Original Article

Relationship Between Bi-Caudate Ratio and White Matter Atrophy in Brain MRI of Multiple Sclerosis

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Abstract

Background: Multiple sclerosis (MS) is one of the most common and debilitating neurological diseases. Brain magnetic resonance imaging (MRI) is critical to determine the prognosis of MS. Using simple and accessible techniques is one of the researchers' concerns. So far, limited studies have been conducted on evaluating the relationship between the Bi-caudate ratio (BCR) and white matter atrophy in brain MRI of patients with MS. Therefore, in this study, we decided to evaluate this relationship.

Materials and Methods: In this cross-sectional study, which was conducted to determine the relationship between BCR and white matter atrophy in brain MRI patients with MS, patients with MS who were evaluated by MRI at Imam Hossein Hospital (Tehran-Iran) in 2022 were assessed. BCR is determined by dividing the shortest distance between two caudate nuclei by the length of the brain at the imaging. The symbol digit modalities test (SDMT) was used to check the cognitive function of patients, and the relationship between BCR and MS-related parameters was evaluated. Expanded disability status score (EDSS) was also evaluated. A significance level was considered less than 0.05.

Results: Eighty-five patients with a mean age of 40.73 ± 8.45 years and female gender was more prevalent (65.9%). The mean EDSS in all participants was 2.64 ± 2.49, and the mean BCR was 0.11 ± 0.03. EDSS score, age of the disease onset, SDMT score, and BCR were significantly different between different MS types (secondary progressive MS, primary progressive MS, and relapsing-remitting MS) (P-values<0.05). There was a statistically significant relationship between age, disease duration, EDSS score, onset age of the disease, and SDMT score with BCR (P<0.05). There was a statistically significant difference in the amount of BCR between sexes (P<0.045).

Conclusion: BCR is a valuable method for evaluating the condition of multiple sclerosis, and it can be used as a simple and accessible technique for evaluating MS conditions.

Keywords: Atrophy, Multiple sclerosis, White matter, Magnetic resonance imaging

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Introduction

Multiple sclerosis (MS) is an autoimmune chronic demyelinating disease of the central nervous system (CNS). One of the most useful diagnostic methods for diagnosing MS is magnetic resonance imaging (MRI). Hyperintense lesions on T2 weighted (T2W) MRI of the

brain are used to diagnose and determine the progression of MS. Although these imaging are widely used to diagnose the disease, they are not specific and sensitive[5-1].

Typical periventricular lesions in the T2W view are significant for diagnosing multiple sclerosis. The interesting point is the radiological-clinical contrast in these lesions. So that the aggravation or improvement of MRI lesions is not related to the clinical activity of the disease, it seems that brain atrophy in multiple sclerosis is a sign of destruction and an irreversible pathological process that is related to disease activity. In some studies, it has been seen that the gray matter volume of the cerebral cortex has an inverse relationship with the disability score of multiple sclerosis patients (relapsing-remitting multiple sclerosis (RRMS) and Progressive-Relapsing MS (PRMS)) (6-9). On the other hand, gray matter volume has a positive relationship with cognitive activity. Another problem with these imagings is that it is difficult and impractical to compare the brain volume reduction in a 3D view. To turn this finding into a practical method, one-dimensional linear markers should be used. To meet the need for simple but reliable measures of brain atrophy, linear atrophy parameters such as bicaudate ratio (BCR) and third ventricle width (TVW) have been proposed[6-11]. BCR is a surrogate marker of global supra-tentorial white matter atrophy, but its accuracy for the diagnosis of MS is still under investigation[12,13]. In this study, we aimed to investigate the relationship between bi-caudate ratio as a useful and quantitative marker in examining the supratentorial white matter of the brain in multiple sclerosis.

Methods

This cross-sectional study aimed to determine the relationship between BCR and white matter atrophy in the brain MRI of patients with multiple sclerosis.

The inclusion criteria were multiple sclerosis involvement and referring to Imam Hossein Hospital in 2022 for a brain MRI. Exclusion criteria were MRI sequences lacking the necessary quality for interpretation, any bleeding lesion, and the presence of a mass in the brain or skull area.

The imaging of MS patients was reviewed and evaluated respectively to reach the calculated sample size. The sample size was calculated based on the below formula, and it was equal to 60 patients:

$$N_{Disease} = \frac{\left\{z_{1-\alpha/2}\Lambda + z_{1-\beta}\sqrt{\Lambda^2 - \zeta^2(3+\Lambda)/4}\right\}^2}{\Lambda\zeta^2}$$

$$N = \frac{N_{Disease}}{\pi_{Disease}}$$

Patients were grouped based on the type of MS that was diagnosed before, including relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS).

The BCR ratio was obtained by dividing the shortest distance between two caudate nuclei by the length of the brain[14]. The symbol digit modalities test (SDMT) was used to check the brain's cognitive function. In this test, we considered the maximum number of shapes a patient pair with the correct number in 90 seconds as the test answer.

The Symbol Digit Modalities Test (SDMT) evaluates processing speed and sustained attention, mainly assessing intricate visual scanning and tracking abilities. The SDMT is a cognitive assessment with a paper sheet displaying an answer key at the top. It includes nine symbols paired with their corresponding numerical values ranging from 1 to 9. Below this key, there are 120 random occurrences of these symbols. Participants are tasked with recording the numerical equivalents of each symbol within a 90-second time frame, utilizing the answer key as needed. This test can be conducted in written and verbal formats[15].

We also evaluated the patients using the Expanded Disability Status Scale (EDSS). The EDSS is the predominant metric employed to assess disability in individuals with multiple sclerosis (MS). This scale is a robust tool for evaluating the level of disability experienced by patients. The EDSS operates on a scoring range from 0 to 10, where zero indicates a normal neurological examination. In contrast, a score of 10 signifies mortality attributable to MS. Patients who score up to 5 on the EDSS are considered fully ambulatory. Below this threshold, the primary factors influencing the EDSS are the functional systems (FS). In contrast, beyond a score of 5, the ambulation status becomes the principal determinant of the degree of disability.

EDSS scores are as follows:
0. Grade 0 in all FS
1. Grade 1 in any/all FS
2. Grade 2 in 1 or 2 FS; others O/1
3. Grade 3 in 2 FS; grade 3 in 1 FSc/s ½ FS grade 2; grade 2 in 3–5 FS
4. Ambulation 300 m +without aid; FS exceed DSS 3
5. Limited ambulation without aid; FS usually exceeds DSS 4
6. Ambulatory with aid; FS combinations with 3+ grade 3+
7. Wheelchair; FS combinations with 2+ grade 4+
8. Bed patient; FS combinations with several grade 4+
9. Helpless bed patient; FS combinations with most FS grade 4+
10. Death due to MS[16-18]

Statistical analysis: Mean, standard deviation, median, range, frequency, and percentage were used to describe the data. We used the ANOVA statistical test to compare numerical variables and Pearson's correlation coefficient to check the relationship between variables. Analyzes were performed using SPSSv.25 statistical software. A P-value less than 0.05 was considered statistically significant.

We also evaluated the expanded disability status scale (EDSS) of patients. EDSS serves as a highly effective tool for assessing disability levels. This scale operates on a scoring range from 0 to 10, effectively indicating the disability experienced by patients. A score of zero signifies a normal neurological examination, while a score of 10 corresponds to cases resulting in death due to multiple sclerosis (MS). Patients with an EDSS score of 5 or lower are considered fully ambulatory. Up to this threshold, the primary factors influencing the EDSS are the functional systems (FS). In contrast, beyond a score of 5, ambulation status becomes the predominant factor in determining the extent of disability[16].

Ethical consideration: This study was approved by the ethical committee of Shahid Beheshti Medical University (IR.SBMU.MSP.REC.1402.136).

Results

In this study, 85 patients were assessed. The mean age of the patients was 40.73 ± 8.45 years, with a range of 4 to 56 years. Regarding gender distribution, 29 patients (34.1%) were male and 56 (65.9%) were female. We evaluated the patients' clinical data, and the results are seen in Table 1.

The relationship between BCR level and gender was investigated, and it was seen that there was a significant difference between men and women, which was 0.1 ± 0.03 in men and 0.12 ± 0.03 in women, respectively (p-value = 0.045). Correlation between BCR and clinical and demographic data was assessed. The related data are seen in Table 2.

Discussion

In the present study, which was conducted to determine the relationship between BCR and white matter atrophy in the brain MRI of patients with MS, 85 patients were investigated. The mean age was 40.73 ± 8.45 years, and 65.9% were women. The mean EDSS score in all participants was 2.64 ± 2.49, and the mean BCR was 0.11±0.03. Between different MS groups (SPMS, RRMS, PPMS), EDSS score, age of disease onset, SDMT score, and BCR were significantly different. Significant correlations existed between age, disease duration, EDSS score, disease onset age, and SDMT score with BCR. There was a statistically significant difference in the amount of BCR between sexes.

The study by Serag et al. investigated the value of BCR as a marker of white matter atrophy in MRI of patients with multiple sclerosis and ischemic leukoencephalopathy.

Table 1. Clinical data of the patients**.**

	Total	Subgroups			P-value
		SPMS	RRMS	PPMS	
EDSS score	2.64 ± 2.49	4.83 ± 1.57	0.76 ± 1.11	5.5 ± 1.02	<0.001
Age.start disease	32.78 ± 8.76	33.13 ± 8.53	30.42 ± 8.56	40.29 ± 5.17	0.001
SDMT score	20.32 ± 10.19	12.22 ± 7.54	27.19 ± 6.33	10.07 ± 5.14	<0.001
BCR	0.11 ± 0.03	0.14 ± 0.02	0.09 ± 0.02	0.13 ± 0.02	<0.001
Time of disease involvement	8 ± 5.51	10.83 ± 6.66	6.85 ± 5.14	7.29 ± 2.55	0.014

Table 2. Correlation between BCR and clinical and demographic data**.**

		BCR
Age	Pearson Correlation	0.415
	P-Value	0<0.001
	N	85
Time of disease involvement	Pearson Correlation	0.418
	P-Value	0<0.001
	N	85
EDSS score	Pearson Correlation	0.743
	P-Value	0<0.001
	N	85
Age start disease	Pearson Correlation	0.228*
	P-Value	0.036
	N	85
SDMT score	Pearson Correlation	-0.753
	P-Value	0<0.001
	N	85

A total of 115 patients (54 men and 61 women) diagnosed with white matter leukoencephalopathy (MS in 51 patients and ischemic leukoencephalopathy in 64 patients) were examined. The mean BCR was 0.16 ± 0.02, significantly higher than the control group. A cut-off value of 0.13 was found to differentiate between BCR in both patient and control groups with sensitivity, specificity, and accuracy of 99.2%, 100%, and 99%, respectively. The difference in BCR for patients with MS and ischemic leukoencephalopathy was also statistically significant. It was concluded that BCR can be useful as a surrogate marker of global supratentorial white matter atrophy[12]. The current study showed that BCR has a significant relationship with various parameters related to MS disease. These parameters included age of disease onset, gender, patient age, disease duration, EDSS score, and SDMT score. Based on the findings of the current study and the study of Serag et al., it can be said that the status of MS can be understood based on BCR in affected patients, and measuring BCR can be a useful method to determine the patient's condition.

Oset et al. evaluated the predictive value of brain atrophy, serum biomarkers, and information processing speed for early disease progression in multiple sclerosis. This study included 50 patients, and the average follow-up time was 28 months. A statistically significant increase in EDSS, BCR, and TVW scores was observed after 2 years of disease. None of the parameters were significant predictors of achieving no evidence of disease activity status (NEDA). Only the neurofilament light chain (NfL) level significantly affected disease progression, measured as an increase in EDSS[13]. The findings of Oset et al.'s study differed from those of the present study and the study of Serag et al. According to the current study, BCR has a significant relationship with parameters related to MS, such as EDSS. It is significantly different even between the subgroups of this disease, and it is possible to understand the state of the disease based on it, so that the mean BCR in SPMS, RRMS, and PPMS were 0.14±0.02, 0.09±0.02, and 0.13 ± 0.02, respectively. It is important to mention that in the study by Oset et al., it was also acknowledged that a statistically significant increase in the BCR was seen two years after the disease involvement. It seems that there is a need to conduct future studies with a larger statistical population to evaluate the predictive value of BCR for MS disease conditions and prove or disprove the diagnostic value of this method.

Altokhis et al. evaluated predictors of long-term disability in MS using routine MRI data. Eighty-two MS patients (53 women) with more than 10 years of clinical follow-up were assessed. Inter-caudate diameter (ICD) and third ventricle width (TVW) measurements at baseline and follow-up were correlated with the EDSS. A faster rate of lesion volume increase was observed in subjects with conversion to secondary progressive MS. The sensitivity and specificity of both ICD and TVW for predicting disability over 10 years were 60% and 64%. It was concluded that despite the advances in brain imaging and computerized volumetric analysis, ICD and TVW still have high utility because they are simple, fast, and have the potency to predict long-term disability. However, in this study, despite the statistical significance of these measures, these clinical tools are still unreliable[19]. In the current study, it was seen that BCR has a significant relationship with the types of MS and the scores of the disease condition. One of the differences between the present study and Altokhis et al.'s study was that BCR was examined in the current study. However, ICR was examined in Altokhis et al.'s study, but it seems that multiple sclerosis affects the condition of the caudate nuclei. It causes a change in the

diameters of these nuclei, which provides a good diagnostic value by measuring the diameter of these nuclei with MRI. However, more studies are still needed to evaluate this issue.

Milovanovic et al. investigated the reliability of BCR in detecting enlarged lateral ventricles in schizophrenic patients. They reported that there was a significant correlation between BCR and the volume of caudate nuclei and lateral ventricles with the incidence of schizophrenia. It was concluded that BCR is a reliable parameter for the rapid evaluation of enlarged ventricles in schizophrenia[20]. One of the differences between this study and the current study was that the current study was conducted on MS patients. However, the study by Milovanovich et al. was conducted on schizophrenia patients. Based on these two studies, it can be said that using BCR is useful in diseases that can induce brain structure atrophy. However, BCR can be useful for diagnosing or evaluating the status of which diseases need to be investigated in future studies.

Conclusion

It is concluded that BCR is a useful method to evaluate the condition of patients with MS. This method can easily be calculated in MRI and has a good correlation with parameters affecting this disease such as age, sex, duration of disease, EDSS score, age of disease onset, and SDMT score.

Acknowledgment

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Conflict of interest

The authors further declare that they have no conflict of interest.

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