SHORT REPORT

Neuropsychological deficits in multiple sclerosis after acute relapse

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Abstract

Objectives—To examine cognitive and neurological changes and their relation to brain pathology in patients with multiple sclerosis during acute relapse.

Methods—Thirteen patients with multiple sclerosis were examined with a battery of neuropsychological tests during acute relapse and six weeks later. Their performance was compared with the performance of 10 controls matched for age and premorbid IQ. Gadolinium (Gd) enhanced MRI was also performed in patients on both occasions.

Results—The patients with multiple sclerosis performed significantly worse than controls on most tests of attention and memory during acute relapse and in remission. At follow up there was a significant or trend of improvement in performance on some tests of attention for patients in whom the Gd enhanced lesion load had decreased. In this subgroup of patients, their improvement also correlated significantly with the reduction in acute lesion load.

Conclusions—The findings suggest that certain neuropsychological deficits detected during an acute relapse may be reversible, particularly in patients who initially have mild cognitive impairment.

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Keywords: relapse; multiple sclerosis; neuropsychological deficits; gadolinium-enhanced MRI

Few attempts have been made to study cognitive changes in multiple sclerosis during acute relapse. Such studies present considerable methodological difficulties. There is anecdotal evidence from a single case study that cognitive deficits can improve in parallel with neurological symptoms during remission.¹ In addition, our serial study in patients with frequent relapses and remissions provided evidence for the occurrence of "cognitively silent" new lesions which highlights the difficulties in studying the relation between short term fluctuations in cognition and brain pathology.²

Here we tried to document cognitive changes in a group of patients during the early stages of acute relapse and after remission in

relation to neurological changes and MRI abnormalities. We also attempted to ascertain whether cognitive improvement was more likely in certain patient subgroups.

Subjects and methods

Thirteen patients (four men, nine women) with clinical definite multiple sclerosis³ were recruited during an acute relapse. A relapse was defined as the development of new neurological symptoms or abrupt deterioration of existing symptoms lasting more than 24 hours within the past six weeks and confirmed on neurological examination. Patients were excluded if their corrected visual acuity was <6/12 or if they were unable to use a computer touch screen accurately. They were examined at the time of recruitment and about six weeks later after treatment with intravenous methylprednisolone. All patients had a neurological examination and physical disability was assessed using the Kurtzke expanded disability status scale (EDSS).⁴ Four patients had relapsing-remitting disease and nine had secondary progressive disease. Ten healthy controls (three men, seven women) selected to match the patients for age and estimated premorbid IQ, were also examined on two occasions. Informed consent was obtained from all subjects.

The hospital anxiety and depression questionnaire⁵ was administered to all subjects. Scores >10 on either the anxiety or depression subscale were indicative of "caseness". The national adult reading test (NART) was used to estimate premorbid IQ.⁶ A battery of neuropsychological tests to assess attention and memory was administered on both occasions and included the following:

*Paced auditory serial addition test (PASAT)*⁷

Thirty one randomised digits were read out at two second intervals. The subject was instructed to add each digit to the one preceding it. The score was the number of correct responses.

*Stroop*⁸

Names of colours, each printed in a different coloured ink, were presented on a computer screen. The score was the time taken for the subject to name the colours in which the words were printed.

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Table 1 Gd lesion load and scores on tests of attention in the individual patients on the first and second testings

Group	DC	Gd volume (mm ³)			PASAT		Stroop		Symbol digit	
		1st	2nd	Gd%	1st	2nd	1st	2nd	1st	2nd
A:										
1	rr	0	0		12	13	—	—	17.8	16.0
2	sp	0	0		18	19	44.3	55.0	18.0	17.7
3	sp	0	0		12	13	—	—	—	—
4	sp	0	0		6	7	38.7	36.2	22.1	22.5
B:										
5	sp	885	1400		24	19	—	—	12.6	14.3
6	sp	1005	2718		21	22	24.5	29.1	12.4	11.6
7	sp	0	132		15	21	31.1	32.7	11.8	11.9
C:										
8	sp	768	294	62	7	7	40.5	—	23.5	21.3
9	sp	1119	951	15	1	1	30.2	—	30.7	25.3
10	sp	4401	2268	48	13	15	53.2	29.7	26.9	24.0
11	rr	2382	360	85	12	19	41.0	31.8	12.6	11.9
12	rr	144	0	100	24	27	19.5	18.7	16.9	14.3
13	rr	1965	54	97	22	29	27.1	22.8	13.4	14.1

Group = patient group (A, B, C), DC = disease category; sp = secondary progressive; rr = relapsing remitting; Gd% = percentage of improvement in Gd enhanced lesion load.

Symbol digit substitution⁹

The subject was required to name numbers represented by nine different symbols according to a code shown on the computer screen. Eight trials were presented. The mean time taken per trial was recorded.

Digit span forwards¹⁰

The score was the longest sequence of digits that the subject could recall.

Story recall test¹¹

The subject was required to recall a story read aloud to him or her immediately after and following an interval of 20 minutes.

Spatial span

This test was taken from the Cambridge neuropsychological test automated battery (CANTAB).¹² It determined the longest sequence of squares lighting up on the computer screen that the subject could recall accurately.

Other memory tests from the CANTAB (spatial working memory, spatial recognition and pattern recognition tests) were also administered but no significant differences in performance between patients and controls were found.

Brain MRI was performed in the patients with multiple sclerosis using an NMR 1.5 Tesla GE Signa System on both occasions. Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA; 0.1 mmole/kg) was administered intravenously and T1 weighted images with a TR of 540 and TE of 11 were obtained. Thirty six contiguous slices (3 mm thickness) were selected for measurement of lesion volume. A neuroradiologist (GQ) delineated the Gd enhanced lesion areas on hard copies. With reference to this, one rater (JF) used a semi-automated contouring technique¹³ to mark the lesions on the images displayed on a SUNSPARC station. A software lesion volume measurement programme was utilised to compute the total cerebral Gd enhanced lesion load.

STATISTICAL ANALYSIS

Mann-Whitney and Wilcoxon matched pairs signed ranks tests were used to examine between and within group differences. Correla-

tion analysis was performed using Pearson's correlation coefficient.

Results

There were no significant differences between patient and control groups for age (mean 37.15 years and 38.5 years respectively) and premorbid IQ (mean IQ 109.31 and 115.0 respectively). Patients were recruited within a mean of 3.42 weeks (range 1–6 weeks) of the onset of relapse. The mean interval between the two testings was not significantly different between patients and controls (47.54 days and 51.50 days respectively).

Physical disability as assessed on the EDSS scale, had improved significantly in patients at follow up ($z = -2.67$, $p = 0.008$). EDSS scores improved in nine patients and remained unchanged in four. There were no significant differences in the improvement of physical disability between patients with relapsing-remitting disease and those with secondary progressive disease. Patients with multiple sclerosis scored significantly higher than controls only on the depression subscale ($p = 0.021$) on initial testing although scores did not reach "caseness". At follow up, the HAD depression ($z = -2.27$, $p = 0.023$) and anxiety scores ($z = -2.34$, $p = 0.019$) had significantly improved for the multiple sclerosis group but were unchanged in the control group.

Patients were divided into three groups according to the pattern of Gd enhancement: group A: ($n = 4$ (three secondary progressive disease, one relapsing-remitting disease)), no Gd enhancing lesions in the brain detected on either testing; group B ($n = 3$ (all secondary progressive disease)), an increase in Gd enhancing lesion load found on the second testing; group C ($n = 6$ (three relapsing-remitting disease, three secondary progressive disease)), a reduction in Gd enhanced lesion load found on the second testing. Patients with relapsing-remitting disease had a greater reduction in Gd enhanced lesion load than patients with secondary progressive disease (table 1).

Patients performed significantly worse than controls on initial testing in all tests of attention (table 2). At follow up, there was a significant

Table 2 Group mean (SD) scores for tests of attention and memory

Test	1st occasion			2nd occasion		
	MS	Controls	Group difference	MS	Controls	Group difference
Attention:						
PASAT	14.38 (7.21)	21.20 (5.79)	$z=-2.17, p=0.029$	16.31 (8.08)	20.90 (3.54)	NS
Stroop	35.01 (10.27)	23.59 (5.39)	$z=-2.40, p=0.016$	32.00 (10.84)	21.24 (3.89)	$z=-2.52, p=0.012$
Symbol digit	17.44 (5.96)	11.98 (0.94)	$z=-2.97, p=0.003$	16.45 (4.69)	11.86 (1.33)	$z=-2.94, p=0.003$
Memory:						
Spatial span	4.92 (1.62)	6.30 (0.95)	$z=-2.03, p=0.04$	5.08 (1.00)	6.00 (1.25)	NS
% Story recall (immediate)	43.41 (18.66)	64.73 (11.12)	$z=-2.65, p=0.008$	37.27 (17.77)	56.67 (5.91)	$z=-2.32, p=0.02$
Digit span forward	6.62 (1.04)	7.90 (0.99)	$z=-2.56, p=0.01$	6.62 (1.04)	7.50 (1.08)	NS
% Story recall (delayed)	43.13 (21.89)	68.08 (12.96)	$z=-2.54, p=0.01$	43.64 (22.32)	72.71 (12.78)	$z=-2.81, p=0.005$

MS=multiple sclerosis.

improvement on the PASAT ($z=-2.23, p=0.026$) and a trend of improvement on the symbol digit substitution test ($z=-1.84, p=0.065$) in the multiple sclerosis group. Table 1 shows the individual scores of all patients.

The patient subgroups (A, B, C) did not differ significantly in their performance on the tests of attention. Although individual variation in performance was evident, there seemed to be a trend for greater improvement in these tasks in group C patients. The patients with relapsing-remitting disease in this group were less impaired than the patients with secondary progressive disease on initial testing and greater improvement on the PASAT was found at follow up. By contrast, there was little change in the group performance on these tasks for the patients who had no detectable Gd enhancing lesions and a slight deterioration in performance for the patients who had an increase in Gd enhanced lesion load (table 1). The control group's performance on these tasks was unchanged at follow up.

There were significant group differences between patients and controls for the recall tasks (digit span, spatial span, immediate and delayed story recall) on initial testing. Group differences persisted for the immediate and delayed story recall tests at follow up (table 2). Performance did not change significantly for any group in these tests at follow up.

Table 1 shows the individual patient's Gd enhanced lesion load. As we were interested in examining the relation between improvement in neuropsychological performance and Gd enhanced lesion load, only the six patients from group C were selected for the correlation analysis. We found that the improvement in the Stroop and symbol digit substitution test scores correlated significantly with reduction in Gd enhanced lesion load ($r=-0.99, p<0.01$ and $r=-0.82, p<0.05$ respectively).

Discussion

The results of this study highlight the variability of cognitive manifestations and lesion enhancement on MRI during acute relapses of multiple sclerosis. Some patients in our sample failed to show Gd enhancement on both occasions and there was little change in their cognitive performance. For the rest of the patients, variation in the Gd enhancing lesions was to some extent in parallel with the cognitive changes, particularly for the patients who had a

reduction in Gd lesion load. Cognitive improvement seemed to be limited to attentional tasks whereas memory impairment remained unchanged. Psychiatric symptoms were unlikely to have contributed to the patients' neuropsychological performance in view of the HAD scores failing to reach "caseness" and the lack of correlation with the neuropsychological test scores.

In group C, it was apparent that the patients with relapsing-remitting disease had a greater improvement in Gd enhanced lesion load than the patients with secondary progressive disease, in whom it was in parallel with their improvement on the attentional tasks. The patients with relapsing-remitting disease were also less cognitively impaired than those with secondary progressive disease at the outset, suggesting that those who are least cognitively impaired are most likely to improve after a relapse. This would also be in keeping with previous reports that cognitive deterioration is related to a progressive course.¹⁴ A somewhat unexpected finding is the divergent natural history of attention and memory deficits. Immediate and delayed recall deficits in the patients with multiple sclerosis did not change after remission. It is possible that the more entrenched memory deficits may be caused by different neuropathological processes such as axonal and myelin loss whereas attention deficits may be a result of transient inflammatory changes. The discrepancy between MRI cerebral lesion load and clinical relapse is illustrated by our finding that several patients had no enhancing lesions. In addition, the group B patients were found to have an increase in enhancing lesion load at follow up in the absence of any neurological deterioration. This may be because physical disability as measured by the EDSS is more closely related to spinal cord than cerebral lesions. It is also likely that Gd enhancement of acute lesions does not reflect the degree of demyelination or axonal loss, which are the likely substrates of functional impairment.

We acknowledge that this study was limited by the small sample size. None the less, our findings suggest that it may be possible to predict which cognitive deficits may be reversible and which patients are more likely to experience improvement during remission. This information would be relevant in selecting

patients for clinical trials and interpreting the results of treatment.

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