC in Turkish young adults. Morphometric evaluation revealed that patients with MS had significantly thinner CC segments than their neurologically normal counterparts.

To achieve a greater degree of confidence, we would like to highlight certain limitations: The retrospective design of our study rendered a correlation between the results and the clinical status of the participants and also with the progression of the disease.

The small size of our sample is also another limitation, taking into account that there are already some anatomical differences in measurements of the thcorpus callosum even in the normal population, these differences change with age, gender, and race.

As multiple sclerosis usually affects young adults, the age range was narrow to some degree (23–48 years); hence, for generalization of results, it should be tested in a wider age range.

Another limitation is the MRI slice thickness and resolution, we used a 5 mm slice thickness in most cases, and the resolution in some slices was suboptimal for measuring. A longitudinal study with a long follow-up period and a larger sample size is warranted to reinforce our results, taking into account the clinical status of the patients, the subtype of the disease, and even the management protocol.

Despite the highlighted restrictions, the results are still meaningful for addressing the study question.

In this study, we shed light on the morphological changes of the corpus callosum in multiple sclerosis patients. We used linear measurements, which are time-effective, do not require advanced experience, and are also equal to volume measurements that are frequently used in MS patient monitoring.

Corpus callosum index CCI was used for segmentation, as it is ordinarily applied in clinical neurology. Measurements of CC sub-regions in MS patients are not usually covered in other clinical studies since they commonly focus only on the net value of CCI. Our results may serve as reference data for future comparison studies.

Declarations

Competing Interests

The authors declare that they have no competing interests.

All methods were carried out in accordance with relevant guidelines and regulations.

Acknowledgment

None**.**

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Hussam Alabdullah], [Mennan Ece Pirzirenli], [Aslı Tanrıvermiş Sayıt] and [Aymen Warille]. The first draft of the manuscript was written by [Hussam Alabdullah] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency, commercial or

not-for-profit sectors.

Availability of data and material

Not applicable.

REFERENCES

1. Allouh, M. Z., Al Barbarawi, M. M., Ali, H. A., Mustafa, A. G., & Alomari, S. O. (2020). Morphometric Analysis of the Corpus Callosum According to Age and Sex in Middle Eastern Arabs: Racial Comparisons and Clinical Correlations to Autism Spectrum Disorder. Frontiers in Systems Neuroscience, 14(June), 1–11. https://doi.org/10.3389/fnsys.2020.00030
2. Amiri, H., de Sitter, A., Bendfeldt, K., Battaglini, M., Gandini Wheeler-Kingshott, C. A. M., Calabrese, M., Geurts, J. J. G., Rocca, M. A., Sastre-Garriga, J., Enzinger, C., de Stefano, N., Filippi, M., Rovira, Á., Barkhof, F., & Vrenken, H. (2018). Urgent challenges in quantification and interpretation of brain grey matter atrophy in individual MS patients using MRI. NeuroImage: Clinical, 19(2017), 466–475.

https://doi.org/10.1016/j.nicl.2018.04.023
3. Bermel, R. A., & Bakshi, R. (2006). The measurement and clinical relevance of brain atrophy in multiple sclerosis. Lancet Neurology, 5(2), 158–170. https://doi.org/10.1016/S1474-4422(06)70349-0
4. Bermel, R. A., Bakshi, R., Tjoa, C., Puli, S. R., & Jacobs, L. (2002). Bicaudate ratio as a magnetic resonance imaging marker of brain atrophy in multiple sclerosis. Archives of Neurology, 59(2), 275–280. https://doi.org/10.1001/archneur.59.2.275
5. Bloom, J. S., & Hynd, G. W. (2005). The role of the corpus callosum in interhemispheric transfer of information: Excitation or inhibition? Neuropsychology Review, 15(2), 59–71. https://doi.org/10.1007/s11065-005-6252-y
6. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, & Thompson AJ. (2014). Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology, 93(11), 1022–1024. http://www.msif.org/about-ms/publications-
7. Constant, D., & Ruther, H. (1996). Sexual dimorphism in the human corpus callosum? A comparison of methodologies. Brain Research, 727(1–2), 99–106. https://doi.org/10.1016/0006-8993(96)00358-7
8. Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis – a review. European Journal of Neurology, 26(1), 27–40. https://doi.org/10.1111/ene.13819
9. Figueira, F. F. A., Dos Santos, V. S., Figueira, G. M. A., & Da Silva, Â. C. M. (2007). Corpus callosum index: A practical method for long-term follow-up in multiple sclerosis. Arquivos de Neuro-Psiquiatria, 65(4 A), 931–935. https://doi.org/10.1590/s0004-282x2007000600001
10. Giovannoni, G., Butzkueven, H., Hobart, J., Kobelt, G., Sormani, M. P., Thalheim, C., Traboulsee, A., Vollmer, T., Hobart, J., Kobelt, G., Pepper, G., & Sormani, M. P. (2016). Author ' s Accepted Manuscript Brain health : time matters in multiple sclerosis. Multiple Sclerosis and Related Disorders. https://doi.org/10.1016/j.msard.2016.07.003
11. Granberg, T., Shams, S., Aspelin, P., Kristoffersen-wiberg, M., & Fredrikson, S. (2015). MRI-Defined Corpus Callosal Atrophy in Multiple Sclerosis : A Comparison of Volumetric Measurements , Corpus Callosum Area. Lv, 1–6. https://doi.org/10.1111/jon.12237
12. Heliopoulos, I., Papathanasopoulos, P., & Dardiotis, E. (2015). The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome : a systematic review and meta-analysis. https://doi.org/10.1177/1756285615600381
13. Karakaş, P., Koç, Z., Koç, F., & Gülhal Bozkir, M. (2011). Morphometric MRI evaluation of corpus callosum and ventricles in normal adults. Neurological Research, 33(10), 1044–1049. https://doi.org/10.1179/1743132811Y.0000000030
14. Lamantia, A., & Haven, N. (1990). Axon Overproduction and Elimination Developing Rhesus Monkey in the Corpus Callosum of the. July.
15. Lutz, T., Bellenberg, B., Schneider, R., Weiler, F., Köster, O., & Lukas, C. (2017). Central Atrophy Early in Multiple Sclerosis: Third Ventricle Volumetry versus Planimetry. Journal of Neuroimaging, 27(3), 348–354. https://doi.org/10.1111/jon.12410
16. Perez-Alvarez, A. I., Garcia-Rua, A., Suarez-Santos, P., Castanon-Apilanez, M., Ameijide-Sanluis, E., Saiz-Ayala, A., Meilan-Martinez, A., Villafani-Echazu, W. J., Gonzalez-Delgado, M., & Oliva-Nacarino, P. (2018). Valoracion de la atrofia cerebral en la esclerosis multiple mediante el indice de cuerpo calloso [Appraisal of cerebral atrophy in multiple sclerosis by means of the corpus callosum index]. Revista de neurologia, 67(11), 417–424.
17. Pérez-Martín, M. Y., González-Platas, M., Jiménez-Sosa, A., Plata-Bello, J., & López-Segura, A. (2020). Normative Data of the Corpus Callosum Index and Discriminant Validity in Patients with Multiple Sclerosis. J Neurol Neurosci, 11(4), 322. https://doi.org/10.36648/2171-6625.11.1.322
18. Sakai, T., Mikami, A., Suzuki, J., Miyabe-Nishiwaki, T., Matsui, M., Tomonaga, M., Hamada, Y., Matsuzawa, T., Okano, H., & Oishi, K. (2017). Developmental trajectory of the corpus callosum from infancy to the juvenile stage: Comparative MRI between chimpanzees and humans. PLoS ONE, 12(6), 1–22. https://doi.org/10.1371/journal.pone.0179624
19. Sharma, J., Sanfilipo, M. P., Benedict, R. H. B., Weinstock-Guttman, B., Munschauer, F. E., & Bakshi, R. (2004). Whole-brain atrophy in multiple sclerosis measured by automated versus semiautomated MR imaging segmentation. American Journal of Neuroradiology, 25(6), 985–996.
20. Suganthy, J., Raghuram, L., Antonisamy, B., Vettivel, S., Madhavi, C., & Koshi, R. (2003). Gender- and age-related differences in the morphology of the corpus callosum. Clinical Anatomy, 16(5), 396–403. https://doi.org/10.1002/ca.10161
21. Vasileiadis, G. K., Dardiotis, E., Mavropoulos, A., Tsouris, Z., & Tsimourtou, V. (2018). Regulatory B and T lymphocytes in multiple sclerosis : friends or foes ? Autoimmunity Highlights, 1–15. https://doi.org/10.1007/s13317-018-0109-x