Serag and Ragab *Egyptian Journal of Radiology and Nuclear Medicine* (2019) 50:99
https://doi.org/10.1186/s43055-019-0104-x

Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH Open Access

Bi-caudate ratio as a MRI marker of white matter atrophy in multiple sclerosis and ischemic leukocencephalopathy

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Abstract

Background: Brain atrophy measurement is now a cornerstone in basic neuro-imaging science. While assessment of white matter atrophy by visual inspection is subjective, volumetric approaches are time-consuming and not often feasible. Bi-caudate ratio represents a linear surrogate parameter of brain volume that can be derived from standard imaging sequences. This study highlights the value of the bi-caudate ratio (BCR) as a MRI marker of white matter atrophy in patients with multiple sclerosis and ischemic leukoencephalopathy and set a cut-off value to differentiate between patients with white matter atrophy and normal subjects.

Results: A total of 115 patients (54 males and 61 females) diagnosed with white matter leukoencephalopathy (MS in 51 patients and ischemic leukoencephalopathy in 64 patients) were included. Another group of 60 subjects with a normal white matter signal was recruited as a control group. BCR for the patient group ranged from 0.13 to 0.27 (mean (± SD) = 0.16 ± 0.02), while for the control group, it ranged from 0.05 mm to 0.13 (mean (± SD) = 0.09 ± 0.01). The difference between the two groups was statistically significant (*P* value < 0.001). A cut-off value of 0.13 was used to differentiate between the BCR in both patients and control groups with sensitivity, specificity, and accuracy of 99.2%, 100%, and 99%, respectively. The difference in BCR for patients diagnosed with MS and ischemic leukoencephalopathy was also statistically significant (*P* value < 0.001).

Conclusion: The bi-caudate ratio represents a linear measurement of subcortical atrophy that can be useful as a surrogate marker of global supra-tentorial white matter atrophy instead of the usually performed visual and therefore subjective assessment. It is an easily obtained measure that can be performed without complex time-consuming volumetric studies. Our findings also revealed that the BCR is higher in patients with ischemic leukoencephalopathy than in patients with MS.

Keywords: Bi-caudate ratio, MRI, White matter atrophy

Background

MRI plays an important role in the diagnosis of different white matter leukodystrophies. White matter atrophy may be significantly correlated with progressive impairment of the cognitive functions in white matter leukodystrophies [1].

Although an experienced radiologist is able to detect changes in brain volume through a qualitative inspection of brain MRI studies primarily based on ventricular space dilation, a quantitative examination is necessary to accurately identify these changes. The method of choice for their evaluation is the analysis of brain volumes (global brain and brain volume, white and gray substance volume) from three-dimensional sequences and by means of different automated or semi-automated volumetric studies. These methods have been positioned as a gold standard due to their reproducibility and sensitivity. However, they often require some degree of manual supervision. Although they are valid and precise methods, their implementation in daily clinical practice is difficult, as techniques require prior training for proper management and the results can take several hours and require external validation by trained personnel [2].

Linear markers of brain volume, like the bi-caudate ratio (BCR—the minimum inter-caudate distance divided by brain width along the same level), present a valuable alternative that can be applied to standard imaging sequences in daily practice. This allows for a more feasible quantitative assessment of supratentorial white matter atrophy [3].

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In the diagnosis of MS, the presence of typical T2WI lesions in the periventricular white matter is of major importance. However, the progression and regression of T2 lesions correlate poorly with a disability, referred to as the "clinico-radiological paradox" [4]. It has been suggested that atrophy in MS represents destructive and irreversible pathologic processes, making it a more reliable indicator of disease progression than the non-specific T2 lesion load assessment [5, 6]. This widespread atrophy poses challenges in routine radiological evaluations. Therefore, some key one-dimensional atrophy measurements might be useful in the recognition of progressive atrophic changes [4, 7, 8].

This study highlights the value of BCR as a quantitative and therefore objective marker of global supra-tentorial white matter atrophy in patients with MS and ischemic leukoencephalopathy instead of the usually performed visual and therefore subjective assessment. This may have an impact on the progressive impairment of the cognitive functions of the patients. Finally, we test the usefulness of BCR as a linear measure of atrophy in differentiating MS from ischemic leukoencephalopathy.

Methods

This retrospective study was conducted in the period from January 2018 to June 2019. It included 115 consecutive patients (54 (47%) males and 61 (53%) females). The mean age was (± SD) 52.51 years (± 18.2); age range (19–92 years). They were diagnosed with MS ($n = 51$, 44.3%) and ischemic leukoencephalopathy ($n = 64$, 55.7%). All patients underwent MRI examination of the brain at our institution. Inclusion criteria were as follows: past history of white matter demyelination and impairment of the cognitive functions. Exclusion criteria were MRI examination showing concomitant intra-axial hematomas or mass lesions or extra-axial fluid collections associated with significant compression of the underlying brain parenchyma and altering the inter caudate distance, MRI studies significantly affected by motion artifacts and MRI examinations stopped before

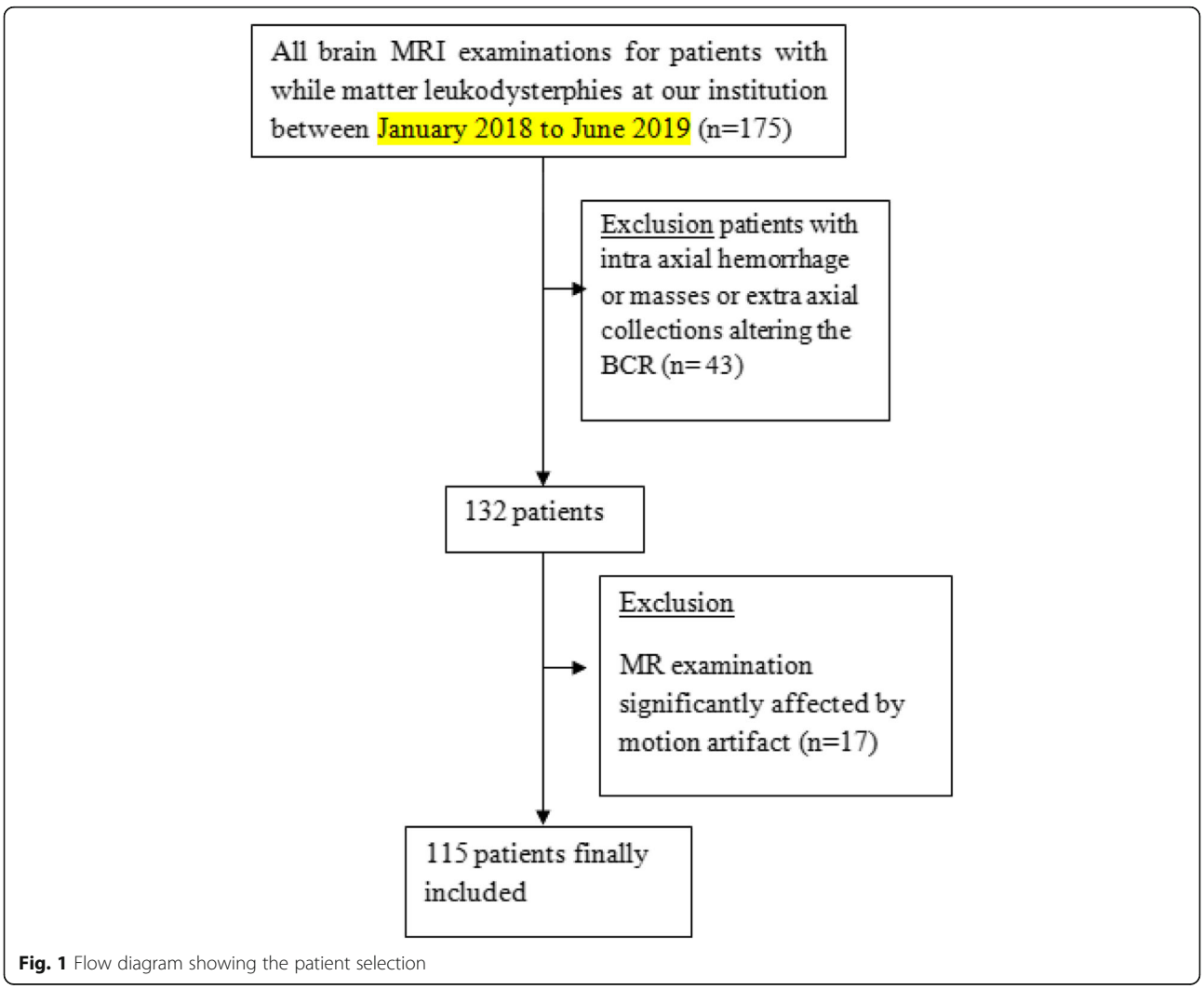

Fig. 1 Flow diagram showing the patient selection

the acquisition ended due to claustrophobia. Of the 175 patients initially selected, 115 were finally included in the study. The flow chart for patient selection is reported in Fig. 1.

Patients underwent MRI examination of the brain using the standard MRI protocol (described below). None of the patients received IV contrast.

Another group of 60 subjects (27 males (45%) and 33 females (55%)) who underwent MRI examination of the brain and had no clinical suspicion or MRI evidence of white matter leukodystrophies was recruited as a control group. They were age- and sex-matched to the patients' group. They underwent MRI scanning for other reasons (e.g., headache, disturbed consciousness level, head trauma). An experienced radiologist reviewed the MRI scans of the controls to ensure that there were no white matter abnormalities. The age of the controls ranged from 19 to 94 years with the mean age (± SD) of 51.3 years (± 7.1). This group underwent MRI examination of the brain using the same imaging protocol as the patient group.

Examination protocol

MRI examinations were performed using a 1. 5-Tesla unit (TOSHIBA, Excelart Vantage). Patients were imaged in the supine position using a 16 channel head coil. Before MR examination patients were asked to remove any metallic objects around the head and neck area.

MRI scan protocol included

T1WI (TR = 464 m.sec, TE = 12 m.sec, FOV = 24 cm, NS = 20, matrix = 192 × 352 pixels) and FLAIR (TR = 7200 m.sec, TE = 100 m.sec, TI = 2000 m.sec, NS = 20, FOV = 24 cm, matrix = 192 × 352 pixels) were obtained in the axial plane using 5-mm contiguous scans. Axial T2WI, sagittal T1WI, coronal T2WI, and coronal FLAIR sequences were also obtained as a part of the basic MRI protocol.

Images were transferred by a computer network to a workstation (Aze Virtual Place FujinRaijin 310) on which images were analyzed quantitatively. A trained radiologist (with more than 10 years of experience in neuro-radiology) who was blinded to clinical information performed the quantitative MRI analysis. The BCR was measured in the FLAIR axial slice where the heads of the caudate nuclei were most visible and closest to one another. The BCR was defined as the minimum inter-caudate distance divided by brain width along the same line (Fig. 2).

Statistical analysis

Data were expressed as number (No), percentage (%)mean (**x**), and standard deviation (SD) and analyzed by an IBM compatible personal computer with SPSS statistical package version 23 (SPSS Inc., Released 2015. IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.). Student's *t* test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann-Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Chi-square test (χ^2) was used to study the association between qualitative variables. A *P* value of < 0.05 was considered statistically significant.

Results

This study included 115 adult patients, 54 males (47%) and 61 females (53%). Their ages ranged from 19 to 92 years (mean (±SD) = 52.51 years ± 18.2). They were further divided into 2 groups, group 1 included 51 patients (44.3%) who were diagnosed with multiple sclerosis (MS) according to the Revised McDonald Criteria, published in 2017 by the International Panel on the Diagnosis of Multiple Sclerosis. Group 2 included 64 patients (55.7%) who were diagnosed with ischemic leukoencephalopathy based on their history and clinical examination.

Another group of 60 subjects was recruited as a control group, 27 males (45%) and 33 females (55%). Their ages ranged from 19 to 94 years (mean age (±SD) of 51.3 years (± 7.1)). They were age- and sex-matched to the patient group. They underwent MRI brain examination for reasons other than suspicion of white matter

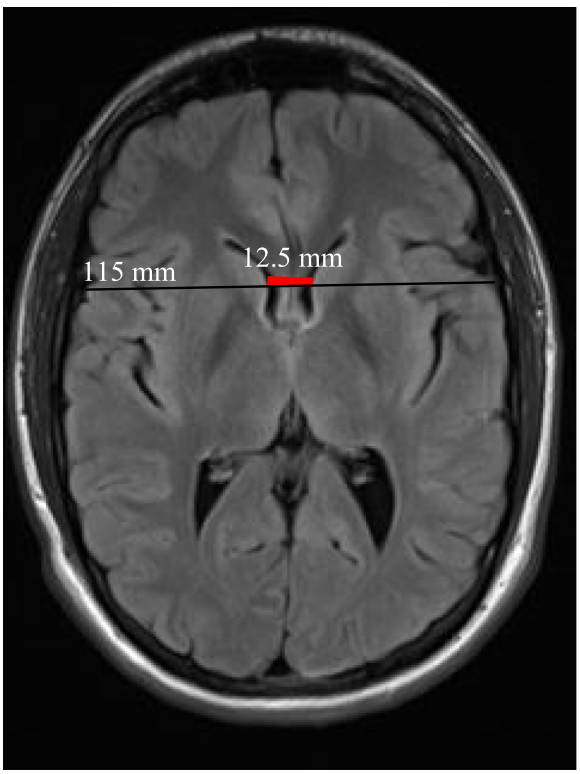

Fig. 2 Axial FLAIR image at the level of caudate nuclei showing the bi-caudate ratio (the inter caudate distance (red line, 12.5 mm) divided by the while brain width at the same level (black line, 115 mm) (BCR = 0.11)

demyelination (headache = 65%, disturbed consciousness level = 13%, head trauma = 13%, convulsions = 6%, suspicion of brain metastasis = 3%). The age and gender distribution of the patients and control subjects included in the study are shown in (Table 1).

Among the patient group the inter-caudate distance ranged from 14.3 to 26.4 mm (mean (± SD) = 18.02 mm (± 2.72)), while for the control group, it ranged from 6.4 to 16 mm (mean (± SD) = 10.79 mm (± 2.25)). The difference between the two groups was statistically significant (*P* value < 0.001).

For the patient group, the whole brain width at the same level ranged from 93 to 119.5 mm (mean (± SD) = 107.07 mm (± 6)), while for the control group, it ranged from 96 to 121.4 mm (mean (± SD) = 107.9 mm (± 5.3)). There was no statistically significant difference between the two groups (*P* value = 0.356).

Among the patient group the BCR ranged from 0.13 to 0.27 (mean (± SD) = 0.16 ± 0.02), while for the control group, it ranged from 0.05 to 0.13 (mean (± SD) = 0.09 ± 0.01). The difference between the two groups was statistically significant (*P* value < 0.001). The mean (± SD) BCR, inter-caudate distances, and whole brain width among the patients and control subjects are shown in (Table 2).

Figure 3 demonstrates increased BCR in a 23-year-old female patient with relapsing-remitting MS, and Fig. 4 represents a box plot of the mean BCR values for both patients and control groups.

Within the patient group, there was no statistically significant difference in the BCR between the males and females (*P* value > 0.05).

Thus, the difference in BCR between the patient and control groups was attributed to the difference in the inter-caudate distance (numerator of the BCR) rather than the whole brain width at the same level. This suggests that atrophy of white matter tracts and ventricular enlargement at the level of the caudate nuclei are responsible for the increased BCR in the patient group. Conversely, the lack of difference in whole brain width (denominator of the BCR) between the controls and the patients suggests that increased BCR is not due to reduced brain width at this level, meaning that the increased BCR represents the caudate nuclei moving laterally due to adjacent white matter atrophy and ventricular dilatation. This makes the BCR a feasible and rapidly obtained a measure of white matter atrophy that can be performed without complex computer-assisted techniques.

A cut of value of 0.13 was chosen to differentiate between the BCR in both patients and control groups, with sensitivity (99.2%), specificity (100%), positive predictive value PPV (100%), negative predictive value NPV (98%), and accuracy (99%), and area under the curve (AUC) was 1.00. Figure 5 represents an ROC curve of the mean BCRs between the patients and controls.

Among the patient group (*n* = 115), 51 patients (44.3%) (group 1) were diagnosed with MS while 64 patients (55.7%) (group 2) were diagnosed with ischemic leukoencephalopathy. The mean BCR for patients diagnosed with MS was 0.15 (± 0.013 SD), while the mean BCR for patients diagnosed with ischemic leukoencephalopathy was 0.17 (± 0.027 SD). The difference between the two groups was statistically significant (*P* value < 0.001). The mean (± SD) BCR, inter-caudate distances, and whole brain width among MS and ischemic leukoencephalopathy patients are shown in Table 3.

Table 1 The age and gender distribution of the patients and control subjects included in the study

Variable	Patient group (*n* = 115)	Control group (*n* = 60)	Test	*P* value
	Mean ± SD	Mean ± SD		
Age	52.33 ± 18.33	39.61 ± 13.82	$t = 4.71$	< 0.001
Gender				
Male	56 (48.7)	27 (45.0)	$\chi^2 = 0.21$	0.642
Female	59 (51.3)	33 (55.0)		

Table 2 The mean BCR (± SD) among the patients and control subjects (IC = inter-caudate)

Variable	Patient group (*n* = 115)	Control group (*n* = 60)	Test	*P* value
	Mean ± SD	Mean ± SD		
IC distance	18.02 ± 2.72	10.79 ± 2.25	17.63	< 0.001
Whole width	107.07 ± 6.00	107.92 ± 5.30	0.92	0.356
BCR	0.16 ± 0.02	0.09 ± 0.01	18.42	< 0.001

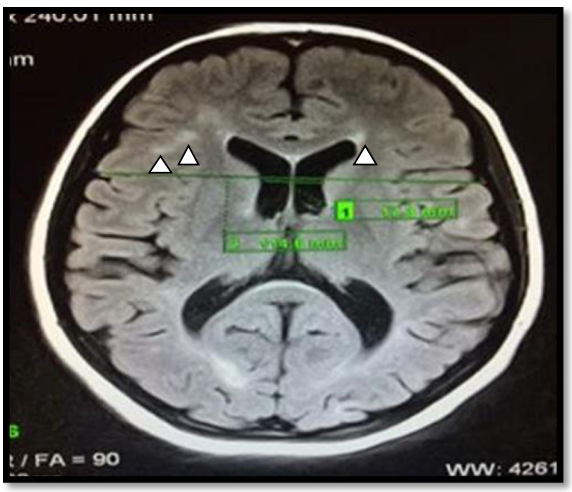

Fig. 3 Twenty-three-year-old female patient with relapsing-remitting MS. axial FLAIR image shows multiple peri-ventricular and subcortical demyelination patches (arrowheads). BCR = 0.15

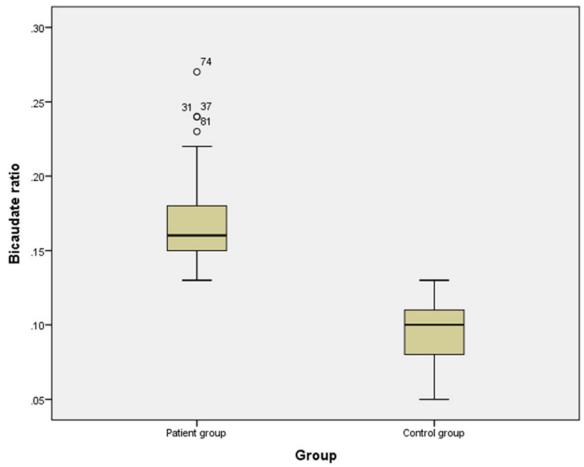

Fig. 4 Box plot showing the BCR values for both patients and control groups

Discussion

Brain atrophy measurement is now a key analysis in basic neuro-imaging science, aging research, and studies of pathologic conditions including MS, Alzheimer's disease, and ischemic leukoencephalopathy. Growing evidence is showing that brain atrophy is a meaningful indicator of neuro-degeneration and clinical disease progression in MS. It can be correlated with the future progression of physical and cognitive disability [9].

Zivadinov R et al. [9] stated that assessment of semi-quantitative linear brain atrophy measures, like third ventricle width and bi-caudate ratio, is validated against more robust quantitative global brain volume indices and that both third ventricle width and bi-caudate ratio were significantly correlated with measures of cognitive processing speed, including the widely used Symbol Digit Modalities Test [9, 10].

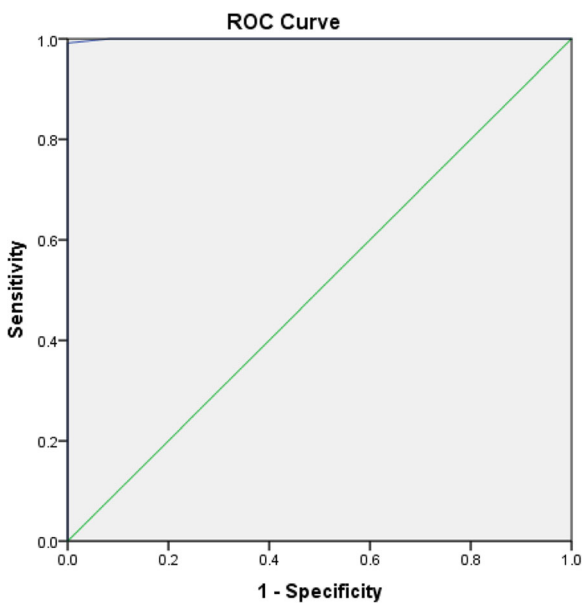

Fig. 5 ROC curve presenting the BCR between the patients and controls

Table 3 The mean BCR (± SD) among MS and ischemic leukoencephalopathy patients

Variable	Group 1 ($n = 51$) Mean ± SD	Group 2 ($n = 64$) Mean ± SD	Test	*P* value
IC distance	16.91 ± 1.61	18.90 ± 3.09	4.15	< 0.001
Whole width	109.53 ± 4.96	105.11 ± 6.06	4.20	< 0.001
BCR	0.15 ± 0.013	0.17 ± 0.027	5.59	< 0.001

In our study, the mean BCR (± SD) for patients diagnosed with MS was 0.15 (± 0.013), while for the control group the mean BCR (± SD) was 0.09 (± 0.01). This was consistent with the study carried out by Bermel et al. [7], on 60 patients with MS and 50 age- and sex-matched control subjects. They found that the BCR (mean (± SD)) was higher in patients with MS (0.11 (± 0.03)) than in controls (0.09 (± 0.02)), suggesting sub-cortical atrophy in MS [7]. The mean BCR for patients with MS was higher in our study.

In our study, the mean BCR for the patient diagnosed with ischemic leukoencephalopathy (±SD) was 0.17 (± 0.027), and this was consistent with the results recorded by Chaves et al. [11]. The patient group in their study was composed of 30 subjects, 17 Alzheimer's disease (8 males, 9 females; age range, 54 to 89 years) and 13 ischemic leukoencephalopathy (7 males, 6 females; age range, 50 to 74 years). The mean BCR for patients with ischemic leukoencephalopathy (± SD) was 0.16 (± 0.046) [11].

The mean BCR for patients diagnosed with MS was 0.15 (± 0.013 SD), while the mean BCR for patients diagnosed with ischemic leukoencephalopathy was 0.17 (± 0.027 SD). This can be attributed to a higher age group for patients with ischemic leukoencephalopathy (mean age for patients with ischemic leukoencephalopathy was 65.4 years, while the mean age for patients with MS was 36.3 years) with more progressive age-related white matter volume loss.

The study was limited by a few number of cases. We only included the cases finally diagnosed as MS by clinical, laboratory, and imaging findings. Patients with insufficient clinical and laboratory data were excluded. Patients with ischemic leukoencephalopathy who were presented by acute infarction or intra-cerebral hemorrhage were also excluded due to the associated edema and mass effect altering the BCR.

Conclusion

BCR represents a linear measurement of sub-cortical atrophy that can be useful as a surrogate marker of global supra-tentorial white matter atrophy instead of the usually performed visual and therefore subjective assessment. It is an easily obtained measure that can be

performed without complex time-consuming volumetric studies. Our findings also revealed that the BCR is higher in patients with ischemic leukoencephalopathy than in patients with MS.

Abbreviations

BCR: Bi-caudate ratio; FLAIR: Fluid attenuation inversion recovery; FOV: Field of view; IC: Inter-caudate; MR: Magnetic resonance; MS: Multiple sclerosis; TI: Time of inversion

Acknowledgements

There is no acknowledgment.

Availability for data and materials

Data will be available upon request via contacting the corresponding author.

Authors' contributions

DS and ER contributed equally to the study design, data collection, analysis, and interpretation of the results. Both authors read and approved the final manuscript.

Funding

There is no funding.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine at Menoufia University in Egypt on November 11, 2019; reference number of approval 191119-RAD-12. All patients included in this study gave written informed consent to participate in this research.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that they have no competing interests.

Received: 7 October 2019 Accepted: 3 December 2019
Published online: 23 December 2019

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