Neuroscience and Behavioral Physiology, Vol. 39, No. 1, 2009

Characteristics of Neurological and Cognitive Status in Patients with Multiple Sclerosis in Relation to the Location and Volumes of Demyelination Foci and the Severity of Brain Atrophy

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Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Multiple Sclerosis, Supplement, No. 4, pp. 46–49, 2007.

A total of 65 patients with clinically significant diagnoses of remitting multiple sclerosis in the stage of remission were studied. Neurological status was investigated with assessment on the FS and EDSS scales, with neuropsychological testing, and MRI scans (1.5 T). The severity of brain atrophy (in terms of the parenchyma volume) and the total volume of foci on T2 images were assessed as proportions of intracerebral volume. The severity of neurological deficit depended on the volume of intratentorial focal lesions and the level of brain atrophy. Cognitive disorders were identified in 89% of patients, and the severity of these was associated with the level of atrophy and the volume of foci on T2 images in the dominant hemisphere.

KEY WORDS: multiple sclerosis, brain atrophy, cognitive disorders, volume of T2 foci.

INTRODUCTION

As the cascade of immune, biochemical, and degenerative processes constituting the pathogenesis of multiple sclerosis (MS) progresses, its development leads to marked focal and atrophic changes in the CNS and consequent stable clinical manifestations [6]. Data from some studies [19] have indicated that the volume of demyelination foci does not correlate with the severity of atrophic brain changes, which suggested that the development of atrophy is independent of the local demyelinating process. Other results have identified a relationship between these pathological processes; the severity of the neurological manifestations and the prognosis are felt generally to be related to the extent of overall brain atrophy [11, 17, 23]. At the same time, the severity of the neurological deficit correlates weakly with the number and volume of demyelination foci in patients with MS [13]. In addition, the appearance of new demyelination foci in the brain is not always accompanied by increases in the neurological deficit [11, 25], but may be reflected in the severity of cognitive impairments (CI) [9].

CI are seen in 40–86% of patients with MS [4, 29]. A wide spectrum of such disorders with negative influences on patients' quality of life, leading to impaired ability to work and degraded social adaptation, has been identified [1, 7, 14, 27]. CI are encountered at the early stages of the disease and can be among the first (and in some cases the only) symptoms of disease onset and exacerbation [16, 24]. Some authors believe [2, 26, 28] that the severity of CI correlates with the volume of demyelination foci and the level of brain atrophy. At the same time, other investigators have found no significant relationship between CI and focal changes [18, 30]. MRI diagnostic criteria emphasize the importance of lesions in the subtentorial brain structures [15], though their clinical significance and contribution to pathogenesis remain incompletely studied. The contradictory nature of the published data makes further study of this question necessary.

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0097-0549/09/3901-0035

TABLE 1. Volume of Demyelination Foci and Brain Parenchyma

Statistical measure	Demyelination foci, mm^3				Measures of atrophy, mm^3			
	right hemisphere	left hemisphere	subtentorial structures	total volume	parenchyma	CSF-containing space	intracranial space	CPV index
M	1169.9	1032.86	61.63	2264.39	403848.60	76704.78	479349.60	0.84
± *m*	996.45	933.34	70.02	1784.37	43893.66	11643.33	4322.80	0.03

The aim of the present work was to investigate the influences of overall brain atrophy and the locations and volumes of demyelination foci on the neurological and cognitive status of MS patients.

MATERIALS AND METHODS

A total of 65 patients (54 men and 11 women) aged 21–46 (mean 37 ± 16) years with remitting MS in the stage of clinical remission (diagnoses were established in accord with the McDonald et al. criteria [22]). All patients were right-handed. Disease duration was 7.5 ± 5 years. Severity was assessed on the Functional Systems Scale (FS) and Kurtzke's Extended Disability Status Scale (EDSS) [21].

Cognitive status was evaluated using psychological tests to assess the severity of the CI most often seen in MS [3]. The 10-word memory test was used to assess short- and long-term memory [12]. Quantitative changes in the volumes of immediate and operative memory, the index of short-term memory, and the ratio of the volumes of immediate and operative memory were evaluated using the "double" test [10]. The stability of attention was addressed using the correction test (Landolt ring version) [5]. Counting skills and the stability of attention was assessed by subtracting sevens from 100 [8]. The Kraepelin test was used to evaluate the productivity of mental work capacity and fatigue [8]. The Paced Auditory Serial Addition Test (PASAT) was used to assess counting skills, the rate of information processing, and the level of short-term information storage, as well as the stability of attention [20]. These six tests yielded data on 19 parameters.

Brain MRI scans were obtained using a standard protocol (Magnetom Vision, Siemens, 1.5 T). MRI patterns in all patients corresponded to the diagnosis of MS. Quantitative analysis of MRI results was performed using the semiautomatic computer program Java Image, which allows signal intensity to be used to identify zones of interest and changes in volume. Total focus volumes were determined separately in the left and right hemispheres and in subtentorial brain structures; measures of atrophy were also determined: the size of the subarachnoid space, the volumes of the ventricles, and the volume of the intracranial space. These data were used to calculate the cerebral parenchyma volume (CPV). Because of the variability of measures of the intracranial space, correlation analysis was performed using the CPV index – the ratio of CPV to the volume of the intracranial space. Correlations between measures were identified using Statistica version 6.

RESULTS AND DISCUSSION

The severity of the neurological manifestations on the EDSS in the cohort of patients studied here was 4.0 ± 1.5 points. MRI results are presented in Table 1.

No predominance of lesions in the right or left hemispheres was seen. The volume of foci in subtentorial structures in 49 patients (75%) was less than 7% of the total volume of foci. Correlation analysis identified a negative relationship ($p < 0.05$; $r = –0.39$) between the volume of foci in subtentorial structures and the CPV index. There were no correlations between the CPV index and the total volume of foci or the volume of foci in each hemisphere. It should be noted that there were negative correlations between the CPV index and the severity of invalidity on the EDSS and the points score on the FS for pelvic dysfunction ($p < 0.05$; $r = –0.36$). The only positive correlation between the volume of foci in subtentorial brain structures was with disease severity on the EDSS ($p < 0.05$; $r = 0.34$). These results indicate the importance of focal lesions in subtentorial structures in disease development. This phenomenon may result from damage to large numbers of nerve fibers with small focus volumes because of the high concentration of conducting pathways per unit volume, which probably also leads to the neurological disturbances. Impairment to spike conduction via damaged afferent pathways may be important for the development of atrophic changes in the brain. The interaction between brain atrophy and the volume of subtentorial foci may result from damage to nonspecific tonic structures of the reticular formation located in the brain stem.

Psychological investigations revealed the presence of CI in 44–92.4% of patients. Of the 19 psychological measures, the group mean values of 17 (89.5%) were below normal. Deviations from normal in the 10-word memory test increased on sequential attempts to reproduce words in 87% of patients. The results of this test provide evidence of

TABLE 2. Correlation of Psychological Test Results with Total Volume of Demyelination Foci and Measures of Brain Parenchyma Volume ($p < 0.05$)

Test	Volume of foci			CPV
	right hemisphere	left hemisphere	subtentorial structures	
Ten-word memory:				
number of words reproduced (5 trials)	NS	$r = -0.42$	NS	NS
words reproduced at 1 h	NS	$r = -0.43$	NS	$r = 0.38$
"Double" test:				
immediate memory	NS	$r = -0.49$	NS	$r = 0.49$
operative/immediate memory	NS	NS	$r = -0.54$	NS
index of short-term memory	NS	NS	NS	$r = 0.39$
Correction test:				
Sn	$r = -0.42$	$r = -0.42$	$r = -0.43$	NS
T	NS	$r = 0.43$	$r = 0.57$	NS
Serial subtraction of 7s from 100:				
T	NS	$r = 0.41$	$r = 0.37$	$r = -0.39$
t	NS	$r = 0.27$	$r = 0.29$	$r = -0.40$
n	NS	NS	NS	$r = -0.50$
Kraepelin counting:				
Quantity of work performed	$r = -0.39$	$r = -0.63$	$r = -0.35$	NS
A_{mean}	$r = -0.39$	$r = -0.40$	NS	$r = 0.71$
PASAT-3 – number of correct responses	NS	$r = -0.39$	NS	$r = 0.40$

Note. NS = not significant.

rapid fatigue of memory processes in patients with MS. The number of words reproduced after one hour was below normal in 41.3% of patients.

The "double" test demonstrated decreases in the volume of operative memory in 92.4% of patients, the volume of immediate memory in 48.5%, and the ability to utilize this in task solving in 81.8%. The index of short-term memory, which characterizes the quality of performance of the whole test, was below normal in 88.7%.

The overall measure characterizing performance of the correction test, i.e., the sensorimotor analyzers index, was below normal in 67.2% of patients. The rate of performance of the correction test was reduced in 75.4% of patients, and accuracy was decreased in 18.5%. Decreases in the results of the serial sevens subtraction from 100 test in 44% of patients were identified from performance time indicators. The number of correct solutions of examples in the PASAT-3 test was below normal in 89% of patients.

Thus, psychological investigations demonstrated CI such as increases in the time taken to perform intellectual-memory tasks, decreases in the rate and rapid fatigue of mental processes, impairments to memory processes, and decreases in the volume of short-term memory.

Psychological test results were compared with the volumes of demyelination foci in the right and left hemispheres and subtentorial brain structures and with the parenchyma volume, i.e., the CPV index (Table 2). Relationships with demyelination focus volumes were seen for 17 psychological measures; the values of eight parameters correlated with CPV. The largest number of test measures correlated with the volume of foci in the left (dominant) hemisphere.

This result allows indirect assessment of the functional asymmetry of the cerebral hemispheres and the significance of lesions to the white matter of the dominant hemisphere to the development of CI. The relationships between several measures and the volume of subtentorial foci indicated the significance of lesions to these structures in the development of these losses in MS.

The severity of atrophic processes in the brain also influenced the development of CI. This was indicated by the positive correlations between the volume of the brain parenchyma and measures characterizing short-term memory, counting skills (the 10-word memory test and the "double" test, the PASAT-3 test, the Kraepelin counting test) and the negative correlations between brain parenchyma volume and the test performance time as well as the number of errors made in the serial sevens from 100 test.

These data indicate that the development of CI in MS depends on both the volume of focal lesions and the severity of atrophic processes.

CONCLUSIONS

1. A positive relationship was found between disease severity on the EDSS scale and cognitive impairments with the severity of overall brain atrophy and the volume of subtentorially located demyelination foci in MS.

2. The largest number of psychological test measures correlated directly with the volume of demyelination foci in the dominant cerebral hemisphere.

3. The negative correlation found between focus volume in subtentorial structures and the volume of brain parenchyma may be evidence for a relationship between focal and diffuse degenerative processes in MS.

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