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Morphometric Analysis of the Third Ventricle in Multiple Sclerosis Patients Using MRI

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Abstract

Third ventricle enlargement has been proposed as a subjective indicator for identifying central brain atrophy in MS patients. This paper seeks to address the anatomical changes of the third ventricle in MS patients by employing simple linear MRI measurements. Fifty brain MRI scans (25 MS patients and 25 healthy controls) performed between 2017 and 2021 were selected. Individuals aged between 23 and 48 years. Five anatomical parameters of the third ventricle were measured by MRI. Results demonstrated that patients' mean third ventricular width (W1) measured in the axial plane at the midpoint of the maximum long axis of the ventricle 6.08±2.34 mm was significantly wider compared to controls 2.67±0.63 mm ($p<0.001$). The same is true for patients' mean third ventricle width (W2) measured at the level of the interventricular foramen 6.64±1.85 mm, which was also significantly wider compared to controls 3.66±0.64 mm ($p<0.001$). We measured the internal transverse diameter of the skull (TD) at the same level of (W2) and calculated the TVR third ventricle ratio where TVR=W2/TD which was statistically significant ($p=0.02$). The difference between the two groups was insignificant regarding height (H) with ($p=0.21$) and length (L) with ($p=0.6$). Data demonstrate that the noteworthy finding was the widening of the third ventricle, regardless of the level of measuring. Changes in height and length were insignificant.

Keywords
third ventricle, multiple sclerosis, MRI, brain atrophy.

Multiple sclerosis MS is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS). 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 et al., 2014). MS is a complicated disease, and its exact etiology is still unknown. In addition to a few recognized possible causes, such as deficiency of vitamin D, obesity, and smoking, several genes can influence disease vulnerability (Pantazou, Schluep, & Du Pasquier, 2015). The sex ratio of MS has consistently increased and affects females three times more than males in most countries (Orton et al., 2006). Relapsing-remitting MS, primary progressive MS, and secondary progressive MS are the three main disease subtypes. Disease activity tends to wax and wane depending on the clinical course (Dobson & Giovannoni, 2019).

Brain atrophy in MS patients starts extremely early in the course of the disease and affects both grey matter and white matter (Ghione et al., 2019). Atrophy is primarily unrelated to noticeable lesions (Fisniku et al., 2008), and develops at a rate that might be up to five times faster than normal aging (Miller et al., 2002). It is believed that severe axonal transection and demyelination cause MS atrophy (Amiri et al., 2018). Furthermore, tissue loss caused by inflammation and demyelination may be somewhat reversible in relapsing-remitting MS (Filippi & Rocca, 2011; Trapp & Nave, 2008), whereas other mechanisms of tissue loss may lead to irreversible axonal damage, particularly in progressive disease (Andravizou et al., 2019). Assessing tissue loss in the (CNS) is attracting considerable interest, as it indicates the net effect of all pathogenic mechanisms that cause tissue destruction throughout the disease (Ghione et al., 2018). The term central atrophy refers to a loss of brain parenchymal volume. This is followed by an increase in the volume of spaces for cerebral spinal fluid (CSF), which is also visibly evident in the enlargement of the ventricular system (Lutz et al., 2017). The expansion of the ventricles in MS has been frequently researched, ranging from a comprehensive assessment of the total amount of (CSF) spaces to specific localized measurements of the third or fourth ventricle (Benedict et al., 2004; Laffon et al., 2014; Müller et al., 2013). The third ventricle is a cavity in the middle of the diencephalon. Atrophy of nearby tissues, particularly the thalami, leads to an enlargement of the third ventricle. It has been demonstrated that people with MS have a larger third ventricle (Cifelli et al., 2002). This study aims to detect the anatomical changes of the third ventricle in multiple sclerosis patients using easy linear MRI measurements and compare the results with the normal population.

Methods

Study Design

This is an observational retrospective case-control study conducted at Ondokuz Mayıs University, Samsun City, Turkey.

Study Setting and Population

Brain MRIs of 50 participants (25 MS patients and 25 healthy controls) were selected from the radiology department database at Ondokuz Mayıs University Hospital. The selected MRIs were performed between 2017 and 2021. The inclusion criteria were: all patients meet the diagnostic criteria of MS and are already enrolled in a management program and they do not have any of the exclusion criteria. Exclusion criteria were: any neurological disease in addition to MS that may affect the gross anatomy of the brain, previous brain surgery, and concurrent or past psychiatric disorder. Age limits were applied to minimize the effect of normal brain atrophy in children and the elderly. The control group was matched with the patients' group for gender and race. The subjects in the control group underwent brain MRI for other indications like headache and were documented to be normal by a neuroradiologist.

Data Management

Routine brain MRI protocol using a 1.5-T MRI machine (Philips, Achieva), axial and coronal T1-weighted turbo spin echo (TR/TE: 3000/80, slice thickness: 5mm, gap: 1mm) was used.

The Radiant DICOM 2020.2.2 program was used to make measurements since it is the same program that is utilized at our institution, the sequential MRI data sets were examined using the trial version that was downloaded from radiantviewer.com on a desktop computer.

To minimize the measurement errors, the observer took the measurements under the supervision of an experienced neuroradiologist; as for intra-rater variability, all the measurements were evaluated two times with an interval of at least four weeks. The average of the two measurements was utilized to get the final value of each variable.

Five measurements of the third ventricle were determined in T1-weighted as follows: Length (L) is a line drawn through the long axis of the third ventricle in the axial plane and parallel to the interthalamic fissure where the ventricle is most visible (figure. 1). (W1) is the width of the third ventricle measured at the midpoint of the previous line and perpendicular to it (figure. 1).

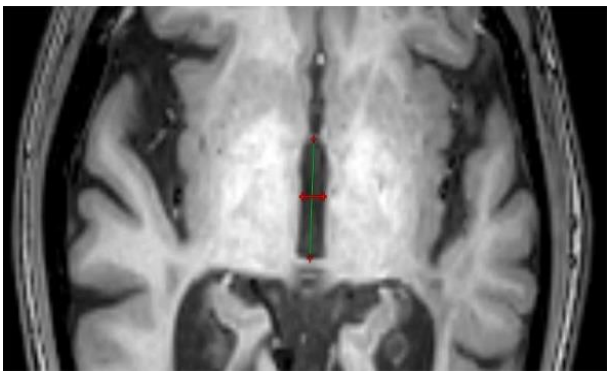

Figure. 1 Axial brain MRI showing the maximum anterior-posterior diameter of the third ventricle which resembles the length (L), it is a line drawn through the long axis of the ventricle parallel to the interhemispheric fissure, the also shows the width of the third ventricle (W1) that measured at the midpoint of (L) and perpendicular to it

(W2) is the maximum width of the third ventricle at the level of the interventricular foramen of Monro in the axial plane (figure. 2).

(TD) is the internal transverse diameter of the skull drawn at the same line as (W2) (figure. 2). Additionally, we calculated the third ventricle ratio TVR = W2/TD.

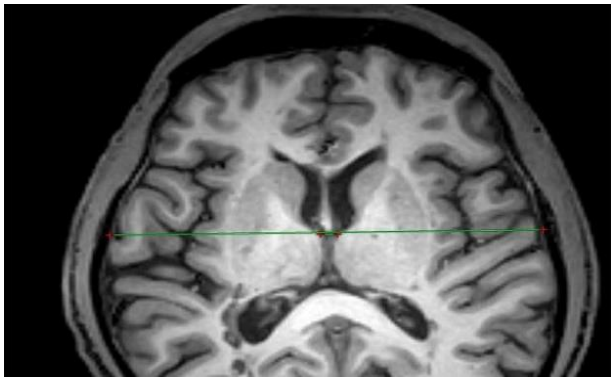

Figure. 2 Axial brain MRI showing the width (W2) of the third ventricle that is measured at the level of the interventricular foramen, and the transverse diameter (TD) of the skull is measured at the same line with W2

(H) is the maximum height of the third ventricle that can be measured in the coronal plane where the foramen of Monro can be visualized (figure. 3).

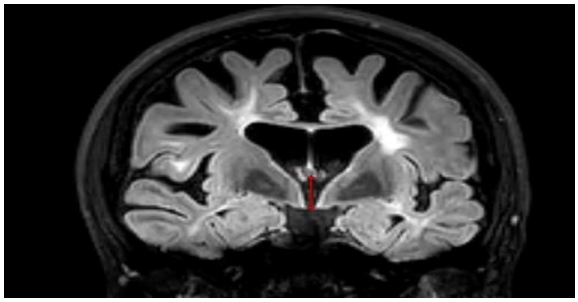

Figure. 3 Coronal brain MRI showing the height (H) of the third ventricle which is the longest vertical line that can be drawn where the interventricular foramen can be visualized.

Data of all the participants were anonymized and patient IDs were known only to clinical staff. Data were examined, cleaned, and integrated into one Excel file and exported to SPSS version 25.

Data Analysis

The study participants' basic clinical and demographical characteristics were analyzed using

SPSS version 25. Statistical indicators were calculated, such as mean, standard deviation (SD), and percentage. We performed the Shapiro-Wilk normality test to determine the statistical tests that would be used. According to the Shapiro-Wilk results, all variables had normality distribution except for gender.

Therefore, 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 significant at $p<0.05$.

Ethical Approval

The study was approved by the ethics committee of scientific research at our university (Ref: B.30.2.ODM.0.20.08./496-569). consent was gained to use participants' data for this study on the condition that all their identities be anonymous.

Results

The demographical and clinical characteristics of patients and controls are summarized in (Table 1). A total of 50 subjects who met the inclusion criteria were enrolled and divided into two groups, patiet group includes 25 subjects with 6 (24%) males and 19 (76%) females, and the mean age was 37±4.08 years. The control group includes 25 subjects 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 patient 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). The results of the measured dimensions of the third ventricle are also given in (Table 1) below.

Results illustrated that patients' mean third ventricular width (W1), measured at the midpoint of the long axis of the ventricle 6.08±2.34 mm, was significantly wider compared to controls 2.67±0.63 mm with (p<0.001). The same was for patients' mean third ventricle width (W2), measured at the interventricular foramen level 6.64±1.85 mm, it was also significantly wider than the control's 3.66±0.64 mm with (p<0.001).

The mean height was 16.20±1.44 mm and 15.84± 0.92 mm in the patient and control groups respectively. As for mean length, the results were 24.68±2.50 mm and 24.30±1.39 mm in the patient and control groups respectively. Our results indicated that there was no significant difference between the two groups regarding height (H) with (p=0.21) and length (L) with (p=0.6). The analysis showed also significant differences between the two groups regarding TVR (p=0.02).

Table 1. Demographic and basic characteristics of the study population and results of anatomic measurements in millimeters.

Variables	Control group *(n=25)*	Patient group *(n=25)*	*P*- value
Age			
Min	23	28	
Max	48	44	
Mean	33.2	37	
(SD)	7.51	4.08	0.04*
Gender			
Male	5	6	
Female	20	19	0.73
Width W1			
Min	1.76	2.58	
Max	3.58	12.20	
Mean	2.67	6.08	
(SD)	0.63	2.34	<0.001*

Width W2			
Min	2.26	4.11	
Max	5.02	10.8	
Mean	3.66	6.64	<0.001*
(SD)	0.64	1.85	
Length L			
Min	19.8	18.4	
Max	26.8	30	
Mean	24.30	24.68	0.6
(SD)	1.39	2.50	
Height H			
Min	13.8	12.4	
Max	18.7	19.30	
Mean	15.84	16.20	0.21
(SD)	0.92	1.44	
TD			
Min	117.6	108.7	
Max	136.6	137.1	
Mean	125.83	125.83	0.12
(SD)	4.79	6.93	
TVR			
Min	0.02	0.03	
Max	0.04	0.09	
Mean	0.03	0.05	0.02*
(SD)	0.01	0.01	

Min: minimum, Max: maximum, (SD): standard deviation, TD: transverse diameter of the skull, TVR: third ventricle ratio, * statistically significant

Discussion

As stated in the Introduction, our main aim is to delineate the anatomical changes in the third ventricle that may occur in MS patients with the help of simple, achievable linear MRI measurements. Conventional magnetic resonance imaging MRI has become an established technique in diagnosing and monitoring MS because of its ability to depict the pathologic characteristics of this illness in exquisite detail.

Even though there are several methods to monitor brain atrophy, manual measures have the benefit of being quick and straightforward to undertake after the MRI test is completed. It was demonstrated that the planimetric measuring technique is as accurate as the semi-automatic volume measurement of the third ventricle, debunking earlier research that claimed manual 2D measurements lacked reliability (Lutz et al., 2017).

The premier remarkable finding in our study was the widening of the third ventricle in MS patients compared to normal subjects, which is in line with previous studies. Different radiological techniques, including transcranial sonography, CT scan, and MRI, have been used to determine the value of the third ventricle width, but there is no agreement on a minimum and maximum threshold value. It ranges from 2.25 mm to 9.2 mm as stated in the literature (Patnaik et al., 2016). As explained in the methods section, we assessed the third ventricle width in two different sites and even in two different levels of MRI slices. The thalamus, which is the main component of the diencephalon, experiences early atrophy in MS (Eshaghi et al., 2018). It is believed that the volume loss of structures adjacent to the third ventricle, specifically the thalamus or the corpus callosum, causes the third ventricle to widen (Cifelli et al., 2002). Thus, it reinforces earlier results that third ventricle enlargement may serve as an indirect surrogate for thalamic atrophy in MS. The thalamic nuclei work as a relay station connecting wide neocortical and subcortical areas and mediating various brain activities. These extensive connections, however,

make the thalamus susceptible to retrograde atrophy. This can be brought on by either localized or diffuse brain injury (Houtchens et al., 2007). Consequently, thalamic injury can result in a vast spectrum of neurological symptoms, namely cognitive symptoms (Riccitelli et al., 2011).

Research has tended to focus on one dimension of the third ventricle, mainly the width of the ventricle in MS patients. To achieve a comprehensive evaluation of the third ventricle anatomy, we investigated the changes in the height and length parameters in MS patients. The mean height in our study was 15.84 mm in normal participants and resembled the maximum vertical line drawn in the coronal plane where the interventricular foramen can be visualized. In 2003 Duffner et al. defined the height of the third ventricle as a vertical line passing through the midst of the interthalamic adhesion in the midsagittal plane. They found that the mean height was 18.6 mm in normal controls (Duffner et al., 2003). We argued that we used an easy method as the demonstration of interthalamic adhesion bears some difficulty with 5 mm MRI slice thickness and even does not exist in all individuals.

The study findings showed that the mean anterior-posterior diameter of the third ventricle was 24.30±1.39 mm in the control group. Lee et al. (2008) used MRI with a 3 mm slice thickness to assess the distance between the anterior commissure (AC) and posterior commissure (PC) in the midsagittal plane. The mean AC-PC distance was 26.3±1.79 mm in their control group, with a mean age of 54.74 years (Lee et al., 2008). We may justify this as the mean age in our study (33.2 years in control group) is younger, and the MRI slice is thicker. Also, Lee et al. measured the distance from the center of the anterior commissure to the center of the posterior commissure. Whereas, we measured the distance from the internal margin of the third ventricle's anterior border to the internal margin of the posterior border.

It is claimed that the best way to study third ventricle enlargement is to use the third ventricle ratio (TVR), which is established by dividing the third ventricle's width at the level of interventricular foramen by the skull's internal diameter along the same line (Singh et al., 2018). We found that the mean value of (TVR) is 0.03±0.01 and 0.05±0.01 in normal and patients respectively, with a significant difference (p=0.02). Virsham Singh, in 2018, reported that on normal CT scans, the mean (TVR) was 0.062 ±0.02 which was greater than the value of (TVR) in our study where it was 0.03±0.01 mm. This is because the mean width of the ventricle was 6.51±2.25 mm in their study and 3.66±0.64 mm in ours. Virsham Singh also reported that because (TVR) does not fluctuate with age, gender, or cerebrum diameter, it can be used as a screening test for hydrocephalus in suspected individuals.

It is plausible that some limitations could have influenced the results obtained. First, there is a lack of correlation with the clinical condition of the patients and their progression with time. Second, given that our findings are based on a limited number of participants, the results from such analyses should be treated with caution. Another limitation is the MRI slice thickness and resolution, we used a 5 mm slice thickness in most cases.

A longitudinal study with a long follow-up period and a larger sample size are warranted to reinforce our results concerning the clinical setting.

In conclusion, we used simple and easy-to-take MRI linear measurements to evaluate the morphological changes of the third ventricle in multiple sclerosis patients. The robust finding was the widening of the ventricle regardless of where to measure the width at the middle of anterior-posterior diameter or the level of the interventricular foramen of Monro. We did not find significant differences regarding the height and length of the ventricle.

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.

Author contributions

All authors contributed to the study's 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.

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Availability of data and material

Not applicable.

Table ligands

Table 1. Demographic and basic characteristics of the study population and results of anatomic measurements in millimeters

Figure captions

Figure. 1 The length (L) of the third ventricle, is a line drawn through the long axis of the ventricle parallel to the interhemispheric fissure in the axial plane where the ventricle is most visible and the width of the third ventricle (W1) that measured at the midpoint of (L) and perpendicular to it

Figure. 2 The width (W2) of the third ventricle that is measured at the level of the interventricular foramen, and the transverse diameter (TD) of the skull that is measured at the same line with W2

Figure. 3 The height (H) of the third ventricle is the longest vertical line that can be drawn in the coronal plane where the interventricular foramen can be visualized

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