COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS: INFLUENCE OF CLINICAL VARIABLES

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Abstract - In this unprecedented study in Iran, 30 ambulatory cases of multiple sclerosis (MS), and 30 demographically matched normal control (NC) cases were evaluated by a brief cognitive screening test, Beck's Depression Inventory (BDI), and the Mini- Mental State Examination (MMSE). Mean scores of the BDI were significantly different in the MS and NC groups, while the mean MMSE scores were not. At least 11 (36.7%) patients were considered cognitively impaired. These cases were older at the time of testing and of symptom onset. Cognitive dysfunction was significantly more common in patients with secondary progressive course (66.7%) compared to the cases with remitting – relapsing (27.8%) course. Mean Expanded Disability Status Scale (EDSS) score was higher in the cognitively impaired cases. No significant difference was observed in the mean BDI scores of the cognitively intact and impaired cases. This study provides an estimate of the frequency of cognitive dysfunction in ambulatory cases of MS, and suggests a correlation between such deficits and age symptom onset, disease course, and physical disability, but not depression.
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INTRODUCTION

The view that cognitive function is spared in the majority of patients with MS (1,2,3) has been firmly laid to rest. It is now accepted that approximately 50% of those attending hospital (4, 5, 6) and slightly fewer community based patients (7) show evidence of cognitive impairment. Memory, attention and abstracting abilities are commonly impaired, with relative sparing of language functions (8,9,10). The pattern of cognitive decline in MS is similar to that in subcortical dementias (7) and related to the severity of the pathological process as detected by magnetic resonance imaging (MRI) (11 - 15).

The influence of clinical variables on cognitive performance of MS patients has not been fully elucidated. Previous cross - sectional studies of hospitalized patients found no correlation between the severity of cognitive impairment and either duration of the disease or the degree of the disability (8, 16 - 20). On the other hand, other studies have demonstrated that cognitive dysfunction and physical disability may be positively correlated (7, 21). Longitudinal studies have not contributed to clarify the problem, since evidence both for (22) and against (23) progressive cognitive decline has been reported.

A better knowledge of the relationships between neuropsychological impairment and other clinical aspects in MS should help to clarify the pathogenesis and the natural history of cognitive decline in MS. In this study the effects of clinical variables on several cognitive functions were evaluated.

MATERIALS AND METHODS

Ambulatory patients with clinically definite MS (24), referred to the neurology clinic of Shariati Hospital were considered for the study.

Patients were excluded if they had an upper limb or visual dysfunction significantly interfering with neuropsychological performance, a history of psychiatric or neurological disorder other than MS, impairment of consciousness, or were afflicted by a medical condition that could cause such an impairment (e.g., diabetes mellitus, hepatic or renal disease), had a history of alcohol or drug abuse, a clinical relapse in the previous month, or were treated with steroids or psychotropic drugs.

Thirty consecutive patients underwent

outpatient evaluation as part of a cross - sectional study (23 women and 7 men). A neurological examination was conducted to provide ratings of patients regarding disease course, duration of illness from symptom onset, and severity of physical disability using the Kurtzke Expanded Disability Status Scale (EDSS) (25). Educational level was defined as the total years of formal education. Thirty normal healthy adults were matched individually to the MS patients based on age (± 3 yrs), education (± 1 yr), and gender. Subjects were excluded if they had a history of drug abuse, psychiatric disturbance or any other nervous system disorder, or required the use of prescription medications.

All the MS patients and the normal control (NC) subjects, underwent neuropsychological assessment using a brief cognitive test battery, consisting of Controlled Oral Word Association Test (COWAT) (26), Paced Auditory Serial Addition Test (PASAT) (27), and UCLA Memory Test (UCLA) (28), that primarily evaluate recent memory, attention, and concentration. Patients were considered cognitively impaired if they performed abnormally in at least two neuropsychological tests (values below the fifth percentile of the normal population were considered abnormal). The Mini Mental State Examination (MMSE) (29) was also performed on all the MS and NC cases. The presence and the severity of depression was assessed by Beck's Depression Inventory (BDI) (30).

RESULTS

Twenty-three women and 7 men with clinically definite MS entered the study (female to male ratio = 3.28). The median age of the patients was 30.76 yrs (range 20 - 54 yrs; SD = 7.5). The median age of the men and women with MS was 29.8 yrs (SD = 2.85) and 31. 09 yrs (SD=8.70), respectively (Table 1). Median age of the NC group was 31.1 yrs (SD=7.5). Median educational level in the MS and NC group was 12.76 yrs (SD=2.8) and 12.73 yrs (SD = 2.4), respectively. Median age and educational levels were not significantly different in the MS and NC groups ($p>0.4$).

Median age of symptom onset was 24.5 yrs (range = 17 - 43yrs; SD= 5.9); 25.26 yrs (range = 18 - 43yrs; SD= 6.37) in the women, and 22 yrs (range = 17 - 28 yrs; SD = 3.26) in the men (Table 2).

Table 1. Age of MS patients.

Age (yrs)	Female (%)	Male (%)	Sum (%)
< 20	-	-	
20 - 25	6(20)	1(3.3)	7(23.3)
26 - 30	7(23.3)	2(6.7)	9(30)
31 - 35	7(23.3)	4(13.3)	11(36.7)
36 - 40	-	-	-
41 - 45	1(3.3)	-	1(3.3)
46 - 50	-	-	-
51 - 55	2(6.7)	-	2(6.7)
> 55	-	-	-
Sum	23(76.7)	7(23.3)	30(100)

Table 2. Age of symptom onset in MS patients

Age (yrs)	Female (%)	Male (%)	Sum (%)
15 - 18	3(10)	1(3.3)	4(13.3)
19 - 22	7(23.3)	4(13.3)	11(36.7)
23 - 26	5(16.7)	2(6.7)	7(23.3)
27 - 30	4(13.3)	-	4(13.3)
> 30	4(13.3)	-	4(13.3)
Sum	23(76.7)	7(23.3)	30(100)

Mean duration of disease was 6.2 yrs (range = 1-15 yrs; SD= 3.8).

Eighteen patients were classified as having relapsing-remitting (RR) MS, 9 secondary chronic progressive (SP) MS, 2 primary progressive (PP) MS, and 1 benign (31). Both of the patients with (PP) MS were men with spastic paraparesis.

Mean EDSS of the patients was 3.0 (range=

0-6.5 ; SD= 1.9). In the patients with RR course, mean EDSS was 2.0, in the SP group 5.3 and in those with PP course 3.0. In the patient with benign course, the EDSS was 0. Mean EDSS was significantly different between the RR and SP groups (P<0.001), and PP and SP groups (P<0.005). The difference between the mean EDSS of RR and PP cases were not significantly different (P>0.1).

A significant difference existed between the mean BDI scores of the MS and NC groups (P<0.005). Mean MMSE score of MS and NC groups were not significantly different (P>0.05). In 3 MS cases the mean MMSE score was below normal; all of these patients were cognitively impaired according to the other tests employed in this study. The mean scores of the other tests were all significantly different in the MS and NC groups (P<0.001).

Eleven MS (36.7%) patients were considered cognitively impaired, i.e., they gained a score below the fifth percentile of the normal population on more than one test. Five of these cases had an RR course, and six SP (Fig. 1). In other words, of the nine cases with SP MS, six (67%) had cognitive impairment. Therefore, cognitive impairment was significantly related to disease course (rt.= 0.4; P<0.01). Mean EDSS of the cognitively intact and impaired groups were 2.45 (SD = 1.77) and 4.04 (SD = 1.79), respectively.

The difference of these values was statistically significant (P<0.005). In the RR subgroup, the mean EDSS was 1.85 (SD = 0.87) in the cognitively intact cases and 2.6 (SD = 1.63) in the impaired cases, with a significant difference between the two subgroups (P<0.005). However, in the SP subgroup, the difference in mean EDSS of the cognitively intact and impaired groups was 5.25 (SD = 0.69) and 5.5 (SD=1.73), respectively, without a significant difference between the two values (P>0.4).

Mean duration of disease was 6.10 yrs (SD = 3.96) in the cases with cognitive impairment and 6.36 yrs (SD = 3.96) in the intact subgroup, without a significant difference.

Mean BDI score between the cognitively impaired and intact subgroups was 15.54 (SD = 6.61), and 14.21 (SD = 7.26), respectively, with no significant difference (P>0.2). Only one of the eleven patients with cognitive dysfunction was male. Most of the women with (SP) MS were cognitively impaired. Correlation of cognitive dysfunction with female sex did not reach statistical significance (P=0.29).

The cases with cognitive dysfunction were significantly older than those with normal cognition (P<0.005). Median age of patients was 33.91 yrs (SD=11.31) in the impaired subgroup, and 29.0 yrs (SD=3.87) in the intact cases (Fig. 2).

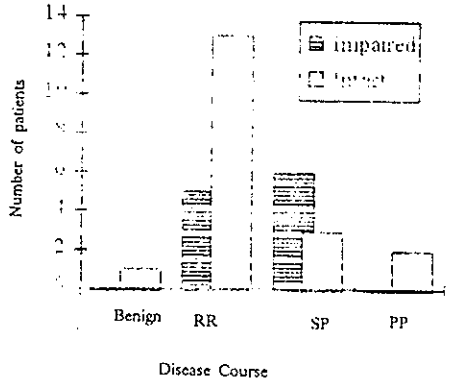

Fig. 1. Cognitive status by disease course

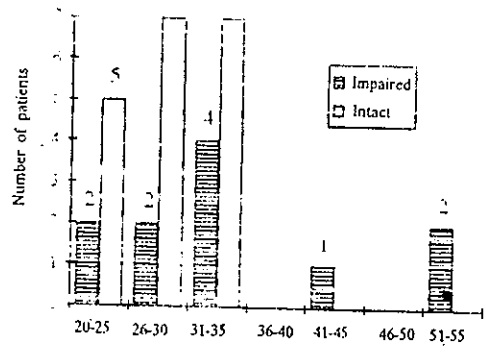

Fig. 2. Cognitive status by age (at the time of testing)

Patients with cognitive dysfunction were also significantly older at the time of symptom onset ($P<0.005$). The mean age of onset was 27.36 yrs (SD = 8.22) and 22.48 yrs (SD = 3.30) in the impaired and intact subgroups, respectively.

DISCUSSION

Findings of present study suggest that the frequency of cognitive dysfunction in ambulatory MS patients is at least 30% that is less than the 50% to 60% (4 - 6) estimates derived from previous neuropsychological studies of patients undergoing evaluation or treatment at other university-based medical centers. Our exclusion of institutionalized patients, those who were not ambulatory, or could not tolerate testing due to severe visual or motor impairment, and patients who had experienced an attack in the month before testing could have resulted in an underestimation of the overall frequency of cognitive dysfunction. On the other hand, this method of case selection, enables us to provide an estimate of cognitive impairment in a specific subgroup of MS patients, i.e., those who are fully ambulatory.

The higher frequency of cognitive deficits in patients with later disease onset agress with the fact that newly diagnosed MS has a worse prognosis, a more chronic course, and causes greater disability in older patients (32, 33).

Previous studies have yielded controversial results regarding the correlation between physical disability and cognitive deficits (7, 8, 16 - 21, 34). However, we found a significant difference between mean EDSS scores of cognitively impaired and intact cases in the patients with RR course. The discrepancy between the current study and previous negative findings may be explained by differences in test battery composition. The present screening battery may be more accurate in assessing the cognitive deficits caused by white matter involvement. Alternatively, it is possible that these results are sample specific. The lack of significant correlation between cognitive impairment and physical disability, as suggested by most studies, could be explained by the fact that EDSS reflect mainly cerebellar, brain stem and spinal cord involvement. In this study, cognitive dysfunction was not significantly correlated with disease duration and this has been noted by numerous other investigators (19, 23). The finding of cognitive dysfunction in patients with clinically isolated syndromes suggestive of MS, of with MS at early stages, and in patients with mild disability, raises the possibility that even selective damage to specific areas related to cognition, such as prefrontal and limbic structures, might cause cognitive decline in MS. Patients with SP course had worse neuropsychololgical performance than patients with RR or PP course. It is known that cognition is more frequently and severely affected in patients with chronic progressive MS, i.e., pateints with SP and PP MS (8, 20, 35). In the present study, only two patients had a PP course, both with spastic paraparesis as the dominant clinical manifestation. The small number of PP cases makes it difficult, if not impossible to draw definite conclusions, but none of the latter two patients were cognitively impaired, while more than 60% of those with SP MS had such deficits. The latter group of patients, compared with the PP MS group, had been shown to have brain involvement of greater extent as detected by MRI, despite similar degrees of physical disability (15, 36, 37). Several pathophysiological mechanisms have been suggested to explain this difference, such as greater spinal cord involvement in PP cases, and presence of small brain lesions beyond the resolution of the present scanners; the former seems more plausible. But why do patients with RR MS have better cognitive performance than those with SP MS? MRI studies have found similar lesion loads in these two groups (37). It may be possible that confluence of lesions, the nature of the lesion itself (degree of demyelination and/or axonal degeneration), or

their location could influence cognitive function.

Mean BDI scores were not significantly different between the cognitively intact and impaired subgroups, although the MS cases had a higher BDI score than the NC group. These findings suggest that while the frequency and severity of depression are significantly higher in MS patients, it does not have a meaningful association with cognitive dysfunction.

The pathophysiology of depression in MS and its relationship with cerebral involvement is a matter of considerable debate (8, 38, 39). However, depressive symptomatology in MS patients is likely to be a complex, multifactorial process, involving both psychosocial and neurologic factors (40).

Traditional cognitive screening instruments, like the MMSE, while assessing a wide range of functions, do not appear to be effective in screening MS patients (41). The mean MMSE score of MS and NC cases was not siginficantly different, and only three of our MS patients had below normal scores.

This study suggests that at least one-third of all ambulatory MS patients are cognitively impaired and that among clinical varaibles age at the time of testing and at the time of symptom onset, degree of physical disability, and disease course are correlated with neuropsychological performances. Cognitive abnormalities are frequently overlooked, sometimes in an attempt to avoid further distress in patients already burdened with an incurable disease. This neglect must be stopped. Brief screening procedures have been developed that obviate the need for extensive neuropsychological testing. They should be incorporated into all evaluations of MS patients including treatment trials.

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