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RESEARCH

Transcranial ultrasonography as a predictor of disease progression in multiple sclerosis

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Abstract

Background Development of novel biomarkers for multiple sclerosis (MS) is of utmost importance to improve the capability to predict disease progression and disability. Transcranial ultrasonography (TCS) is a noninvasive imaging technique that allows the visualization of major parenchymal structures. This study aimed to evaluate the role of parenchymal transcranial sonography as a predictor for disease severity and progression in MS patients. Sixty patients with clinically definite Multiple sclerosis divided into two groups, relapsing–remitting MS (RRMS) group and chronic progressive MS (CPMS) group were included.

Results There was a statistically significant increase in the mean diameters of the third ventricle, both frontal horns of lateral ventricle in RRMS and CPMS group compared to control values, and in CPMS group compared to RRMS group. Expanded Disability Status Scale (EDSS) score was significantly positively correlated with the diameter of right frontal horn of lateral ventricle in CPMS group. Linear regression analysis revealed that diameters of right frontal horn of lateral ventricle and third ventricle were independent predictors for MS severity.

Conclusions TCS can be used as a simple noninvasive tool for prediction of disease severity and progression in MS patients.

Keywords Multiple sclerosis, RRMS, CPMS, EDSS, Transcranial sonography

Background

Multiple sclerosis (MS) is a chronic autoimmune–inflammatory disease of the central nervous system (CNS). Clinically, MS is characterized by a variable combination of symptoms. Demyelination can be abrupt or have an insidious onset and variable severity [1]. Large numbers of biomarkers have been tested in last years to try to predict response, disease progression, prognosis and outcome of MS. The markers are broadly divided into immunogenetic, laboratory or imaging-based [2]. Despite the diverse number of these biomarkers, they lack simplicity and clinical applicability [3]. Parenchymal

Transcranial sonography (TCS) is a technique that displays the brain parenchyma and the intracranial ventricular system through the intact skull [4]. TCS has evolved as a sensitive and reliable method in measuring widths of third and lateral ventricles which was markedly widened in various primary neurodegenerative disorders [5]. The detection of central brain atrophy (accounted for by ventricular system widening) in MS has been addressed as an important determinant of clinical disease burden and was regarded as has become a clinically relevant biologic marker of MS disease process [6, 7]. Brain atrophy is evident even in the earliest stages of MS. Ventricular diameter was found to correlate well to MS duration, disease severity and disability as assessed by EDSS [8]. Hence, this study was conducted to investigate the role of parenchymal transcranial sonography (TCS) as a simple bedside predictor of disease severity and progression in MS patients.

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Fahmy *et al. Egypt J Neurol Psychiatry Neurosurg*   (2024) 60:16

Page 2 of 5

Methods

This is a cross-sectional study conducted on 60 Egyptian patients (from both sexes) with clinically definite Multiple sclerosis (according to the revised McDonald diagnostic criteria 2017) [9]. Sample size calculation was performed using G*POWER (3.1.9.7) Statistical software. Patients were recruited from neurology department and Multiple Sclerosis Unit, Cairo University hospitals, between November 2019 and January 2021. MS patients were divided into two groups: RRMS group which included 30 patients with relapsing–remitting MS and CPMS group which included 30 patients with chronic progressive MS. Exclusion criteria included: patients with a relapse in the past 3 months, patients with MS mimics as Neuro Myelitis Optica (NMOSD), Systemic Lupus Erythematosus (SLE), Sarcoidosis, patients with other medical disorders causing brain atrophy (vasculitis, recurrent strokes, uncontrolled diabetes, hypertension). Participants in this study were subjected to: (1) assessment of clinical disability: using the Expanded Disability Status Scale (EDSS) [10]. (2) B-mode transcranial sonography (TCS) for assessment of brain parenchyma. TCS was carried out at the neuro-sonology unit, of the Neurology department, Cairo University hospitals. TCS was performed by a single experienced certified neurosonographer, who was blinded to the subjects' clinical data throughout the entire study. The study was done using a high-resolution ultrasonography instrument (PHILIPS IU22x MATRIX, California, US, L 1–5 transducer), equipped with a 2.5 MHz Phased array transducer. Via the transtemporal window, assessment was performed across the thalamic plane to assess the diameter of 3rd ventricle, right and left frontal horns of the lateral ventricle. Assessment of brain atrophy parameters was done by measurement of diameter (cm) of the third ventricle and both frontal horns of lateral ventricles. The sonographic assessment was carried through the ventricular plane (plane of the thalamus). For sonographic approach of this plane, the transducer should be upwards tilted about 20° starting from the axial midbrain plane. The landmark structure of this plane is represented by the highly echogenic pineal gland [8]. Measurements of width of the ventricles were performed if the frozen image was zoomed two to threefold from the ipsilateral to the contralateral inner layers of the hyperechogenic ependyma. Each frontal horn was assessed contralateral to the side of insonation (Rt. frontal horn is assessed via Lt trans temporal window and vice versa). For the exact site of obtaining measurements, it was recommended for the third ventricular width to measure the minimum width insonated and for the contralateral frontal horn, the width was obtained at the most frontal position at which the bilateral frontal horns were in junction [8]. In this study, we used the

Egyptian cutoff values, the third ventricle diameter was considered dilated if ≥ 0.23 cm, the left frontal horn of lateral ventricle was considered dilated if > 0.37 cm, and the right frontal horn of lateral ventricle was considered dilated if > 0.36 cm [11]. Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., released 2017, Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables, while non-parametric Mann–Whitney test was used for non-normally distributed quantitative variables. For comparing categorical data, Chi square (χ^2) test was performed. Correlations between quantitative variables were done using Spearman correlation coefficient. Linear regression analysis was done to predict EDSS using significant sonar parameters. *p* values less than 0.05 were considered as statistically significant.

Results

The age in RRMS group ranged from 20 to 45 with a mean age 30.33 ± 7.19 years, while in CPMS group, it ranged from 20 to 47 years with a mean age 33.62 ± 7.34 years. There was no significant difference in mean age between both groups, ($p = 0.104$). RRMS group included 13 males (43.3%) and 17 females (56.7%), while CPMS group included 20 males (66.7%) and 10 females (33.3%), the difference in sex distribution between both groups was statistically significant ($p = 0.04$). The age of disease onset, duration of MS and EDSS scores of the study groups are represented in Table 1. There was a significantly longer disease duration and higher disability scores in the CPMS group compared to RRMS group ($p = 0.020$ and < 0.001, respectively). The range and mean of measured sonographic parameters in the studied groups are represented in Table 2. There was significant differences between the mean values of measured sonographic parameters mean in RRMS and CPMS groups compared to normal values ($p < 0.001$). Moreover, there was a statistically significant difference between RRMS and CPMS regarding all measured sonographic parameters ($p < 0.001$), as shown in Table 3. There was no correlation between EDSS score and sonographic parameters in RRMS group, while in CPMS group, EDSS scores was significantly positively correlated with the diameter of right frontal horn of lateral ventricle (r = 0.530, $p = 0.008$), Table 4. Linear regression analysis revealed that diameters of third ventricle and right frontal horn of lateral ventricle were independent predictors of EDSS in MS patients ($p = 0.03$ and < 0.001, respectively), Table 5.

Fahmy *et al. Egypt J Neurol Psychiatry Neurosurg*   (2024) 60:16

Page 3 of 5

Table 1 Clinical characteristics of the studied groups

	RRMS group					CPMS group					*P* value
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	
Age	30.33	7.19	28.50	18.00	45.00	33.62	7.34	32.50	20.00	45.00	0.104
Age of disease onset	24.83	6.68	24.00	12.00	41.00	26.54	8.32	25.50	16.00	42.00	0.406
Duration of illness (years)	5.77	5.86	4.00	1.00	28.00	8.33	6.11	6.50	2.00	27.00	0.020*
EDSS	2.48	1.09	2.50	0.50	4.50	5.83	0.76	5.50	5.00	7.00	< 0.001*

*Significant, EDSS: Expanded disability status scale, RRMS: Relapsing–Remitting MS, CPMS: Chronic Progressive MS, SD: standard deviation

Table 2 Measurements of parenchymal sonographic parameters in the studied groups

	RRMS				CPMS			
	Mean	**SD**	**Minimum**	**Maximum**	**Mean**	**SD**	**Minimum**	**Maximum**
Third ventricle diameter (cm)	0.81	0.05	0.75	0.89	0.88	0.02	0.76	0.89
Right frontal horn of lateral ventricle diameter (cm)	0.86	0.04	0.79	0.94	0.93	0.03	0.79	0.95
left frontal horn of lateral ventricle diameter (cm)	0.83	0.06	0.74	0.94	0.93	0.02	0.85	0.94

RRMS: Relapsing–Remitting MS, CPMS: Chronic Progressive MS, SD: standard deviation, cm: centimeter

Table 3 Comparison of sonographic parameters between the study groups

	RRMS		CPMS		*P* value
	Mean	**SD**	**Mean**	**SD**	
Third ventricle diameter (cm)	0.81	0.05	0.89	0.001	< 0.001*
Right frontal horn of lateral ventricle diameter (cm)	0.86	0.04	0.94	0.01	< 0.001*
Left frontal horn of lateral ventricle diameter (cm)	0.84	0.05	0.93	0.01	< 0.001*

*Significant RRMS: Relapsing–Remitting MS CPMS: Chronic Progressive MS, cm: centimeter

Table 4 Correlation between EDSS score and sonographic parameters in the studied groups

EDSS score	RRMS		CPMS	
	r	**P value**	**R**	**P value**
Third ventricle diameter (cm)	0.2	0.29	0.29	0.16
Right frontal horn of lateral ventricle diameter (cm)	0.12	0.51	0.53	0.008*
Left frontal horn of lateral ventricle diameter (cm)	− 0.06	0.71	0.33	0.112

*Significant RRMS: Relapsing–Remitting MS CPMS: Chronic Progressive MS, EDSS: expanded disability status scale, r: correlation coefficient, cm: centimeter

Table 5 Linear regression to detect independent predictors of disease severity in MS patients

Model		Unstandardized coefficients		Standardized coefficients	t	*P* value	95.0% Confidence Interval for B	
		B	**Std. error**	**Beta**			**Lower bound**	**Upper bound**
EDSS score	(Constant)	− 7.68	1.91		− 4.02	< 0.001*	− 11.53	− 3.83
	Right frontal horn of lateral ventricle diameter (cm)	10.59	2.4	0.305	4.41	0.001*	4.76	15.4
	Third ventricle diameter (cm)	7.437	3.315	0.200	2.243	0.030*	0.764	14.110

*Significant, EDSS: expanded disability status scale

Fahmy *et al. Egypt J Neurol Psychiatry Neurosurg* (2024) 60:16

Page 4 of 5

Discussion

Increasing evidence has demonstrated that neuronal and axonal damage within the central nervous system (CNS) contributes substantially to the development of permanent disability in patients with MS. Characteristic reliable biomarkers for recognition of MS progression are extremely important. Recognizing biomarkers of disease progression and severity is one of the key objectives of MS-related research. The possibility to use those biomarkers would significantly facilitate clinical decisions at the stage of diagnosis and treatment. These markers, which predict the course and prognosis, will enable choosing optimum treatment and its escalation at the relevant stage [12]. Transcranial sonography allows for indirect assessment of brain atrophy by the measurement of the width of the third ventricle, which reflects an early and bedside biomarker for disease subtle progression [13]. Evidence suggests MS patients exhibit significant gray matter atrophy from the early stages of MS with significant ventricular system widening that has been detected in patients with clinically isolated syndrome [14]. Measurement of ventricular diameter has become a clinically relevant biomarker of MS disease process [6]. Assessment of ventricular diameters by TCS is a reliable tool to monitor brain atrophy and associated ventricular enlargement [15], particularly in MS patients [16]. In the present study, we found that patients with CPMS had a significant longer third ventricular and wider right and left frontal horn of lateral ventricles compared to patients with RRMS, a finding which was in accordance with Puz et al. [12]. A prospective 2-year followup study of patients with MS conducted by Kallman et al. [17] indicated progression of disability in patients whose third ventricle diameter was > 5 mm than those whose third ventricle width was < 5 mm at the baseline. Moreover, Schminke et al. [18] revealed a statistically significant increase in the mean diameter of the third ventricle among people with MS when measured with TCS as compared to controls. The current study revealed that measures of the third ventricle and lateral ventricles assessed by TCS were significantly correlated with EDSS scores. This was in agreement with Puz et al. [12] who reported a significant correlation between the diameters of the third ventricle and the frontal horns of the lateral ventricles, and EDSS scores among the patients with MS. Moreover, Guenter et al. [19] reported that third ventricle width measured with TCS was correlated with physical disability and cognitive performance in MS patients. In this study, linear regression analysis revealed that diameters of right frontal horn of lateral ventricles and third ventricle were independent predictors of severity of MS. To the best of our knowledge, no previous study examined this relationship.

The main limitations of this study were: the significant difference between both groups regarding sex distribution; however, previous studies addressed that female sex is clearly predominant in RRMS, with a sex ratio between 2 and 3. While in progressive MS, the sex ratio almost balances out, or sometimes male progressive cases outnumber females [20, 21]. Moreover, the effect of sex on TCS parameters is controversial and several studies reported no influence of sex on TCS measurements [22]. Another limitation was that transcranial atrophy parameters depend mainly on the quality of the temporal acoustic window and its dependency on the experience and skills of the investigator [15].

Conclusion

Parenchymal TCS can be used as simple prognostic marker for disease progression and severity in MS patients. Advantages of TCS are low costs, short investigation times, noninvasiveness, unlimited repeatability, bedside availability and lower dependency on patient's compliance. It is supposed that frequent evaluation of brain atrophy by TCS would be of great benefit in assessing progression of the disease and following the response to a given therapy. Future research is needed to study the correlation between TCS and brain MRI findings to suggest the possibility of using TCD for early detection of disability and progression in MS patients.

Abbreviations

MS	Multiple sclerosis
TCS	Transcranial ultrasonography
RRMS	Relapsing–remitting MS
CPMS	Chronic progressive MS patients
EDSS	Expanded Disability Status Scale
CNS	Central nervous system
NMOSD	Neuro myelitis optica spectrum disorder
SLE	Systemic lupus erythematosus
SPSS	Statistical package for the social sciences
MRI	Magnetic resonance imaging

Availability of data and materials
The data sets generated and/or analyzed during the current study are not publicly available due to the current Cairo University regulations and Egyptian

Fahmy *et al. Egypt J Neurol Psychiatry Neurosurg*   (2024) 60:16

Page 5 of 5

legislation but they are available by a reasonable request from the corresponding author.

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