TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2009; 39 (4): 525-529
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0802-29

Funda KAPLAN[1]
Mehmet Hamid BOZTAŞ[2]
Canan YÜCESAN[1]
Yasemin GENÇ[3]
Nezih YÜCEMEN[1]
Nermin MUTLUER[1]

[1] Department of Neurology, Faculty of Medicine, Ankara University, Ankara - TURKEY
[2] Department of Psychiatry, Faculty of Medicine, Ankara University, Ankara - TURKEY
[3] Department of Biostatistics, Faculty of Medicine, Ankara University, Ankara - TURKEY

Risk factors for depression in multiple sclerosis patients

Aim: A search of the English language literature found only one study that reported there was no relationship between depression and functional systems impairment based on Kurtzke's functional systems score in MS patients. The present cross-sectional study was planned to test that result.

Materials and Methods: The study included 37 relapsing-remitting MS patients (25 female, 12 male) with an Expanded Disability Status Scale score ≤ 5.5. The patients underwent a complete neurological and psychiatric examination during a clinically stable phase of their illness.

Results: Twenty out of the 37 MS patients (54.1%) were determined to have depression. While cerebellar functional system impairment was observed in 15 of the 20 depressed MS patients (75%), it was observed in only 7 of the 17 MS patients without depression (41.2%) (P = 0.037). Cerebellar findings in neurological examination (OR = 7.6, P = 0.022) and a history of depression (OR = 9.7, P = 0.032) were significantly associated with having depression in MS patients.

Conclusions: Cerebellar findings in neurological examination and history of depression were independent risk factors for the presence of depression in MS patients during a clinically stable phase of their illness.

Key words: Multiple sclerosis, depression, cerebellum

Multipl skleroz hastalarinda depresyon risk etmenleri

Amaç: İngilizce literatürde multipl sklerozlu hastalarda depresyon ile herhangi bir fonksiyonel sistem tutulumu (Kurtzke) arasında ilişki olmadığını bildiren sadece bir çalışma vardır. Bu sonucu test etmek için bu kesitsel çalışma planlanmıştır.

Yöntem ve Gereç: Bu çalışmaya genişletilmiş özürlülük durum ölçeği <5,5 olan, atak ve iyileşmelerle seyreden 37 MS hastası (25 kadın, 12 erkek) dahil edilmiştir. Hastalara, hastalıklarının stabil döneminde ayrıntılı nörolojik ve psikiyatrik muayene yapılmıştır.

Bulgular: 37 hastanın 20'sinde (% 54,1) depresyon saptanmıştır. Depresyonu olan bu 20 hastanın 15'inde (% 75), depresyonu olmayan diğer 17 hastanın 7'sinde (% 41,2) serebeller fonksiyonel sistem bozukluğu saptanmıştır (P = 0,037). Nörolojik muayenede serebeller bulguların varlığı (OR = 7,6, P = 0,022) ve özgeçmişte depresyon öyküsünün olması (OR = 9,7, P = 0,032), MS'li hastalarda depresyon ile anlamlı istatistiksel ilişki göstermiştir.

Sonuç: Nörolojik muayenede serebeller bulgular ve özgeçmişte depresyon öyküsün varlığı, MS'li hastaların klinik olarak stabil oldukları evrede depresyon için bağımsız risk faktörleridir.

Anahtar sözcükler: Multipl skleroz, depresyon, serebellum

Received: February 20, 2008
Accepted: January 12, 2009

Correspondence
Canan YÜCESAN
Department of Neurology, Faculty of Medicine, Ankara University,
Ek bina, K blok, 3. kat,
06100 Talat Paşa Bulvarı,
Ankara - TURKEY

canan.yucesan
@medicine.ankara.edu.tr

Introduction

Multiple sclerosis (MS) is a chronic neurological disorder characterized by central nervous system inflammation, axonal demyelination, and the formation of sclerotic plaques. Among MS patients, 22%-54% have a lifetime risk of major depression according to epidemiologic studies (1). While the relationship between depression and functional disability in MS has been widely investigated, the relationship remains contentious. Moreover, it is not clear if depression is a result

of the lesions in particular brain regions in MS patients. Depression may be independent of the disease, may be a reaction to the disease, or may be directly related to the lesions of the disease.

We wanted to know if there was a relationship between depression and functional systems impairment in neurological examination that could indicate the risk factors for depression in MS patients. A search of the English language literature found only one study that reported there was no relationship between depression and functional systems impairment based on Kurtzke's functional systems score in MS patients (2). We designed this prospective study to test that result.

Method

This study included relapsing-remitting MS patients that were examined at the outpatient MS clinic at the Ankara University Faculty of Medicine Hospital between July 2004 and December 2005. Only patients with an Expanded Disability Status Scale (EDSS) score ≤ 5.5 were included the study. Patients with any chronic disease other than MS were excluded. Functional systems and disability level of the patients were assessed during a clinically stable phase of their illness based on Kurtzke's functional system scores and EDSS, respectively, by a member of the study team (F.K.) (3). Then the patients were interviewed with the Structured Clinical Interview for DSM-IV to determine if they were depressed (4) (M.H.B.). Furthermore, all patients were administered the Mini-Mental Status Examination (MMSE). The research protocol was approved by local medical ethics committee.

Data analysis was performed in 2 steps. First, the independent variables were analyzed using the chi-square test, Fisher's exact test, or Student's t test. Then, to determine the independent risk factors for having depression in MS patients, multiple logistic regression analysis was performed following the forward elimination approach. All variables with P values < 0.25 in univariate analysis were included in multivariate analysis. All computations were carried out with the SPSS v.11.5 (SPSS Inc., Chicago, IL, USA). Statistical values are given as mean ± standard deviation (SD), median, or percentage. Any P value < 0.05 was considered significant.

Results

Thirty-seven relapsing-remitting MS patients (25 female and 12 male) were included in the study. Mean age of the patients was 37.6 ± 9 (range: 20-55) years, mean disease duration was 152 ± 97 (range: 9-332) months, mean time between last attack and the study examination was 19 ± 21 (range: 2-73) months, and mean MMSE score was 27.9 ± 2.2 (range: 20-30). The median number of attacks was 4 (range: 2-20) and median EDSS score was 3.5 (range: 2-5.5). Nineteen of the 37 patients (51.3%) were using an immunomodulatory drug (17/19 used interferon beta, 2/19 used glatiramer acetate) (Table 1).

Twenty of the 37 patients were determined to have depression (54.1%), according to their psychiatric evaluation (Table 1). There were no differences between the depressed and non-depressed MS patients regarding sex, age, duration of disease, time between last attack and psychiatric evaluation, MMSE score, number of attacks, and interferon use (P > 0.05 for each) (Table 2).

Mean EDSS score was 3.6 ± 0.9 (range: 2-5.5) in depressed MS patients and 2.9 ± 1.1 (range: 1.5-5.5) in

Table 1. Characteristics of the study sample (n = 37).

Variables	Statistic	Min-Max
Male/Female (n)	12/25	-
Depression, Yes/No (n)	20/17	-
Use of immunomodulatory drugs Yes/No (n)	19/18	-
Age (years)	37.6 ± 9	20-55
Duration of disease (months)	152 ± 97	9-332
Time between last attack and study examination (months)	7	2-73
MMSE score	29	20-30
Number of attacks	4	2-20
EDSS score	3.3 ± 1.2	2-5.5
Visual system	1	0-4
Brain stem	1	0-4
Pyramidal	2	0-4
Cerebellar	1	0-3
Sensorial	2	0-4
Bowel-bladder	1	0-2
Mental	0	0-1

Values are mean ± standard deviation for age, duration of disease, and EDSS score; median for others. EDSS: Expanded Disability Status Scale; MMSE: Mini-Mental Status Examination.

Table 2. Distribution of demographic measures, history of depression, and EDSS and functional system scores in depressed and non-depressed MS patients.

	Depression			P
	No	Yes	Total	
Gender				
Male, n (%)	7 (58.3%)	5 (41.7%)	12	0.295
Female, n (%)	10 (40%)	15 (60%)	25	
Age (years) (mean ± SD)	38.2 ± 10.3	37.1 ± 8.2	37	0.713
Duration of disease (months)	140.8 ± 105.1	165 ± 92.5	37	0.611
Time between last attack and study examination (months)	7 (2.3-73)	7.5 (2.3-55)	37	0.460
MMSE score	29 (20-30)	28 (25-30)	37	0.346
Number of attacks	4 (2-11)	4 (2-20)	37	0.869
Interferon use				
No	7 (41.2%)	10 (58.8%)	17	0.591
Yes	10 (50%)	10 (50%)	20	
History of depression				
No	15 (55.6%)	12 (44.4%)	27	0.073
Yes	2 (20%)	8 (80%)	10	
EDSS score				
EDSS $\leq$ 3	9 (60%)	6 (40%)	15	0.157
EDSS >3	8 (36.4%)	14 (63.6%)	22	
Brain stem				
No	9 (60%)	6 (40%)	15	0.157
Yes	8 (36.4%)	14 (63.6%)	22	
Cerebellar				
No	10 (66.7%)	5 (33.3%)	15	0.037
Yes	7 (31.8%)	15 (68.2%)	22	
Bowel-bladder				
No	9 (60%)	6 (40%)	15	0.157
Yes	8 (36.4%)	14 (63.6%)	22	
Mental				
No	16 (53.3%)	14 (46.7%)	30	0.097
Yes	1 (14.3%)	6 (85.7%)	7	

EDSS: Expanded Disability Status Scale; MMSE: Mini-Mental Status Examination.

non-depressed MS patients; the difference was not statistically significant (P = 0.056). Although the difference in mean EDSS was not statistically significant between the depressed and non-depressed MS patients, we used an EDSS cutoff score of 3 to eliminate the effect of disability on having depression. EDSS score was ≤ 3 in 15 patients (group 1) and was > 3 in 22 patients (group 2). While 6 patients in group1 had depression (40%), 14 patients in group 2 did not (63.6%); the difference was not statistically significant (P > 0.05) (Table 2).

Functional systems involvement was considered to be present (if the score was ≤ 1) or absent (if the score was 0) according to Kurtzke's functional systems score (3). The presence of any functional system involvement was compared between depressed and non-depressed MS patients instead of the scores due to the small study population. While cerebellar functional system impairment was observed in 15 of the 20 depressed MS patients (75%) in neurological examination, it was observed in only 7 of the 17 non-depressed MS patients (41.2%); the difference was statistically significant (P = 0.037). The presence of other functional systems involvement, including pyramidal, brainstem, sensorial, bladder and bowel, visual, and mental functional systems, was similar in depressed and non-depressed MS patients (P > 0.05 for each).

Table 3 shows the results of multiple logistic regression analysis, including all remaining variables with univariate analysis P values < 0.25. Although univariate analysis P values for age, sex, and interferon use were > 0.25, we also included them in multivariate analysis. Table 3 shows that cerebellar findings were significantly associated with having depression (odds ratio (OR): 7.6; 95% CI: 1.3-43.2) according to multivariate analysis. In addition, a history of depression resulted in having depression later in the course of the disease (OR: 9.7; 95% CI: 1.2-76.8). Other variables studied with multivariate analysis had no statistical significance.

Table 3. Results of multiple logistic regression analysis of the risk indicators for depression in MS patients.

	OR (95% CI)	P
Cerebellar findings		
Yes	7.6 (1.3-43.2)	0.022
No	1.00	
History of depression		
Yes	9.7 (1.2-76.8)	0.032
No	1.00	

OR; Odds ratio; CI; confidence interval.

Discussion

Depression is reported to occur in 22%-54% of MS patients in different studies (1). Clinical depression was observed in 54.1% of MS patients in the present study, which is compatible with some previous reports. It has been reported that emotional disorders occur most frequently immediately after an MS attack and that emotional disorders might be strongly influenced by disease activity at the time of examination (5). To exclude this probability, we studied MS patients during a phase of disease remission.

Interferon use, age, and sex were unrelated to depression in the present study, which is similar to the results of other studies (1,2,6). Furthermore, level of disability had no effect on depression, as reported by Gottberg et al. (7); however, some studies have reported a relationship between depression and disability (8,9). The lack of such a relationship in the present study may have been because we only included MS patients with an EDSS score ≤ 5.5.

A past history of depression was related to a 9.7-fold increase in the likelihood of having depression, according to the present study's results. It is understandable that patients with a past history of depression are more likely to have depression in the present. It is interesting that cerebellar findings were associated with an almost 7.6-fold increase in the likelihood of having depression, as compared to the absence of cerebellar findings in neurological examination, which was independent of the other factors studied and is reported here for the first time. What might be the reason for this result? First, it may be related to the small study population, a major limitation of the study. Second, the MS patients in the present study were recruited from an MS outpatient

clinic and might not be representative of the MS population in general. Depression was reported less frequently than in our study in another recent MS study based on a Swiss population (7). The higher frequency of depression in the present study might have resulted in a more exaggerated relationship between depression and cerebellar findings. Third, lesions located in cerebellum and/or anywhere else along the path from the cortex to cerebellum may cause not only cerebellar findings in neurologic examination, but also depression in MS patients. There have been some reports suggesting that the cerebellum might play a role in mood regulation (10-14); however, findings regarding the relationship between mood regulation and the cerebellum are inconsistent.

According to the results of the present study, in addition to patients with a past history of depression, patients with cerebellar findings in neurological examination should be aware of the potential to develop depression. Nonetheless, due to our small study population, the results should be confirmed by research including larger MS populations; if they confirmed, it will be important for future research.

References

1. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. Am J Psychiatry 2002; 159: 1862-1868.
2. Gilchrist AC, Creed FH. Depression, cognitive impairment and social stress in multiple sclerosis. J Psychosomatic Res 1994; 38: 193-201.
3. Kurtzke JF. Rating neurological impairment in multiple sclerosis: An expanded disability status scale EDSS. Neurology 1983; 33: 1444-1452.
4. First MB, Spitzer RL, Gibbom, M, Williams J. Structured Clinical Interview for Axis 1 DSM-IV Disorders, Biometrics Research Department, New York State Psychiatric Institute, New York Patient Edition 1994 (SCID-I/P, Version 2.0).
5. Dalos NP, Rabins PV, Brooks BR, O'Donnel P. Disease activity and emotional state in multiple sclerosis. Ann Neurol 1983; 13: 573-577.
6. Porcel J, Rio J, Sanchez-Betancourt A, Arevalo MS, Tintore M, Tellez N et al. Long term emotional state of multiple sclerosis patients treated with interferon beta. Mult Scler 2006; 12: 802-807.
7. Gottberg K, Einarsson U, Fredrikson S, von Koch L, Holmqvist LW. A population-based study of depressive symptoms in multiple sclerosis in Stockholm county: association with functioning and sense of coherence. J Neurol Neurosurg Psychiatry 2007; 78: 60-65
8. Tsivgoulis G, Triantafyllou N, Papageorgiou C, Evangelopoulos MF, Kararizou E, Sfagos C et al. Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. Acta Neurol Scand 2007; 115: 67-72
9. Ayatollahi P, Nafissi S, Eshraghan MR, Kaviani H, Tarazi A. Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. Mult Scler 2007; 13: 275-277
10. Escalona PR, Early B, McDonald WM. Reduction of cerebellar volume in major depression: a controlled magnetic resonance imaging study. Depression 1993; 1: 156-158.
11. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561-579.
12. Starkstein SE, Robinson RG, Berthier ML, Price TR. Depressive disorders following posterior circulation as compared with middle cerebral artery infarcts. Brain 1998; 111: 375-387.
13. Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ et al. Neuroanatomical correlates of externally and internally generated human emotion. Am J Psychiatry 1997; 154: 918-925.
14. Schutter DJ, van Honk J. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. J Psychiatry Neurosci 2005; 30: 91-97.