Stress differentially predicts multiple sclerosis relapses

[1,2]Shahram Oveisgharan MD, [1]S Simindokht Hosseini MD, [4]Mohammad Arbabi MD, [1,3]Shahriar Nafissi MD

[1]Neurology department, [3]Iranian Center of Neurological Research, [4]Psychiatry department, Tehran University of Medical Sciences, Tehran, Iran; [2]Surveillance Department, Isfahan Cardiovascular Research Institute, Isfahan, Iran

Abstract

Background and Objective: For decades, stress has been postulated as a risk factor for multiple sclerosis (MS) relapses. Because of conflicting results in previous studies we conducted a prospective study to investigate this relationship in a less studied, Middle Eastern population. *Methods:* In this prospective study, 57 Iranian MS patients were followed trimonthly for 12 months. Possible stressful events (measured with validated Persian version of Paykel's questionnaire) and quality of life (measured with validated Persian version of the Multiple Sclerosis Impact Scale questionnaire) were assessed in successive visits in addition to other variables. Relapses were enquired and confirmed clinically by a Neurologist. Main analysis was done by use of Mixed Generalized Linear Model. *Results:* Mean age of the participants was 33.5 ± 7.4 years, 81% were females, and all were receiving interferons. Number of stressors, not the stress severity measures, reached near significance in predicting relapses (p=0.054), and showed a trend towards significance in predicting severe relapses (p=0.082). Education and number of previous relapses were the only variables that had a near significance interaction with number of stressors in its association with MS relapse. This association was only significant among subjects with less than college education (P=0.008) and subjects with more than 2 relapses (p=0.038).

Conclusion: Number of stressors, not their severity, was associated with MS relapses among Iranian patients. This association had interaction with education and history of previous relapses; it was significant only among lower educated patients or patients with more prior relapses.

INTRODUCTION

Multiple Sclerosis (MS) is the most frequent demyelinating disease of the central nervous system, affecting about 2.5 million people worldwide, and can cause loss of many years of healthy life.[1] In its most common form, seen in 85-90% of the patients, it has a relapsing-remitting course. Factors identified as relapse promoters are infections, high-dose cranial radiation, termination of pregnancy, and Central Nervous System (CNS) trauma.[2] Stress had been postulated as a risk factor for MS relapse since 1877.[3] Although some studies has found no association between stress and MS relapse or even a protective role[4,5], most studies, reviews and meta-analysis have found stress as a MS relapse provoking factor.[3,6,7] A meta-analysis of 14 studies has found stress as a relapse provoking factor, but of moderate size.[8] This effect size was not changed significantly by study design, use of validated vs. invalidated stress measurement, being female, or age of participants. We speculated that other factors might be important in moderating stress MS association such as education and MS patients' quality of life. Also, most studies have been done in Western countries, and we were interested to see if the stress-MS association exists among Iranian MS population.

METHODS

Fifty seven consecutive patients with clinically definite MS (McDonald criteria)[9] with a relapsing-remitting course were recruited at a MS clinic in Shariati Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. The study was in accordance with the protocol and ethical principles stated in the Declaration of Helsinki, and was approved by ethical committee of Tehran University of Medical Sciences. Written informed consent was obtained from all patients, after the description of the study process. Patients with major co-morbid disease and substance users were excluded. Patients were included if they had Expanded Disability Status Scale (EDSS) less than 5.

Address correspondence to: Shahriar Nafissi, Neurology ward, Shariati Hospital, North Kargar St., Tehran, Iran. Tel: +98 912 1060727, Fax: +98 21 88633039, Email: s_nafissi@yahoo.com

Sociodemographic and disease related information were recorded in previously prepared forms at the inclusion. Stressful events were assessed by Paykel's checklist for recent life events, covering 65 clearly defined events, also containing a question about any additional stressful event not specifically included in the checklist. They were asked if each event had happened in the previous three months. Patients were asked to score distress associated with each event with a number from 1 to 20. Events that were directly caused by MS were omitted from the list. A validated Persian version of Paykel's questionnaire was used.[10]

Every patient filled the checklist at the beginning of the study, and trimonthly up to four times. Number of stressors, sum and mean of the severity scores, were calculated as the indices of stress for each three months period. Patients were asked about stressors in an independent manner from the exacerbations, to decrease the possible biases caused by distress associated with the exacerbation itself. Quality of life (QoL) was also assessed trimonthly, by means of a validated Persian version of the MSIS-29 (Multiple Sclerosis Impact Scale) questionnaire.[11] MSIS-29 is a MS-specific QoL questionnaire that measures self-reported disease impact on patient's day-to-day life. The MSIS-29 consists of 29 questions assessing the physical and psychological impact of MS on patient's daily life; higher scores indicate lower QoL. MSIS-29 is proven to be a reliable and sensitive measure to assess the impact of MS on the patient's quality of life and to monitor physical and psychological aspects of health in MS patients in longitudinal studies.[12, 13]

Patients underwent a thorough neurological examination by a Neurologist at entry and every three months thereafter. The examiner remained the same during the study period. EDSS and Kurtzke Functional Systems Scores (FSS) were determined. Type of exacerbation and its severity, determined by the examiner's evaluation, and need to admission and methylprednisolone pulse therapy were recorded by the Neurologist.

SPSS software (SPSS Inc., version 20, Chicago, USA) was used for data analysis. Mixed Generalized Linear Model was used as the main type of analysis, with logit function as the link function for outcome variable (relapses). Mixed model is preferred over Generalized Estimating Equations when there is unbalanced data (4 of our 57 patients did not participate in the 4th follow up visit). In our model, multiple measurements on a single patients were entered in the model by use of autoregressive covariance matrix. Interested variables were entered as fixed effects.

Independent sample t-test or Mann-Whitney test was used to compare continuous variables according to normality. Chi square statistics was used to assess relation between discrete variables. $P < 0.05$ was considered statistically significant.

RESULTS

The study patients' characteristics are shown in Table 1. Their mean age at the study entry was 33.5 (18-49) years, and 81% were females. All the patients were receiving IM IFN β-1a once every week, except one who was receiving subcutaneous IFN β-1b every other day. Some of the patients also used group B vitamins, calcium and vitamin D supplements, and low dose antidepressants. Fifty three out of 57 patients completed one year of follow up and only four patients (7%) did not attend the 4th follow up session.

There were 42 relapses recorded during the one year follow up. The estimated relapse rate was 0.73. Twenty five patients (44%) did not experience any exacerbation; 23 patients (40%) had one exacerbation, eight (14%) had two and one patient had three exacerbations during the study period. Patients who experienced relapses during the study period had more relapses in their previous disease courses (P-Value =0.007). Severity of the exacerbations was clinically estimated as mild in 38%, moderate in 29%, and severe in 33%. In 54.7% of relapses, hospital admission and corticosteroid pulse therapy were required.

Table 2 shows determinants of relapses in the first visit of our study patients. Number of previous relapses was the only significant predictor of relapse. None of stress measures (number, mean, and sum of stressors) was associated with relapse in the three months prior to visit. Subjects with relapses had 3.10±1.92 stressors which was comparable with subjects without relapse (4.00±3.28). Also, when the analysis was restricted to severe relapses (defined by use of corticosteroid pulse), stress measures remained non-significant in associations.

Table 3 shows results of Generalized Linear Mixed Models (GenLinMix) which were used to analyze association between stress and relapses during follow up of our patients for 12 months. Number of stressors, not the stress severity measures, was the only factor which reached near significance in predicting relapses (p=0.054), and showed a trend towards significance in predicting severe relapses (p=0.082).

Table 1: Patients characteristics at entry

Total patient number =57 patients

Age at first MS manifestation, mean year (SD[†],range)	28.83 (7.43, 8-46)
Age at diagnosis, mean year (SD[†],range)	30.08 (7.10,12-46)
Age at entry, mean year (SD[†],range)	33.51 (7.37,18-49)
Marital status 　Single, n(%) 　Married, n(%) 　Divorced/widowed, n(%)	 14 (24.6) 39 (68.4) 4 (7.1)
Education, mean year (SD[†])	12.49 (3.75)
<= 12 years	34 (59.6)
> 12 years	21 (36.8)
Unknown	2 (3.5)
No. of pervious exacerbation, median (range)	2(1-10)
No. of pulse till entry, median (range)	2 (0-7)
EDSS at entry, mean (SD[†],range)	2.16 (1.44,0-5)

[†]SD: Standard Deviation; EDSS: Expanded Disability Status Scale

Table 4 shows GenLinMix when another potential confounding variable was added to the above model. Education and number of previous relapses were the only variables that had a near significance interaction with number of stressors. Table 5 shows stratified GenLinMix between number of stressors and relapses in different educational groups (those with less than college vs. college or higher education). Only among lower education group, number of stressors was significant predictor of relapses. Also, there was no significant difference between lower vs. higher educational groups in the number of stressors (3.39±3.13 vs. 3.06±2.62, respectively, p=0.635). Among lower education patients, number of stressors was also predictive of severe relapses which needed corticosteroid uses (coefficient=0.183, p=0.030). However, stress severity did not have any effect.

Table 2: Association of potential risk factors with first-visit relapse and severe relapse (defined by use of corticosteroid pulse) rates

	Corticosteroid Pulse	Relapse
Sex	0.58[†]	0.10[†]
Age	0.38[†]	0.58[†]
Education	0.64[†]	0.896[†]
Marital status	0.65[†]	0.268[†]
Number of previous exacerbations	0.13[†]	0.04[†]
EDSS	0.32[†]	0.19[†]
Number of stressor	0.47[†]	0.53[†]
Mean of stressor	0.73[†]	0.56[†]
Sum of stressors	0.31[†]	0.282[†]
MSIS	0.49[†]	0.43[†]

[†] Numbers are P values.
EDSS: Expanded Disability Status Scale; MSIS: Multiple Sclerosis Impact Scale

Table 3: Generalized Linear Mixed Models for analysis of association between stress and relapses during follow up of our patients for 12 months

	Relapse	Use of corticosteroid
Coefficient=0.108; P=0.054	Coefficient=0.128; P=0.082	Number of stressors
Coefficient=0.004; P=0.264	Coefficient=0.007; P=0.143	Sum of stressors
Coefficient=0.012; P=0.648	Coefficient=0.040; P=0.305	Mean of stressor severity score

Number of previous relapses was another factor with near significant interaction with number of stressors on its effect on relapses. Table 5 shows number of stressors to be a significant predictor of relapses only among subjects with more than 2 relapses prior to the study. Among this group, number of stressors reached near significance in prediction of severe relapses which required use of corticosteroids (coefficient=0.198, p=0.053).

DISCUSSION

In our study, we found number of stressors, not their severity, as a relapse promoting factor among Iranian MS patients. This association had an interaction with education and previous relapses: stress was a relapse risk factor only in lower educated patients and in those with more relapses.

In a meta analysis of 14 studies, Mohr *et al.* found stress related to MS exacerbation homogenously.[8] In another published study after this meta-analysis, Mitsonis *et al.* found MS women who experienced more stressful life events were at greater risk of MS relapses.[6] However, Nisipeanu and Korczyn found stress as a risk reduction factor for MS relapses.[5] They found less relapses during Persian Gulf War of 1991 among 32 Israeli MS patients who were exposed to threat of missile attacks. Severe stress (exposure to missile attacks in Nisipeanu and Korczyn's study) can induce release of cortisol which is anti-inflamatory and is different from moderate stressors which we experience in our daily lives. This hypothesis is in line with MS animal model studies, experimental allergic encephalomyelitis, in which stressors such as foot shock delayed or diminished the severity of the disease, but milder stressors increased the severity of the disease.[14]

We did not find any association between perceived severity of stressors and MS relapses. Likewise, Mitsonis *et al.* did not find severity of stressors associated with MS relapses, although the severity was judged by trained Psychiatrists, not the patients.[6] Likewise, Potagas *et al.* did not find stress severity associated with MS relapses in

Table 4: Generalized Linear Mixed Models for analysis of association between stress and relapses during follow up of our patients for 12 months when a second potentially confounding variable was added

	Coefficient (P Value) of their interaction	Coefficient (P Value) of number of stressors	Coefficient (P value) for the added predictor
Age[†]	-0.009(0.936)	0.109 (0.246)	0.227(0.688)
Gender	0.057(0.667)	0.011(0.964)	-0.033(0.962)
Marital status	0.081(0.579)	0.040(0.765)	-0.145(0.811)
Disease duration[†]	-0.027(0.821)	0.135(0.155)	-0.271(0.635)
Education	0.231(0.079)	-0.043(0.700)	-1.083(0.062)
Quality of life (MSIS)	0.040(0.747)	0.073(0.314)	-0.341(0.542)
EDSS at entry	0.043(0.334)	-0.010(0.94)	-0.059(0.747)
Number of previous relapses	0.045(0.094)	-0.058(0.600)	-0.003(0.976)

[†]Age: categorized to less than vs. equal to or greater than 35; disease duration: less than vs. equal to or greater than 4; education: equal to or less than vs. greater than 12 years; MSIS: equal to or less than vs. greater than 50; MSIS: Multiple Sclerosis Impact Scale; EDSS: Expanded Disability Status Scale

Table 5: Subgroup analyses of association between number of stressors and MS relapses

Subjects	Odds Ratio	95% confidence interval for Odds Ratio	P value
With less than college education	1.21	1.05-1.39	0.008
With college or higher education	0.96	0.77-1.19	0.71
With history of 1-2 relapses	1.01	0.86-1.20	0.87
With history of ≥ 3 relapses	1.19	1.01-1.41	0.04

a prospective study[15], although they found number of stressors related to MS relapse. Warren *et al.* found stress severity related to the MS relapses[16], but it was done in a case-control study which may suffer from recall bias.

As far as we are aware, none of previous studies has controlled for interaction between stress and other related variables in association between stress and MS relapse. In our study, like previous studies, the association between stress and MS relapses was modest, with Odds Ratio=1.11, and it seems logical to find subpopulations in which the association exists or is the strongest. We found education and previous relapses to have significant interactions with number of stressors in its association with relapses; the association existed only among lower educated patients and patients with more previous relapses. It is possible that higher educated patients use coping strategies such as emotion-focused coping to solve their stressors more efficiently than lower educated one. Jean *et al*. showed that among MS patients high levels of psychosocial distress was associated with the use of emotion-focused coping strategies.[17]

Our study has some limitations; it was clinic-based, not population-based study. We could only study 57 subjects, in view of the small sample size, a modest effect may be overlooked due to lack of power. Our study had a prospective design but stress related questions were asked retrospectively which may result in recall bias. However, the questionnaires were filled every three months, and the recall bias could be less with repeated asking, and the analysis method (Generalized Mixed Linear Model). We could not use MS relapses objective measures, such as gadolinium enhanced MRI lesions, although we had strict clinical measures, and all the patients were clinically examined by one Neurologist.

The strengths of our study included use of a novel statistical method, generalized linear mixed model to control for correlations within a subject; search for interaction between potential confounding variables with number of stressors on its association with MS relapses; and use of validated instruments for measurement of stress related parameters and MS patient's quality of life.

In conclusion, we found number of stressors, not their severity, associated with MS relapses among Iranian patients. This association had interaction with education and history of previous relapses in a way that it was significant only among lower educated patients or patients with more than 2 prior relapses. We believe these findings have implications for clinicians in their consultations to patients, and researchers to explore more the association between stress and MS.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. WorldHealthOrganization. Neurological disorders: public health challenges. Geneva: World Health Organization, 2006.
2. Vollmer T. The natural history of relapses in multiple sclerosis. *J Neurol Sci* 2007; 256 (Suppl 1):S5-13.
3. Artemiadis AK, Anagnostouli MC, Alexopoulos EC. Stress as a risk factor for multiple sclerosis onset or relapse: a systematic review. *Neuroepidemiology* 2011; 36(2):109-20.
4. Gasperini C, Grasso MG, Fiorelli M, *et al*. A controlled study of potential risk factors preceding exacerbation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; 59(3):303-5.
5. Nisipeanu P, Korczyn AD. Psychological stress as risk factor for exacerbations in multiple sclerosis. *Neurology* 1993; 43(7):1311-2.
6. Mitsonis CI, Zervas IM, Mitropoulos PA, *et al*. The impact of stressful life events on risk of relapse in women with multiple sclerosis: a prospective study. *Eur Psychiatry* 2008; 23(7):497-504.
7. Goodin DS, Ebers GC, Johnson KP, Rodriguez M, Sibley WA, Wolinsky JS. The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1999; 52(9):1737-45.

8. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *BMJ* 2004; 328(7442):731.

9. Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58(6):840-6.

10. Pourshabbaz A. The relationship between life events stress and personality in patients with leukemia. Tehran: Tehran University of Medical Sciences, 1995.

11. Ayatollahi P, Nafissi S, Eshraghian MR, Tarazi A. Cross-cultural adaptation of the Multiple Sclerosis Impact Scale (MSIS-29) for Iranian MS patients. Evaluation of reliability and validity. *Tehran University Medical Journal* 2006; 64(1):62-8.

12. McGuigan C, Hutchinson M. The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure. *J Neurol Neurosurg Psychiatry* 2004; 75(2):266-9.

13. Ayatollahi P, Nafissi S, Eshraghian MR, Kaviani H, Tarazi A. Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. *Mult Scler* 2007;13(2):275-7.

14. Bukilica M, Djordjevic S, Maric I, Dimitrijevic M, Markovic BM, Jankovic BD. Stress-induced suppression of experimental allergic encephalomyelitis in the rat. *The International Journal of Neuroscience* 1991; 59(1-3):167-75.

15. Potagas C, Mitsonis C, Watier L, *et al*. Influence of anxiety and reported stressful life events on relapses in multiple sclerosis: a prospective study. *Mult Scler* 2008; 14(9):1262-8.

16. Warren S, Warren KG, Cockerill R. Emotional stress and coping in multiple sclerosis (MS) exacerbations. *J Psychosom Res* 1991; 35(1):37-47.

17. Jean VM, Beatty WW, Paul RH, Mullins L. Coping with general and disease-related stressors by patients with multiple sclerosis: relationships to psychological distress. *Mult Scler* 1997; 3(3):191-6.