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BRAIN AND LESION VOLUMES CORRELATE WITH EDSS IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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ABSTRACT

Background: Demyelination and neurodegeneration are hallmarks of multiple sclerosis (MS). Axonal damage is considered to be the leading factor for persisting disability in the course of the disease. In different studies, expanded disability status scale (EDSS) scores have been found to correlate with brain atrophy, lesion load, or both.

Objective: To assess the possible correlations between EDSS scores and volumes of brain, grey and white matter, and subcortical structures in patients with relapsing-remitting multiple sclerosis.

Subjects and Methods: 46 patients with RRMS were included in the study. Total brain volume, grey and white matter volumes were calculated using SIENAX, and subcortical structure volumes were obtained using FIRST, parts of FSL. EDSS was scored by a qualified rater. Statistical analysis was performed.

Results: Moderate negative correlation of EDSS was demonstrated with total brain volume, grey and white matter volume, volumes of left and right pallidum, putamen, caudate nucleus, n. accumbens ($p<0.01$), and with the volumes of left and right thalamus ($p<0.05$). Moderate positive correlation was found between EDSS and T2 lesion volume ($p<0.01$). Correlation between EDSS and hippocampal volumes was weak.

Conclusions: Our results demonstrate that in patients with relapsing-remitting multiple sclerosis, higher disability correlates with lower volumes of brain, grey and white matter, and some subcortical structures, but also with higher T2 lesion load. We support the hypothesis about a possible causal relationship between white matter damage and brain atrophy, as well as the role of both demyelination and neurodegeneration for disability in MS.

Keywords: multiple sclerosis, EDSS, volumetric study, lesion load

BACKGROUND

It has been widely accepted that multiple sclerosis (MS) presents not only with inflammatory demyelination but also with a parallel neurodegenerative process. It begins early in the course of the disease and with time leads to destruction of axons, which, together with myelin lesions, causes reduction of brain volume. Though the latter decreases progressively with age even in healthy persons, the degree of reduction is significantly higher in patients with MS [1]. The detection of such changes is made possible by the widespread use of modern magnetic resonance techniques in scientific research, as well as in diagnostics and monitoring of patients with MS. Some authors state that not demyelination, but axonal damage is the main reason for disability in MS, as it has been demonstrated in studies with experimental models [2].

Contrast enhancing lesions in patients with relapsing-remitting MS, on the other hand, were found to correlate with the occurrence of relapses, with the presence of myelin degradation products in the cerebrospinal fluid, and with higher expanded disability status scale (EDSS) disability scores [3]. Correlation of EDSS scores with bilateral periventricular location of the lesions, with accumulation of lesions in specific areas such as the thalamus and the middle cerebral peduncle has also been demonstrated [4].

A longitudinal study by Fisniku at al. shows that lesion volume in the beginning of the disease and its increase in the early stages correlate with higher disability in 20 years [5]. Similar results were reported by researchers from the MAGNIMS group [6, 7], who discuss lesion load, but also brain atrophy, as correlating with EDSS and respectively as predictors of disability in the long term.

The presence of tissue damage in regions which are normal appearing on neuroimaging is a well-known fact and is among the possible explanations of the clinico-radiological paradox [8, 9], the conception of which is based on the presence of damage only in the areas where demyelinating lesions can be visualized. Alterations occurring in normal appearing areas, beginning in the early stages of the disease, contribute significantly to brain atrophy. Methods which allow atrophy to be measured are therefore indicative of the degree of total damage, including that in normal appearing areas.

Another important result that has been reported is the presence of moderate to strong correlation between atrophy

and T2 lesion load. This not only demonstrates the dependence between the degree and location of atrophic changes and the clinical phenotype of the disease but also suggests a possible causal relationship between white matter damage and atrophy [10]. A relationship between atrophy and lesion load was also described by Battaglini et al. [11].

The purpose of the present study is to assess the possible correlations between EDSS scores and volumes of brain, grey and white matter, and subcortical structures in patients with relapsing-remitting multiple sclerosis.

SUBJECTS AND METHODS

Forty-six patients with relapsing-remitting MS, 13 (28.3%) males and 33 (71.7%) females, aged 38.6±9.1 years, were included in the study. They were recruited among the inpatients of First neurological clinic, Sveta Marina university hospital, Varna, Bulgaria. Informed consent form was signed by all participants. Total brain volume, grey and white matter volumes were calculated using SIENAX, and subcortical structure volumes (left and right thalamus, putamen, n. caudatus, pallidum, hippocampus, and n. accumbens were obtained using FIRST, both procedures being parts of the FSL software package [12, 13]. Manual corrections were applied to BET, the procedure which strips the skull and some other tissues from the brain, as they are not needed for the analysis. This was done in order to increase the precision of the algorithms and to obtain more reliable results. EDSS was scored by a qualified rater in all patients. Statistical analyses were carried out using SPSS v 17.0 (for Windows). Non-parametric correlation analysis (Spearman's ñ) was applied to estimate association between EDSS scores and volumes of brain, grey and white matter, and subcortical structures.

RESULTS

Moderate negative correlation of EDSS was demonstrated with total brain volume, grey and white matter volume, volumes of left and right pallidum, putamen, caudate nucleus, n. accumbens ($p<0.01$), and with the volumes of left and right thalamus ($p<0.05$). Moderate positive correlation was found between EDSS and T2 lesion volume ($p<0.01$). Correlation between EDSS and hippocampal volumes was weak. Correlation coefficients and levels of significance are shown on Tables 1-3.

Table 1. Correlations between EDSS and volumes of brain, white matter, grey matter, T2 lesion load, left (L) and right (R) thalamus. Coefficients and levels of significance.

Volumes		Total	WM	GM	Lesions (T2)	L Thalamus	R Thalamus
EDSS	Correlation Coefficient (rho)	-0.499**	-0.416**	-0.419**	0.427**	-0.348*	-0.346*
	Sig. (2-tailed)	0.000	0.004	0.004	0.003	0.018	0.018
	N	46	46	46	46	46	46

Table 2. Correlations between EDSS and volumes of left (L) and right (R) putamen, pallidum, and n. caudatus. Coefficients and levels of significance.

Volumes		L Putamen	R Putamen	L Pallidum	R Pallidum	L N.caud.	R N.caud.
EDSS	Correlation Coefficient (rho)	-0.518**	-0.471**	-0.540**	-0.465**	-0.525**	-0.421**
	Sig. (2-tailed)	0.000	0.001	0.000	0.001	0.000	0.004
	N	46	46	46	46	46	46

Table 3. Correlations between EDSS and volumes of left (L) and right (R) hippocampus, amygdala, and n. accumbens. Coefficients and levels of significance.

Volumes		L Hipp	R Hipp	L Amygdala	R Amygdala	L N.acc.	R N.acc.
EDSS	Correlation Coefficient (rho)	-0.139	-0.250	-0.048	-0.270	-0.407**	-0.441**
	Sig. (2-tailed)	0.358	0.094	0.752	0.069	0.005	0.002
	N	46	46	46	46	46	46

**. Correlation is significant at the 0.01 level (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

In this study we measured the volumes of brain, grey and white matter, and subcortical structures in patients with relapsing-remitting multiple sclerosis and assessed the correlations between volumes and disability, represented by the EDSS score of each patient. The fact that we could establish correlations of EDSS with the volumes of different brain structures is not unexpected, considering the characteristics of our subject population and available literature data [14, 15]. We found a weak correlation with hippocampal volumes which can be explained by the known low sensitivity of EDSS to the impairment of hippocampus-related functions, such as cognitive/memory abilities [16].

It is known from the literature that not all researchers have studied and support the hypothesis for relationships between disability and both lesion load and brain volumes. While in some studies emphasis is put on the relationship of disability and EDSS only with axonal injury, resulting in lower brain volumes and atrophy [2], in others the volume of T2 lesions is the only component that is assessed and shows significant correlations with disability [5]. The clarification of these relationships is of great importance because the two phenomena, reduction of brain volumes and accumulation of lesions, result from the two pathological processes that drive the clinical course of MS: neurodegeneration and demyelination. Based on our results, showing significant correlation between EDSS scores and both brain volumes and lesion load, we support the theory that both pathological processes play important roles for causing disability in MS, and none of them should be neglected. Our results are in line with those reported by Popescu et al. [6], Kearney et al. [7], and other authors who regard both atrophy and lesion load as predictors of disability in the long term. Future studies analyzing these parameters would certainly help solving the problem of how to determine standard procedures for monitoring disease course and response to pharmacological treatment [17].

CONCLUSIONS

Our results demonstrate that in patients with relapsing-remitting multiple sclerosis, higher disability correlates with lower volumes of brain, grey and white matter, and some subcortical structures, but also with higher T2 lesion load. We support the hypothesis about a possible causal relationship between white matter damage and brain atrophy, emphasizing the role of both demyelination and neurodegeneration for disability in MS.

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