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Third ventricular enlargement in early stages of multiple sclerosis is a predictor of motor and neuropsychological deficits: a cross-sectional study

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ABSTRACT

Objectives: Whether transcranal sonography (TCS) depicted third ventricular enlargement as a sign of brain atrophy is predictive for neuropsychological deficits in mildly affected patients with multiple sclerosis (MS).

Design: Cross-sectional study of a cohort of mildly diseased patients with MS.

Setting: Neurological MS outpatient clinic at a large teaching hospital in central Europe.

Participants: Fifty-four patients with MS (16 men, 38 women, mean age 40±10 years, mean disease duration 6±5 years; mean Expanded Disability Status Scale 2 ±1.3) and 33 healthy controls (12 men, 21 women; 38 ±11 years) underwent clinical examination, an assessment of the third ventricle width by means of TCS and the Brief Repeatable Battery of Neuropsychological tests for MS, the 25-Feet Foot Walk test, the 9-Hole PEG test, the Beck Depression Inventory and a quantitative fatigue assessment. Statistical analysis was performed with univariate correlation and thereafter by stepwise regression analysis.

Results: Patients' mean third ventricular width (3.9 ±1.6 mm) was significantly wider compared to controls (3.4±0.8 mm). Using stepwise regression analysis models with age, MS duration, third ventricle width and quantitative fatigue assessment as baseline variables, an increasing third ventricle width significantly correlated with the target variables worsening of motor deficits ($p<0.002$), worsening of verbal recall ($p<0.04$) and of visual spatial recall ($p<0.005$). Severity of depression and of fatigue was unrelated to third ventricular width.

Conclusions: In this cohort of patients with MS with mild disease, third ventricular enlargement was indicative for motor deficits and cognitive impairment, even after considering fatigue as a relevant comorbidity. Third ventricular enlargement by means of TCS seems to be a useful, clinically meaningful parameter to stage patients' disease severity. Follow-up studies must show whether an intraindividual future third ventricular increase indeed signals larger cognitive impairment.

ARTICLE SUMMARY

Strengths and limitations of this study

- Use of reliable and robust methods and parameters.
- Inclusion of a healthy control group.
- Cross-sectional study which by itself provides only indirect hints for the future development of neuropsychological sequelae as a result of brain atrophy.

INTRODUCTION

In recent years, it has become increasingly evident that multiple sclerosis (MS) leads to clinically relevant brain atrophy in the disease course and that this process may begin early.[1–10] The clinical correlate of brain atrophy, for example, can be a secondary chronic progression or pure neuropsychological discomfort or symptoms. A few clinical trials that used MRI for brain atrophy evaluation demonstrated that brain atrophy might be influenced by disease modifying therapy.[5 9 10] Owing to these trial findings brain atrophy is emerging as a therapeutic target. Although MRI is the gold standard for diagnosing patients with MS, it has its own methodological limitations for assessing brain atrophy.[11] There is considerable ongoing debate owing to MRI costs as to how regularly or with which indication MRI should be repeated during the disease course. Does our interest in rate of increase of brain atrophy justify repeating MRI at one or two yearly intervals when a patient is stable and without suggestion of relapse?

An alternative to MRI for imaging the cerebral ventricular system is transcranial sonography (TCS). In patients with MS, an enlargement of the third ventricle correlated with brain atrophy on MRI scanning leading

to the suggestion that third ventricular enlargement might be a surrogate marker of brain atrophy in patients with MS. Until today, three cohorts of patients with MS have been evaluated clinically and by means of TCS. In the first cohort,[12 13] the severity of the clinical handicap as indicated by the Expanded Disability Status Scale (EDSS) score[14] and the severity of the handicap in several neuropsychological tests increased, the wider the third ventricle was. This group of patients showed a median EDSS score of 5.5 and a mean duration of the disease of 9.4 years. In two other groups of less severely affected patients, mostly with relapsing-remitting MS (median EDSS 2.0, mean disease duration 6 years), such correlations were observed inconsistently.[15 16] Thus, if TCS is to be considered useful for observing brain atrophy over the disease course, it should also consistently demonstrate clinical correlations in patients with less severe disease. Apart from brain atrophy, fatigue might be a possible confounder of neuropsychological sequelae. This aspect has not been addressed in any previous TCS studies. The aim of this study is to address both aspects—brain atrophy and fatigue—in a cohort of mildly diseased patients with MS—as both are possible indicators of the risk of neuropsychological sequelae.

PATIENTS AND METHODS

All participants gave their informed consent.

The study population (patients and controls) has been described in detail in a previous report in which the focus was firmly laid on the methodological approach of ultrasound examination.[17] In this report, we focus on the neuropsychological findings. For the convenience of reading the manuscript we provide a list of abbreviations used in table 1.

Briefly, we investigated the following:

A. *Patients*: The patient group consists of 54 patients with MS (16 men, 38 women, mean age 40±10 years, mean disease duration 6±5 years; mean EDSS 2±1.3 (median EDSS $2^{[1-3]}$)) with definitive relapsing-remitting MS according to the 2005 revised McDonald criteria.[18] All patients received a disease-modifying therapy interferon (INF)-β-1b subcutaneous (n=22), INF-β-1a subcutaneous (n=19), INF-β-1a intramuscular (n=12); glatiramer acetate (GM; n=1). All investigations were performed with the patients in a stable condition without any signs of a relapse within the last month. The TCS examiners were aware of the diagnosis but not of the clinical severity of MS in the patients. All examinations (TCS, EDSS, neuropsychological testing) were performed within 2 days in each patient and in each normal participant, respectively.

B. *Control participants*: Seventy healthy participants (31 men, 39 women, mean age 41±15 years, age range 18–79 years) without any diseases of the central nervous system or vascular risk factors served as controls for the ultrasound examinations. Regarding age there was no difference between genders. In each participant, atherosclerotic carotid artery disease was excluded by means of carotid duplex ultrasound using the same equipment with a 4–10 MHz linear array transducer. The normative third ventricular width data were generated from all 70 controls. Of the control group 33 (12 men, 21 women, 38±11 years) with a level of education comparable to the patients participated in the neuropsychological testing.

C. *Ultrasound investigations*: All TCS investigations were performed with a high-end ultrasound device Acuson Antares (Sonoline) with a colour coded 1–4 MHz phased array transducer. The third ventricle was visualised through the preauricular temporal acoustic window at a cross-sectional image plane; it is identified as an anechogenic/hypoechogenic space with hyperechogenic horizontal boundary lines (corresponding to the ventricle walls) lying in front of the pineal gland and between the basal ganglia structures (figure 1A). The width of the third ventricle was assessed as the minimum distance between the inner boundaries of both hyperechogenic lines after they were displayed strictly parallel at the thalamic insonation plane (figure 1B). The ultrasound investigations were performed by MM and JV. The interobserver agreement[17] in assessing third ventricular width showed a coefficient of determination of R^2=0.97. Using Bland-and-Altman-Plot statistics, the mean of the interobserver difference was 0.24 mm with the 1.96 SD boundaries at 1.06 and −0.56 mm, indicating that interobserver variability in assessing third ventricle width lies well under 1 mm.

Table 1 List of abbreviations used throughout the text

TCS	Transcranial sonography
25-Foot Walk	25-Feet Foot Walk
9HP dom hand	9-Hole-PEG test of the dominant hand
9HP non-dom hand	9-Hole-PEG test of the non-dominant hand
SRT	Selective Reminding Test
SPART	Spatial Recall Test
SDMT	Symbol Digit Modalities Test
PASAT	Paced Auditory Serial Addition Test
WLG	Word List Generation test
BDI	Beck Depression Inventory
FSMC	Fatigue Scale for motor and cognitive function
MSFC	Multiple Sclerosis Functional Composite

Clinical assessments

All patients were classified according to EDSS. For neuropsychological assessment, we conducted the Brief Repeatable Battery of Neuropsychological Tests for MS[19] which includes the following: the Selective Reminding Test (SRT) to evaluate verbal learning ($SRT_{total\ recall}$) and its delayed recall ($SRT_{delayed\ recall}$); the Spatial

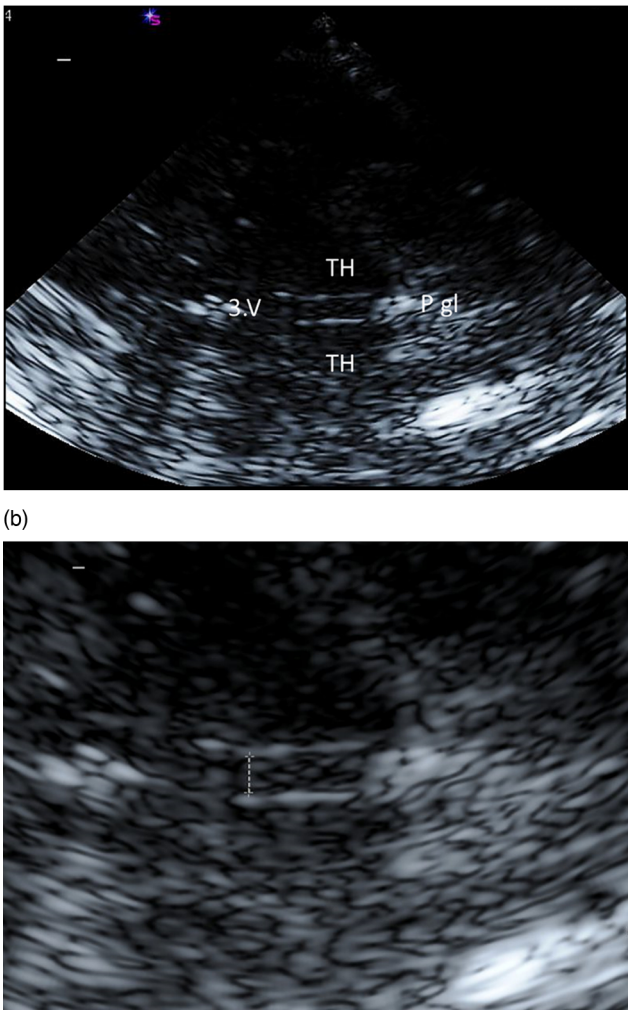

Figure 1 Typical transcranial sonographic cross-sectional image of the basal ganglia and third ventricle plane. (A) Overview and (B) enlargement of the A's centre with the ventricle measurement line (dotted line) between its inner boundaries. 3 V, third ventricle indicated by the hyperechogenic lines between both thalami; P gl, pineal gland; TH, Thalamus.

Recall Test (SPART) with a total and a delayed recall of visual spatial learning ($SPART_{total\ recall}$ and $SPART_{delayed\ recall}$, respectively); the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT 2-s and 3-s versions) to measure the speed of information processing and the Word List Generation Test (WLG) for assessing verbal fluency. The actual severity of depressive episodes was assessed by Beck Depression Inventory (BDI; 0–84 points).[20] The actual fatigue severity was assessed by means of Penner's Fatigue Scale for motor and cognitive function (FSMC), a scale that provides separate assessments of motor function ($FSMC_{motor}$; 0–50 points), cognitive function ($FSMC_{cognitive}$; 0–50 points) and a total of both ($FSMC_{total}$; 0–100 points).[21] In addition to these neuropsychological tests we performed the 25-Feet Foot Walk test and the 9-Hole PEG test out of the MS Functional Composite (MSFC).[22] All tests were performed by two trained MS nurses who were unaware of the ultrasound data (ie, blinded); the neuropsychological testing took place in a quiet room in the early afternoon. Neither the patients nor the control participants took sedative or other medications which could lead to cognitive impairment. Apart from age, disease duration and EDSS all other variables including width of the third ventricle were transformed to z-values using the controls as reference population according to the following formula[23]:

$$Z = (test_{patient} - mean_{controls})/SD_{controls}$$

For tests with two runs, the respective average values were used.

STATISTICAL ANALYSIS

Results are reported in mean±SD. Depending on their respective normal/not normal distribution, group comparisons were performed with the t test or non-parametric Wilcoxon Rank-Sum test. Univariate correlation analysis results are reported with non-parametric Sprearman's r. For multivariate analysis, stepwise regression analysis was used. All analyses were performed using MATLAB Statistics Toolbox. A p value of <0.05 was considered significant, where as a p value between 0.05 and 0.1 was considered a trend.

RESULTS

Patients' mean third ventricular width (3.9±1.6 mm) was significantly wider compared to controls (3.4±0.8 mm, $p<0.005$). As reported previously, the width of the third ventricle over all patients with MS was significantly related to EDSS (Spearman $r=0.446$, $p<0.005$) and to MS duration ($r=0.319$, $p<0.005$) but not to age.[17]

Compared to controls, performance of patients with MS was worse, highly significantly so, in all motor tasks (table 2). The neuropsychological tests showed significant differences in the $SPART_{delayed\ recall}$, the SDMT and the PASAT 2 s version tests, while $SRT_{total\ recall}$ and $SRT_{delayed\ recall}$, $SPART_{total\ recall}$ and WLG did not. PASAT 3 s version showed a trend ($p=0.06$) that patients performed worse. Patients exhibited statistically highly significantly higher FSMC scores than the controls. According to Penner *et al*[21] a slight fatigue begins at a score of 22 points in both fatigue categories; thus, according to the mean values our patients were slightly fatigued while the controls did not exhibit any fatigue. With respect to depression, the differences were highly significant, but given the wide range of the scales and the resulting clinical meaning of these differences, they only marginally impress.

Within the patient group univariate correlations were performed between the baseline variables (age, disease duration, third ventricle width and FSMC) and each target variable (table 3). When more than one baseline

Table 2 Mean±SD of the raw data of the 3. Ventricle width and of the motor and the neuropsychological tests in controls and patients

	Controls	Patients with MS	p Value
Width of 3. Ventricle (mm)	3.4±0.8	3.9±1.6	<0.005
25-Foot Walk	3.7±0.5	4.8±2.7	<0.005
9HP dom hand	16.7±1.8	19.7±3.3	<0.0001
9HP non-dom hand	17.7±1.9	21.1±5.8	<0.001
$SRT_{total\ recall}$	61.9±7.6	58.9±9.4	ns
$SRT_{delayed\ recall}$	11.1±1.1	11.3±1.2	ns
$SPART_{total\ recall}$	21.9±4.3	20.8±4.7	ns
$SPART_{delayed\ recall}$	7.9±1.6	6.9±2.2	0.01
SDMT	75.5±17.1	61.2±19.3	<0.0001
PASAT 3 s	46.3±8.1	42.3±10.9	0.06
PASAT 2 s	36.2±7.4	31.2±9.7	0.006
WLG	27.5±6.3	25.5±6.3	ns
BDI	1.6±2.1	5.9±4.9	<0.0001
FSMC cognitive	15.5±5.1	23.7±8.7	<0.0001
FSMC motor	16.2±5.2	27.9±8.7	<0.0001
FSMC total	30.7±21.9	51.3±17.4	<0.0001

9HP dom hand, 9-Hole-PEG test of the dominant hand (in s); 9HP non-dom hand, 9-Hole-PEG test of the non-dominant hand (in s); 25-Foot Walk, 25-Feet Foot Walk (in s); BDI, Beck Depression Inventory (0–84 points); FSMC, Fatigue Scale for motor and cognitive function (0–50 points for $FSMC_{motor}$ as well as $FSMC_{cognitive}$ and 0–100 points for $FSMC_{total}$); MS, multiple sclerosis; ns, not significant; PASAT, Paced Auditory Serial Addition Test (PASAT 2 s and 3 s versions; number of correct namings); SDMT, Symbol Digit Modalities Test (number of correct namings); SPART, Spatial Recall Test with a total and a delayed recalls; SRT, Selective Reminding Test with a total and a delayed recalls; WLG, Word List Generation Test (number of correct namings).

variable was significantly correlated with the target variable a stepwise regression analysis model was performed including all baseline variables as input variables and the target variable as output variable. All motor targets were significantly related to age, third ventricle width and $FSMC_{motor}$ but not to disease duration; after stepwise regression analysis third ventricle width and $FSMC_{motor}$ remained significantly correlated. $SRT_{total\ recall}$ was significantly correlated with age and third ventricle width, of which only third ventricle width remained significant after multivariate analysis. $SRT_{delayed\ recall}$ was correlated significantly only with $FSMC_{cognitive}$. $SPART_{total\ recall}$ correlated with MS duration and third ventricle width in the univariate analysis; after multivariate analysis only third ventricle width gained significance (p=0.005). $SPART_{delayed\ recall}$ was significantly correlated with age and third ventricle width. SDMT showed significant correlations with age and third ventricle width and a trend with $FSMC_{cognitive}$; after multivariate analysis only age and third ventricle width remained significant.

PASAT3 s, PASAT2 s and WLG did not show any correlation to age, MS duration, third ventricle width and $FSMC_{cognitive}$.

BDI was unrelated to age, MS duration and third ventricle width. As to be expected, there was a good correlation between BDI and FSMC total.

FSMC total and $FSMC_{cognitive}$ exhibited no correlation with age, MS duration and third ventricle width; only $FSMC_{motor}$ showed a slightly significant correlation with MS duration after multivariate analysis (for this analysis fatigue as a baseline variable was excluded from the multivariate model).

To summarise our correlation analysis, we found third ventricle width increase significantly correlated not only with worsening of motor symptoms but also with decreasing cognitive abilities. Regarding motor symptoms fatigue is a relevant independent covariable. Regarding cognitive impairment age and fatigue are of relevance. However, for the speed of information processing our models found no possible explanatory hint for the observed differences when compared to the controls. Fatigue was not correlated with third ventricle width in most of its aspects.

DISCUSSION

The primary aim of our study was to demonstrate that third ventricle enlargement indicates neuropsychological impairment in addition to motor impairment. We were able to demonstrate such a relationship, even when fatigue was additionally considered. Our results are in agreement with Walter *et al*[16] for a cohort of patients with MS similar to ours, in agreement to Berg *et al*[12] who investigated a cohort of patients with MS with more severe disease of longer disease duration and in agreement with a study in a general population.[24] Schminke *et al*[15] did not find such relationships in a cohort of patients with MS with a disease severity comparable to our cohort. However, Schminke *et al* did find Spearman's r correlation coefficients similar to ours and to the study of Walter *et al*[16] Schminke *et al* investigated 27 patients; thus, it might be reasonable to consider that the sample size of Schminke *et al* had been undersized to reach significance. Assuming this, it seems reasonable to admit that there is a clinically relevant correlation

Table 3 Univariate correlations (Spearman's r) and multivariate regression analysis between the baseline variables age, MS duration, third ventricular width and Fatigue Scale for motor (FSMC m) and cognitive (FSMC c) function and the target variables of the motor and neuropsychological tests

	Baseline variables		3. Ven W	FSMC m or c	
	Age	MS dur			
	r				After multivariate regression analysis the
Target variables	p Value				target variable remained significantly correlated
25-Foot Walk	0.30	0.18	0.38	0.43	3. Ven W (p=0.002), FSMC m (p=0.01)
	<0.05	ns	<0.005	<0.005	
9HP dom hand	0.38	0.17	0.40	0.37	3. Ven W (p=0.002), FSMC m (p=0.004)
	<0.005	ns	0.0001	<0.005	
9HP non-dom hand	0.23	0.09	0.43	0.33	3. Ven W (p=0.002), FSMC m (p=0.0006)
	0.06	ns	<0.0001	<0.008	
$SRT_{total\ recall}$	−0.31	−0.12	−0.32	−0.20	3. Ven W (p=0.04)
	0.01	ns	<0.0001	ns	
$SRT_{delayed\ recall}$	−0.08	0.12	−0.05	−0.40	FSMC c (p=0.001)
	ns	ns	ns	0.001	
$SPART_{total\ recall}$	−0.11	−0.26	−0.21	−0.05	3. Ven W (p=0.005)
	ns	0.03	0.08	ns	
$SPART_{delayed\ recall}$	−0.37	0.09	−0.29	0.00	Age (p=0.003), 3 Ven W (p=0.03)
	<0.005	ns	0.01	ns	
SDMT	−0.42	−0.19	−0.43	−0.21	Age (p=0.008), 3 Ven W (p=0.008)
	<0.001	ns	<0.0005	0.08	
PASAT 3 s	−0.15	0.09	−0.06	0.02	
	ns	ns	ns	ns	
PASAT 2 s	−0.22	0.08	−0.16	0.03	
	ns	ns	ns	ns	
WLG	−0.21	0.11	−0.03	−0.18	
	ns	ns	ns	ns	
BDI	0.04	−0.07	0.02	0.67	
	ns	ns	ns	<0.0001	
FSMC c	0.09	0.13	−0.01		
	ns	ns	ns		
FSMC m	0.12	0.23	0.16		MS dur (p=0.04)
	ns	0.06	ns		
FSMC total	0.0	0.12	0.05		
	ns	ns	ns		

Apart from age and MS duration (both in years) analysis with all other variables were performed using their respective z-values.
3 Ven W, third ventricle width; 9HP dom hand, 9-Hole PEG test of the dominant hand; 9HP non-dom hand, 9-Hole PEG test of the non-dominant hand; 25-Foot Walk, 25-Feet Foot Walk; BDI, Beck Depression Inventory; FSMC, Fatigue Scale for motor (m) and cognitive (c) function; MS dur, disease duration of multiple sclerosis; ns, not significant; PASAT, Paced Auditory Serial Addition Test (PASAT 2 s and 3 s version); r, Spearman's correlation coefficient; SDMT, Symbol Digit Modalities Test; SPART, Spatial Recall Test with a total and a delayed recall; SRT, Selective Reminding Test with a total and a delayed recall; WLG, Word List Generation Test.;

between motor and neuropsychological sequelae and third ventricle enlargement over the whole range of disease stages. In our patients at an early stage of the disease, we could not demonstrate a correlation between increasing ventricular diameter and worsening of all the neuropsychological tests used. Berg *et al*, however, who examined patients with MS at a more advanced stage of disease using the same test battery, did find such a clear correlation between increasing ventricle size and worsening performance in all of the tests.

We included in our neuropsychological assessment a well-validated fatigue scale hoping that we would find a correlation between fatigue and ventricle width. Unfortunately, fatigue alone did not reveal a correlation to third ventricle enlargement suggesting that fatigue is not simply the result of generalised brain atrophy. Using MRI techniques, Yaldizli *et al*[25] found corpus callosum atrophy correlating with fatigue; Riccitelli *et al*[26] suggested that atrophy of the primary sensorimotor area is likely to contribute to MS-related fatigue; Morgante *et al*[27] suggested that central fatigue in MS is probably due to a dysfunction of cortical motor areas involved in movement preparation. A neuroanatomical allocation of fatigue is still being debated, but at least, our findings that motor disability was related to motor fatigue might support clinically the hypothesis of Morgante *et al* and Ricitelli *et al*.

The most relevant limitation of TCS to assess brain atrophy is its poor ability to examine cortical structures

compared to MRI. The question is whether for investigations on a regular routine basis the knowledge of such subtle MRI brain atrophy markers is necessary for patient's management. Other limitations of TCS, such as the ultrasound penetration of the temporal skull, are less relevant because most patients with MS belong to an age group with usually good penetration conditions. A limitation of our study is its cross-sectional design. Our data does not allow the conclusion that future brain atrophy increase will be accompanied by worsening of the neuropsychological deficits although the report of Kallmann *et al*[13] might lead to such a suggestion. To demonstrate this more accurately a follow-up has to be performed.

To summarise, our study strengthens previous findings that third ventricle width as a marker of brain atrophy can be considered predictive for motor and neuropsychological sequelae. It seems that this relationship is valid over the whole range of disease stages. Fatigue, however, was not related to ventricular width in this cohort of patients.

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Contributors MM contributed to the design of the study, performed the ultrasound investigation and wrote the manuscript. RE and AM collected the data, performed the data analysis and revised the manuscript. KK recruited the patients and revised the manuscript from the clinical point of view. JV contributed to the study design, performed the ultrasound investigations and revised the manuscript. PS contributed to the design of the study, writing of the manuscript and revised it carefully.

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