Memory impairment in multiple sclerosis and its determinant factors

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ABSTRACT

الأهداف: دراسة مدى انتشار تدهور الذاكرة بين المرضى المصابين بتصلب الأعصاب المتعدد، بالإضافة إلى اكتشاف العوامل المحددة لدرجة تدهور الذاكرة.

الطريقة: أُجريت هذه الدراسة المقطعية في قسم الأعصاب بمستشفى شافا، كيرمان، إيران وذلك خلال الفترة من فبراير إلى نوفمبر 2008م، وشملت هذه الدراسة 100 مُصاباً بتصلب الأعصاب المتعدد. لقد تم اختيار عينة المرضى التي تضمنتها الدراسة بواسطة طريقة العينة المريحة، وبعد ذلك تم تسجيل بيانات المرضى التالية: العمر، والجنس، ومستوى التعليم، ونوع العمل، وتاريخ المرض بما فيه ظهور الأمراض الأخرى، وتاريخ أخذ الأدوية. لقد تمت معاينة المرضى وعمل اختبار لحالتهم العصبية باعتماد مقياس تمديد حالة الإعاقة، فيما تم تقييم حالة الذاكرة بواسطة استبيان اختبار الحالة العقلية والمكون من 7 فقرات.

النتائج: أشارت نتائج الدراسة بأن 71% من المرضى كانوا يعانون من تدهور الذاكرة حيث كان 35% من هؤلاء المرضى مصاباً بتدهور الذاكرة الخفيف إلى المتوسط، و19% منهم مصاباً بتدهور الذاكرة المتوسط إلى الحاد، و17% من هؤلاء المرضى مصاباً بتدهور الذاكرة الحاد. لقد كان هناك علاقة كبيرة من الناحية الإحصائية بين درجة تدهور الذاكرة والعوامل التالية: العمر، والتعليم، ومدة المرض، ومدة العلاج، ونوع الدواء المأخوذ في الفترة الحالية، ودرجة مقياس تمديد حالة الإعاقة.

خاتمة: أثبتت الدراسة بأن تدهور الذاكرة من الإعاقات المنتشرة بين مرضى تصلب الأعصاب المتعدد، وهذه الإعاقة قد تسوء بزيادة العمر، وزيادة مدة المرض، ولذلك فإنه يجب معاينة مثل هؤلاء المرضى على فترات متقطعة من أجل تقييم حالة الذاكرة ومدى تدهورها.

Objectives: To determine the prevalence of memory impairment and to explore the determinant factors of memory impairment severity in patients diagnosed with multiple sclerosis (MS).

Methods: A cross-sectional study was conducted in the Neurology Center of Shafa Hospital in Kerman, Iran between February and November 2008 on 100 MS patients whose diseases were confirmed by a neurologist. Patients were recruited by the convenience sampling method. Data regarding age, gender, education, and occupation were collected; medical history including co-morbidities and drug history was recorded. All the patients were examined with routine neurological examination and the Extended Disability Status Scale (EDSS), and memory impairment was assessed by standard metal status questionnaire in 7 segments.

Results: Generally, 71% of patients had memory impairment. Among the affected patients, 35% of patients had mild to moderate, 19% had moderate to severe, and 17% had severe memory impairment. The relationship between the severity of memory impairment and age, education, duration of disease, the duration of treatment, currently used drug, and EDSS score was statistically significance.

Conclusion: Memory impairment is a common disability in MS patients, which worsen with age and longer duration of disease. Such patients with chronic disease should be intermittently screened for memory impairment.

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Multiple sclerosis (MS) is the most commonly diagnosed demyelinating disease of the CNS, which is due to a chronic inflammatory process in the CNS. The mean age of onset is 20-30 years old, and women are approximately 1.4-3.1 times more likely to

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be affected.[1,2] Considering the age of patients, MS is an important cause of disability in young adults.[3] The disease prevalence has been estimated at more than 30 per 100,000 in Southern Europe,[2,3] which is one of the regions with a high prevalence of the disease.[4] A previous study in Kerman reported a prevalence of 30-60 per 100,000.[5] Memory, cognition, and judgment impairments are among common features of MS, which have been somewhat neglected; while, they have a marked importance in devastating outcomes compared to physical problems. There are a wide range of changes, from an apparent impairment to a completely hidden one, which cannot reveal the primary changes even by complicated psychological investigations.[2] In such patients, memory impairment includes problems with information processing,[6,7] using semantic properties of information,[8] verbal memory,[9] executive functions of memory,[10] immediate memory and learning capacity,[11] and long term memory.[11,12] Briefly, MS causes significantly diminished performance across all memory variables whilst, some studies report that short-term memory is intact.[10,13] The prevalence of memory deficits in MS patients is around 40-60%.[11] In one study,[14] approximately 25% of the patients had normal memory performance, while around 22% exhibited severe amnesia-like disturbance, and 53% showed mild to moderate memory impairments. Previous assessments of memory disturbance in MS patients have yielded controversial findings regarding the prevalence of memory deficits,[11,14] and its relationship to socioeconomic status.[4] In this study, the aim was to investigate the prevalence of memory impairment among MS patients in Kerman, and to describe the most important factors that contribute to memory dysfunction.

Methods. This cross-sectional study was performed in the Neurology Center of Shafa Hospital in Kerman, Iran between February and November 2008. The participants were 100 patients with MS, selected using consecutive sampling. They were recruited from the Neurology Center of Shafa Hospital in Kerman City, and also from private neurology clinics. Patients with a clinically confirmed MS diagnosis and the presence of McDonald's criteria on MRI[2] were included in the study. Patients with a history of neurologic disease other than MS (for example, stroke, traumatic brain injury), history of mental retardation, psychotic disorders, dementia or psychological disorders, especially depression (Beck questionnaire if necessary) were excluded from the study. Informed consent was obtained from all the patients before enrollment. Approval was obtained through the ethics committee of the Vice Chancellor for Research of Kerman University of Medical Sciences.

In this study, demographic data (age, gender, education, and occupation) were recorded in a questionnaire, and a standardized test was used to evaluate memory function. The standardized memory impairment recognition test[15] includes 7 indexes (**Table 1**), which are utilized for assessment of different parts of the memory system. All sections of the memory assessment questionnaire were completed by asking family members of patients, and also some parts were double checked against their medical records. Scores for each of the 7 sections, and a total score was calculated. A score of 80 or more was considered as normal memory, a score of 60-80 was considered as mild to moderate memory impairment, and a score of 40-60 indicated moderate to severe dysfunction. Those with scores lower than 40 were considered to have severe memory disturbances. The patient's Expanded Disability Status Scale (EDSS)[6] was determined by a neurologist.

All the data were analyzed using the Statistical Package for Social Sciences for windows, version 10 (SPSS Inc., Chicago, IL, USA). To compare the proportions between the 4 groups of memory impairment for variables of patient and disease, we used Kruskal-Wallis, and to compare means between them, one-way ANOVA test with Post Hoc test was applied. To find any correlation between memory impairment and other variables, Spearman correlation was used. *P*-values less than 0.05 were considered significant.

Table 1 - Memory assessment questionnaire.

Test	Assessment
A. Repeating numbers	Attention scale
B. Relevant pairs learning	New learning (verbal memory)
C. Visual memory (hidden things)	Power of verbal memory and weakness of learning
D. Visual memory (reconstruction of seen scheme)	Visual memory impairment
E. Telling a story due to immediate recall	Short verbal memory
F. Irrelevant words	Ability of learning new information
G. Secondary (long-term) memory and Personal perception	Recalling personal and historical events Asking about time and place, which shows the recent memory

Table 2 - The degree of memory impairment by different demographic variables.

Characteristics	Degree of memory impairment				
	Normal memory (N=29)	Mild to moderate (N=35)	Moderate to severe (N=19)	Severe (N=17)	*P*-value
Gender (male %)	27.3	31.8	18.2	22.7	0.88
Age (mean±SD)	27.97±7.3	33±9.6	35.16±8.6	38±9.6	<0.001
Education (%)					
Below diploma	5	10	40	45	
Diploma	19.15	44.7	19.15	17	
Bachelors	58.6	34.5	6.9	0	
Masters	33.3	66.7	0	0	
Doctorate	100	0	0	0	
Duration of disease, years (mean±SD)	2.9±3.6	5.8±5.7	3.6±2.2	6.1±4.9	0.002

Results. The mean age of the patients was 32.8±9.3, and 78% of patients were female. Approximately 71% of the patients had memory impairment, of which 35% of them had mild to moderate impairment, 19 patients (19%) had moderate to severe dysfunction, and 17 (17%) had severe impairment of memory function. A considerable portion of the patients were housekeepers (34%). **Table 2** summarizes the results of demographic variables among the various degrees of memory impairments. The relation between age and severity of memory impairment was significant (p=0.001) as the older patients had severe types of memory impairment. To determine the association between severity of memory impairment and demographic variables (age and education), Spearman correlations were computed. They were both significant. Age and severity of dysfunction were positively correlated (r=0.384, p<0.001). Education and severity of dysfunction were negatively correlated (r=−0.557, p<0.001). The mean duration of disease was 68.31±6.66 months, with the normal memory patients having the least duration, and the patients with severe memory impairment having the longest disease course. One-way ANOVA test showed a significant difference between groups (p=0.002). Tomhone's T^2 post hoc test showed that the difference between normal and severe groups for disease duration was significant (p=0.037). **Table 3** summarizes the analysis of disease characteristic and cognitive performance (raw score) among the various degrees of memory function. Seventy-nine patients were using intramuscular interferon-beta-a1

Table 3 - Disease characteristics and cognitive performances.

Characteristics	Cognitive performance impairment				
	Normal memory (N=29)	Mild to moderate (N=35)	Moderate to severe (N=19)	Severe (N=17)	*P*-value
Onset and treatment interval (mean±SD)	16.12±30.41	39.94±51.47	34.19±38.61	85.29±102.28	0.003
Duration of disease (%)					0.002
<5	39.6	37.7	15.1	7.6	
5-10	18.6	25.9	29.6	25.9	
<10	15.0	40.0	15.0	30.0	
Last Drug (%)					0.028
Avonex	39.2	39.2	11.8	9.8	
Rebif	20.0	20.0	10.0	50.0	
Betaferon	22.2	27.8	22.2	27.8	
Mitoxantrone	7.7	38.5	38.5	15.3	
EDSS score (%)					<0.001
0 & 1	42.8	46.9	8.2	2.1	
>1	15.7	23.5	29.4	31.4	
Symptom (%)					0.86
Sensory	32.6	34.8	15.2	17.4	
Visual	27.3	45.4	21.2	9.1	
Brain stem	25.6	35.9	17.9	20.6	
Cerebellar	18.2	45.4	36.4	0.0	
Non specific	25.0	25.0	25.0	25.0	

EDSS - Exercise Disability Status Scale

(Avonex) during their disease, with a mean duration of 25.21±19.26 months. Twenty-four patients were using subcutaneous interferon-beta-a1 (Rebif) for 13.37±13.02 months, and 24 were using interferon-beta-b1 (Betaferon) for 12.36±10.49 months. Thirteen patients used Mitoxantrone during their disease for 12.08±7.8 months. All the patients used Solomedrol during the acute phase of disease. In the normal memory group, 79.3% of patients used Avonex whilst, 78.9% of patients with memory impairment used Avonex during their disease. Spearman correlation shows no significant correlation between the severity of memory dysfunction and the duration of use if each drug during the disease; however, there was a significant difference (p=0.028) between the last used drug and severity of the impairment. Avonex takers had less severe impairment of memory, while patients who were using Mitoxantrone, Betaferon, and specially Rebif showed a range of severe impairments. The most frequently observed symptoms among men and women were brain stem (45.4%) and sensory symptoms (47.5%). There was no significant difference between gender and severity of memory impairment (p=0.88). Seventy percent of the patients were mono symptomatic at the onset, while others had more than one symptom. No significant difference was seen between mono/poly symptomatic type of onset and the degree of memory impairment. Sensory impairment was the most common symptom (46%) among patients who did not have memory dysfunction, whilst other symptoms were brain stem, visual, cerebellar, and non-specific (including headache, tremor, urinary symptoms, musculoskeletal pain, and seizure) impairments. The same pattern was seen among patients with memory impairment. The relation between any of the symptoms and the degree of memory disturbance was not significant. The mean interval between time of diagnosis and time of treatment initiation was 16.12±30.41 months in patients with normal memory function. Evaluating the relationship between mentioned interval and the severity of memory impairment, a significant difference was discovered (p=0.003). Tukey's post hoc test displayed that the difference between normal and severe memory impairment groups regarding the interval between diagnosis and treatment, was significant (p=0.001), while the differences between severe groups and moderate to severe or mild to moderate groups were borderline statistically (p=0.053 and p=0.064). Among the patients, the minimum EDSS score was 0 and the maximum score was 7.5. Spearman correlation revealed a significant positive relation between EDSS score and the severity of memory dysfunction (r=0.535, p<0.001). As shown in **Table 3**, most patients with a score >1 had severe types of memory dysfunction. Assessing the memory impairment test, more frequent mistakes were in visual memory and short verbal memory.

Discussion. Multiple sclerosis is known to be the most common demyelinating disease of the CNS, and a major leading cause of disability in young adults. Some of the common features of MS are memory and cognitive impairment. There is controversy on the relationship between memory impairment and clinical variables. Some studies reported that memory dysfunction is related to impairment of other cognitive functions, lower socioeconomic status, chronic progressive type of MS, use of anti-anxiety medication,[16] years of evolution,[11] clinical features of MS, and neurological disability,[17] and mainly, the disease course.[11,17] But not related to severity of physical disability, duration of MS symptoms, or depression.[11,13] Significant memory improvement has been reported in MS patients after treatment. Appropriate patient selection is important, because patients with moderate to severe memory impairment gain greater benefit with treatment.[18] Some studies have shown that memory impairment in most MS patients is relatively mild and potentially treatable.[19]

The present study shows that 71% of MS patients exhibited memory impairment. This observed difference may be due to lower socioeconomic status and lower educational level in our area. Most of our patients were between 20-29 years old, which is approximate to the peak age of disease, and similar to a previous study that was performed among an MS population in Kerman, Iran.[5]

Although the results of our study showed that there is a direct significant relation between age and severity of memory impairment, some recent studies discuss that early onset of disease seems to be a desirable factor.[3] Seventy-eight percent of our patients were female, which is 4.8 folds greater than men, while the female/male ratio reported in recent studies is 1.4-3.1.[2] Although the prognosis of MS among women is better than men,[3] we found no significant relation between gender and the degree of memory impairment.

With increasing years of evolution of the disease, the disability of the patient becomes greater,[4] which is identical to the results of our study. Duration of use of each drug during the disease did not have a significant relationship with the degree of memory disturbance, however, the last used drug had a significant relation, since fewer patients who used Avonex as their last drug, showed less moderate to severe or severe impairments. Presumably this relation is caused by different choices for the first drug, since most of the patients choose Avonex as the first drug during their course of disease, because of its weekly injections. On the other hand, people with the secondary progressive type of MS chose

Mitoxantrone as their first drug. Some recent studies show that Avonex had beneficial effects on the domains of information processing and learning/memory in MS patients.[20] Previous studies have shown that immunomodulator drugs such as interferon-beta-1b, in addition to a decrease in the relapse rate and slowing of the disease progression, inhibits deterioration of cognitive impairment in MS patients.[21]

Although in our study there was no specific relation between mono/poly symptomatic type of onset and severity of memory impairment, some studies report that the mono symptomatic type of onset causes a better prognosis than poly symptomatic.[2] In contrast to our results, Thornton et al[17] reported that clinical features of MS are related to memory dysfunction. The interval between diagnosis and time of treatment initiation had a negative correlation with severity of the memory disturbance, but there is no definite conclusion on this relationship in previous studies, as the appropriate medication may not have been introduced at an early stage.[2] As the duration of disease evolution increases, disability scale and EDSS score of the disease course rise distinctly. Our results, similar to Thornton's study,[17] show a significant direct relation between EDSS score and degree of memory impairment. However, some studies reported that memory dysfunction is not related to physical disability.[11,13]

Evaluating patient mistakes in the memory impairment test, patients had the most frequent mistakes in visual memory and short verbal memory. Other studies exhibited significant impairments in executive processes,[10] information processing,[6,7] using semantic properties of information,[8] verbal memory,[9] immediate memory and learning capacity,[11] and long term memory.[11,12] All in all, there is a significant impairment across all memory domains,[9,17] whereas short-term memory, language, and global intellectual efficiency were normal.[10,13]

The main limitation of this study was its cross-sectional nature and having no healthy age matched control group.

In conclusion, memory impairment is a common disability in MS patients, which worsens with age and longer duration of disease. Such patients with chronic disease should be intermittently screened for memory impairment. Mistakes in visual memory and short verbal memory were the most commonly diagnosed features of memory impairment. Patients using Avonex had better memory function in comparison with other drugs in our study; however, further investigations will help in confirming these results.

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