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A preliminary path analysis: Effect of psychopathological symptoms, mental and physical dysfunctions related to quality of life and body mass index on fatigue severity of Iranian patients with multiple sclerosis

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Depression, Anxiety, Stress, Quality of Life, Body Mass Index, Fatigue Severity

Abstract

Background: Multiple sclerosis (MS) is a neurological disease with fatigue as most prevalent symptom. Psychopathological symptoms, physical and mental dysfunctions and body mass abnormalities potentially could deteriorate fatigue. Thus, in this study, we aimed at evaluating the effect of these factors on fatigue severity of MS patients.

Methods: In this cross-sectional study, 162 patients with mean age of 34.1 ± 9.4 (16-58 years) were recruited by consecutive sampling. All the patients, after completing demographic information were evaluated using Persian versions of Fatigue Severity Scale (FSS), depression, anxiety and stress scale (DASS-21), and short form Health Survey Questionnaire (SF-36).

Results: Correlation analysis showed a significant relationship between fatigue severity and depression, anxiety, stress, physical component summary (PCS) and mental component summary (MCS) ($P < 0.01$). Findings of path analysis demonstrated that PCS is the only variable which has a direct effect on fatigue severity ($\beta = -0.278$, $P < 0.05$). Moreover, the strongest standard coefficient (β) belonged to cause and effect relationship between MCS and depression ($\beta = -0.691$, $P < 0.0001$).

Conclusion: Present study made the role of psychopathological symptoms and physical and mental dysfunctions prominent in exacerbation of fatigue severity. Moreover, we can refer to more sensible effect of physical dysfunction related to life on fatigue.

Introduction

Multiple Sclerosis (MS) is a neurological, degenerative, progressive, and chronic disease caused by demyelination in central nervous system (CNS).[1] Meanwhile, fatigue is a prevalent and irritating symptom in MS and there exists a little

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understanding of its causes.[2] This symptom appears in more than three fourths of the patients, but may be one of the least understood.[3]

Chronic nature of the disease, having no prognosis, no exact treatment and engaging the person in youth and middle age cause numerous psychological symptoms, within which the most prevalent are depression, anxiety and stress.[4] Psychopathological symptoms could potentially increase fatigue severity in patients. Existing data also show a relation between fatigue and depression,[5-15]anxiety[15-20] and stress.[11,15,21] In addition, fatigue is definitely linked to decrease in quality of life (QOL),[14,15,22-25] in both physical[26-28]and mental[27,29] dimensions, though the question of how fatigue affects quality of life is not clearly answered.[30] Perhaps fatigue by itself is affected by impairment in QOL. One of the main deficiencies of previous researches in this respect was their emphasis on QOL being affected by fatigue. In these studies, mental and physical dysfunctions are assumed to be related to QOL and its role on exacerbation of fatigue levels as one of MS outcomes is neglected. In fact, we may ask whether it is possible that fatigue be affected by disorders stemmed from mental and physical aspects of QOL, indirectly or through intermediary factors. Moreover, it seems that abnormality in body mass index (BMI) regarding its probable complications (obesity, weakness and thinness) is related with the fatigue resulted from MS. In fact, in people with fatigue, these outcomes can be effective. To this aim, studies have demonstrated the relation between BMI levels and increase of fatigue in professional truck drivers,[31] systematic lupus erythematosus,[32] and obese patients[33] as well as working population;[34] but BMI disorder and fatigue exacerbation in MS patients have not been evaluated directly. Scrutinizing background factors which cause fatigue can firstly increase our level of understanding and secondly cause development of appropriate planning and intervention protocol so as to increase coping and compatibility levels with these problems for different specialists (e.g. neurologists, psychologists, psychiatrists, etc.). Thus, the present study aimed at evaluating the effect of psychopathological symptoms, mental and physical dysfunctions and BMI on fatigue severity of MS patients through path analysis pattern.

Materials and Methods

Patients

Present research was performed using a cross-sectional design on MS patients under supervision of MS Society of Guilan Province (North of Iran). 162 patients were chosen by consecutive sampling method. Inclusion criteria included suffering from MS disease based on McDonald criteria[35] with confirmation of diagnosis by a neurologist. The existence of MS disease is determined by symptoms and clinical characteristics of the patient and also clinical evidence of lesion in two or more regions of central nervous system (CNS). In order to confirm the damage, paraclinical measures such as magnetic resonance imaging (MRI), evoked potential (EP) and cerebrospinal fluid (CSF) were conducted and patients who had a record at MS Society received confirmed diagnosis of disease based on mentioned findings. Moreover, the exclusion criteria involved: (1) Acute attack of MS disease; (2) severe cognitive problems in a way that patient could not be able to fill out the questionnaires or answer to the interviewer; and (3) existence of any debilitating disease or physical complications along with MS.

Procedures

This research was performed in MS Society of Guilan province and also Imam Reza Specialized and Sub-specialized Clinic in 2010. Rationales and method of performing the research was explained to eligible patients and they were assured that all related evaluations shall remain confidential. Thereafter, upon receiving informed consent, they were accepted to the research. Some of data gathering methods included clinical and demographic information and the others were related to mental and physical dysfunctions, fatigue severity and psychopathology symptoms of MS patients. Subjects must have first answered demographic information questions and then filled other questionnaires under supervision of a psychologist who was present at the location of study.

1. Demographics

Demographic characteristics of patients including age, gender, marital status, education level, duration of disease (month), number of relapse times, number of hospitalizations and type of MS were recorded. Type of MS was extracted from their recorded files in MS Society.

2. Fatigue severity scale (FSS)

Persian version of this tool was used to evaluate fatigue severity. The tool was invented by a neurologist called Lauren Krupp to evaluate fatigue in MS patients, a 9-item scale evaluating fatigue within a range of 1 to 7. Criterion validity of this tool has been reported to be 0.68 and its internal consistency coefficient as 0.88.[36] Checking different aspects of FSS Persian version in MS patients indicates that the Persian version is an appropriate psychometric tool in evaluation of MS patients.[37]

3. Depression, anxiety, stress scale (DASS-21)

This was first introduced by Lovibond & Lovibond (1995),[38] and the Persian version of it was used to evaluate psychopathology resulted from depression, anxiety and stress of the patients. Recent studies in

the field of neurologic disorders appearing in psycho-neuro forms have also confirmed this tool capable of evaluating several symptoms.[39] DASS includes 21 questions, each of 3 sub-scales of which includes 7 questions and scores of each is gained through sum of scores of related questions.[38] There are evidences confirming preliminary reliability and preliminary structure validity of Persian translation of DASS.[40]

4. Short-form health survey questionnaire (SF-36)

Taking advantage of this questionnaire, we evaluated physical and mental dysfunctions related to QOL. This instrument was designed by Ware and Sherbourne,[41] containing 36 questions and provides two summary measures of function; physical component summary (PCS) and mental component summary (MCS).[26] Each question in the tool gets from 1-100 scores and the nearer the score to 100, QOL is considered as better. In this field, a study was performed to measure the validity and reliability of Persian translation of SF-36 and the findings indicated its appropriateness to evaluate the perceptions of health.[42]

5. Body mass index (BMI)

Participants were weighed (light wearing and without shoes) via an identical analog-spring balance with accuracy of 100 gr (0.1 Kg) and their height was measured via a tape meter installed on the wall. Using the following equation BMI of the patient was calculated: BMI = weight (Kg) / height $(m)^2$.[43]

Statistical analysis

Pearson and Spearman correlation coefficients was used to investigate the relation hypotheses. Moreover, we used path analysis to determine the effective factors on fatigue severity in MS patients. This method is one of numerous statistical tests, subset of "Structural Equation Modeling" (SEM). This model is used to study direct and indirect effects of cause variable's upon effect variable. In fact, in path analysis, some variables directly and some indirectly and a group through both ways may affect dependent variable. Finally, data were analyzed by the SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

Considering inclusion and exclusion criteria, 162 patients within the age range of 16-58 years and mean of 34.1 ± 9.4 years were recruited. 29.6% of the patients were male and 70.4% female (due to more prevalence of the disease in women). As for the marital status, 21% were single, 75.9% married, 0.6% widow, and 2.5% were divorced. Again, 7.4% had primary school education, and 14.7%, 49.7% and 28.2% were of middle school, high school and university graduates, respectively. Mean duration of the disease (months) were 56.9 ± 56.1 month. About 11.1% of MS patients had no relapse of the disease, but 18.5%, 16.7%, and 15.4% had experienced once, twice and three time relapses, respectively. Moreover, record of 38.3% of the patients suggested more than 3 times relapse of the disease. Hospitalization background of participants showed that 38.3% were not hospitalized at all, and upon clinical biography 36.4%, 11.7%, 5.6% and 8% were hospitalized one, two, three and more than three times, respectively. It should also be mentioned that 72.8% of patients were of relapsing-remitting (RR) type, 2.5% primary progressive (PP) and 21% secondary progressive (SP). There were 3.7% patients with unknown type of MS. Eventually, BMI value in examined subject was 25 which according to World Health Organization (WHO-2004) is reflecting overweight of the patients.

Correlation analyses

Table 1 shows correlation coefficients among investigated variables in MS patients. A significant negative relation between fatigue severity and PCS ($r = -0.432$) and MCS ($r = -0.343$) was found ($P < 0.01$). There was a significant positive relation with depression ($r = 0.367$), anxiety ($r = 0.309$) and stress ($r = 0.282$) ($P < 0.01$). However, no considerable relation was seen between fatigue and BMI (Table 1). Upon Spearman statistical analysis, no statistically significant correlation was observed between fatigue

Table 1. Pearson Correlation Matrix in MS Patients

Variable	1	2	3	4	5	6	7	8	9
Age	1								
Duration	0.417**	1							
Depression	0.238**	0.119	1						
Anxiety	0.129	0.002	0.723**	1					
Stress	0.139	0.002	0.820**	0.770**	1				
PCS	-0.367**	-0.114	-0.607**	-0.644**	-0.546**	1			
MCS	-0.188**	-0.026	-0.711**	-0.658**	-0.700**	0.661**	1		
BMI	0.227**	-0.027	-0.020	0.037	-0.031	-0.157*	-0.046	1	
Fatigue	0.265**	0.123	0.367**	0.309**	0.282**	-0.432**	-0.343**	0.065	1

PCS: Physical component summary; MCS: Mental component summary; BMI: Body mass index

* $P < 0.05$ ** $P < 0.01$

and gender variable (r = -0.032), number of relapses (r = 0.136) and number of hospitalizations (r = 0.054). Meanwhile, there was significant relation between fatigue and marital status (r = 0.243, P < 0.01) and level of education (r = -0.237, P < 0.01).

Path Analysis

Path analysis stages on the basis of regression analysis in the research were as follows (Table 2):

1) At stage one, demographic variable was selected which upon Pearson correlation test had stronger significant correlation with fatigue severity [patient's age (r = 0.265, P<0.01)], and then independent variables were all investigated through regression analysis to analyze the path for the purpose of predicting fatigue severity and to the aim of recognition stronger variable in predicting fatigue.

2) At stage two, the defined stronger variable in first step [PCS (β = -0.278, P < 0.05)] was considered as dependent variable and the rest of variables in the pattern were used as independent variable for prediction of PCS under regression analysis, upon which three variables of anxiety, MCS and the patient's age became significant; then stronger variable [anxiety (β = -0.386, P < 0.0001)] was identified and along with remaining variables, again went under regression analysis for prediction and continuation of the path.

3) In third stage, anxiety as dependent variable and the remaining variables were also considered as independent variable and through regression analysis the predictive rate of anxiety was specified by them.

4) Upon recognition of stronger predictive variable in previous stage [stress (β = -0.477, P < 0.0001)], again the other variables went under regression analysis with the given factor (dependent variable), upon which two variables of depression and MCS became significant.

5) Stronger predictive variable [depression (β = 0.664, P < 0.0001)] in form of dependent variable to predict and continue the path was analyzed through regression analysis with remaining factors and this way MCS and age became significant.

6) Recognizing stronger predictive variable [MCS (β = -0.691, P < 0.0001)] at previous stage, again other variables (BMI and age of patient) went under regression analysis with the given variable (dependent).

7) Eventually, in this stage regression analysis was performed on age of patients which was the strongest predictor (β = -0.188, P < 0.05) at previous stage with BMI variable and this way, path analysis on the basis of regression in this step was completed. The whole results regarding regression analysis are shown in table 2.

Important to note, apart from the previous steps (1 to 6) of regression analysis that independent variables had a causal relationship (one-way) with dependent factors, this does not apply to the seventh step (the last stage) that the independent variable (BMI) had a correlational relation (bidirectional) with the dependent variable (age).

Figure 1 shows the path pattern of variables regarding fatigue severity. Arrows are indicators of path from cause to the effect. In fact, this diagram shows the most effective predictive factors of fatigue severity in MS patients. In this diagram, BMI is an exogenous variable and the remaining variables are endogenous. Also, (e) is error variable which appears accidentally or because of other effective variables, not being taken to account in the model. As seen in this figure, PCS was the only variable which directly affects fatigue severity and it had no indirect relation (β = -0.278, P < 0.05). Anxiety variable had also an indirect relation, but the other dependent variables (except for BMI) had many indirect path relation. It should be remembered that anxiety and PCS variables within independent variables had allocated path relation to themselves most of the times, in form of dependent variable role (effect). Meanwhile, MCS variable was defined as the only existing variable of regression analysis which most of the times had dependent variable role (cause). Interesting point was that the largest of standard coefficient (β) belonged to causal relation between MCS and depression (β = -0.691, P < 0.0001). Eventually, as it is noticed in path relation, only BMI variable had correlation relation (↔) which could not be considered a causal relation (β = 0.227, P < 0.05). Causal relations are totally shown in figure 1.β value obtained in steps 1 to 7 of regression analysis (Table 2) was considered as the path coefficient which is an estimate of independent variable direct influence's rate on dependent variable. In order to determine indirect effect of independent variables on dependent variable, β coefficients of indirect paths are multiplied by each other. Total effect of independent variables on independent variable is calculated from sum of indirect and direct paths multiples. Table 3 shows the direct and indirect effects of variables in final step.

The table results in Table 3 indicate that despite negative value of direct effect, its effect size was more than indirect effect's values. Therefore, we could say that PCS which had significant direct relation with dependent variable of fatigue severity was more important and at the same time sum of indirect effects had less effect on fatigue. The value of final existing R^2 in the research was 0.22 indicating that independent variable in path analysis pattern explains 22% of fatigue severity changes in form of dependent variable.

Table 2. Findings of regression analyses (steps 1 to 7 to determine the significant relation between dependent and independent variables)

Steps	Independent variables	β	P	R2	Dependent variable
1	Depression	0.211	0.129	0.220	Fatigue
	Anxiety	0.003	0.982		
	Stress	-0.100	0.485		
	PCS	-0.278	0.013		
	MCS	-0.056	0.628		
	BMI	-0.007	0.925		
	Age	0.118	0.142		
2	Depression	-0.141	0.160	0.586	PCS
	Anxiety	-0.386	0.000		
	Stress	0.154	0.139		
	MCS	0.369	0.000		
	BMI	-0.074	0.172		
	Age	-0.219	0.000		
3	Depression	0.217	0.019	0.636	Anxiety
	Stress	0.477	0.000		
	MCS	-0.174	0.017		
	BMI	0.056	0.261		
	Age	-0.034	0.511		
4	Depression	0.664	0.000	0.704	Stress
	MCS	-0.239	0.000		
	BMI	-0.015	0.741		
	Age	-0.061	0.188		
5	MCS	-0.691	0.000	0.523	Depression
	BMI	-0.080	0.157		
	Age	0.126	0.030		
6	BMI	-0.003	0.969	0.036	MCS
	Age	-0.188	0.020		
7	BMI	0.227	0.004	0.052	Age

PCS: Physical component summary; MCS: Mental component summary; BMI: Body mass index

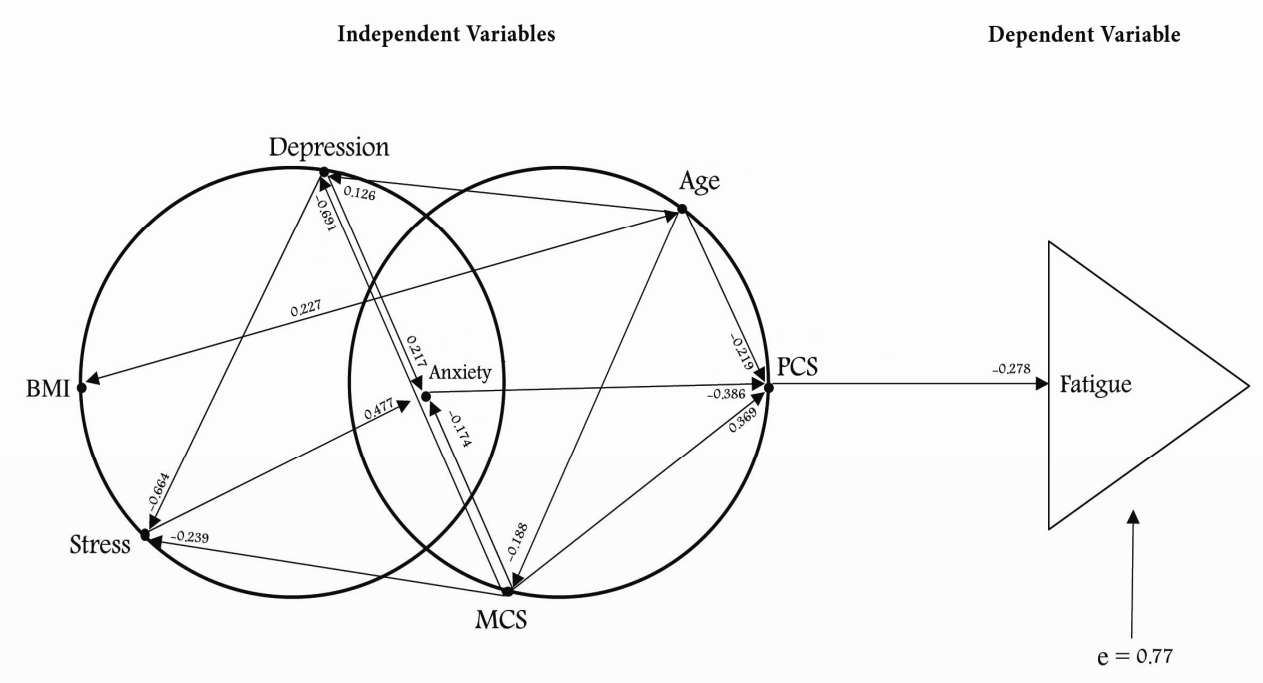

Figure 1. Theoretical fatigue model in MS patients using variables of depression, anxiety and stress, PCS, MCS, BMI and Age (N-162)

(e) = Not explained variance of fatigue severity variable $R^2 = 0.22$ $e\sqrt{1-R^2} = 0.88$ $e^2 = 0.77$

PCS: Physical component summary; MCS: Mental component summary; BMI: Body mass index

Table 3. Direct and indirect effects of variables in final model

Effect	Direct	Indirect	Total
PCS	-0.278	–	-0.278
Age	–	0.099	0.099
MCS	–	-0.172	-0.172
Anxiety	–	0.107	0.107
Depression	–	0.057	0.057
Stress	–	0.051	0.051
Total direct and indirect effect	-0.278	0.142	-0.136

PCS: Physical component summary; MCS: Mental component summary

Discussion

In this study we tried to provide an integrated mathematical model to investigate the effective factors on fatigue severity. Only PCS showed a direct relationship with fatigue severity. Limited evidencesindicated that physical characteristics such as movement are lower in MS patients than general population.[44] Using SF-36 in a study, lower scores were reported only for physical dimensions in MS patients in comparison to Canadian general population.[45] Considered pattern of relations supports the probability of indirect relation of psychopathological symptoms, MCS, and age of patient to fatigue in MS patients by a path including PCS. These factors finally have been related to fatigue severity through PCS.

Negative coefficient of PCS in relation to fatigue severity (-0.278) is indicative of exacerbation of fatigue severity along with decrease of PCS and those capabilities related to it (such as physical functions). Along with this finding, an investigation on two groups of MS patients and those affected by chronic fatigue syndrome (CFS) demonstrated that in both groups worse PCS in SF-36 was significantly related to more fatigue; but in none of them MCS was related to fatigue severity.[26] Explaining the findings of this study is based on biological interpretations; it was shown that CNS fatigue is caused due to increase in neurotransmitters such as dopamine and also increase in cortical activation in MS patients.[46,47] Dopamine may suppress cortical cellular excitability,[48] too. It seems rational that fatigue stemmed from brain lesions and abnormalities in MS and impairment in physical functions have a close relation, because to Compensation, Increased neuronal activity, fatigue also increases. In line with it, cortical motor activation of patients has been investigated during a fatiguing hand exercise.[49] In this evaluation, functional magnetic resonance imaging (fMRI) showed high level of brain activation in MS group in comparison to the healthy group. In addition, high level of neuronal activity was observed as functional compensatory activity to overcome premature motor fatigue. In fact, stimulation of neuronal activity increases metabolism and triggers perception of fatigue.

Except PCS in this study, other variables were related to fatigue severity through intermediary factors. In fatigue severity pattern, sum of positive path coefficient of age of patient (0.099) indicates the recent factor to be related to fatigue severity in form of a set of causal relations through intermediate variables such as MCS, PCS, anxiety, depression and stress, increase of which leads to exacerbation of fatigue in patients. Previously, impact of patient's age on some of these intermediary factors was also investigated. Chylova et al.,[50] in evaluation of mental status of two groups of MS patients (through SF-36), found that depression in MS patients was related to physical and mental health only in older group. On the other hand anxiety was just related to health (physical and mental) in younger patients. Meanwhile, results of studies done by Da Silva et al. showed that age of patient has a positive relation with depression scores.[51] That is to say the increase of age and consequently downfall of physical strength of patients on the one hand influences physical aspects of life and on the other hand, decrease of physical ability plus inability to contribute to scope of activities related to social functions causes manifestation of negative attributions like inability particularly to play one's role and finally decrease in mental aspects related to QOL; problems which naturally end in fatigue exacerbation in MS patients.

Sum of MCS negative path coefficients (-0.172) in fatigue severity pattern shows that this variable is related to fatigue via an equation in form of *"collective or molecular causal relations"*, So that, reduction in mental dimensions of QOL (mental health and vitality) Due to the influence on factors such as anxiety, depression, stress and PCS can increase the levels of fatigue. Previously, in a study on 87 patients with definite diagnosis of MS (56% RR), it was seen that the most significant statistical prediction regarding MCS (in SF-36) was allocated to depression.[29] Moreover, Fruehwald et al.[52] proved an existing strong and significant relation between depression, anxiety and QOL; but depression was

defined as a strong predictor of QOL decrease.

Moreover, according to the theoretical model of fatigue severity, sum of positive path coefficients of anxiety (0.107) shows that increase in scores of anxiety factor is parallel to indirect rise of fatigue demonstration. It should be mentioned that anxiety is related to fatigue severity, only by one path and through intermediation of PCS. Beiske et al. showed in one part of their investigation that those patients reporting fatigue were 5.1 times more at risk of anxiety symptoms.[19] These researchers added that their findings were indicative of a strong relation between fatigue and anxiety. There is a probability that occurrence of a debilitating disease which somehow pushes the person to total dependence, brings him expectations for unpredictable problems and more mental and physical restrictions, problems which cannot be controlled by patient, giving him/her severe helplessness feeling and lack of control on his fate and environment. On the other hand, endangering health especially in a gradual form in which the individual observes exactly how progressive is his disability, could cause serious vague and continuous feeling of disturbance and apprehension. These types of feelings could maximize fatigue states, because anxiety, sadness and tension are the basis of emotional dimension of fatigue.[53] Furthermore, anxiety is related to increase of autonomic nervous system (ANS) response which may help feeling of fatigue.[18]

Sum of depression positive path coefficient (0.057) defines that as depression symptoms grow with regard to stress, anxiety and PCS variables, levels of fatigue also increase. Ketelslegers et al. found the relation between fatigue and depression in MS patients through their studies.[12] Brown et al. also expressed that anxiety, depression and fatigue in MS patients were appropriate predictors of each other.[11] As a whole, these studies were in line with Lewinsohn's model, because they declared that fatigue is related to emotional and psychological problems and this model also explicitly expresses that fatigue will lead to psycho-social disability and if persists, depressed mood.[7]

Sum of stress positive path coefficients (0.051) demonstrates that increasing effect of stress in life would result in maximizing fatigue levels via intermediary factors. Today, it is found that psychological stresses make this disease active.[54] Longitudinal study of Ackerman et al,[55] illustrated that stress is considered as an activating factor in relapse of MS disease. In reality, there is a strong relation between stress and exacerbation of MS. When we think of fatigue to happen upon exacerbation of the disease[2] or fatigue could be main characteristic of a relapse,[56] then the nature of role of stress in fatigue of MS patients becomes evident. Eventually, BMI is a variable with a correlation connection to the age of patient in which none of the two variables is considered as the cause or effect of the other and there exists only a simple correlation between them. This positive correlation coefficient (0.227) is indicative of increase of BMI values upon increase of age of patients. One of the interpretations could be dietary change of MS patients as they age, because food imbalance is prevalent in MS.[57] Researchers have analyzed amount of food material intake of women with MS. After comparing their findings with current recommendations in this respect, they found that absorbed material were more than elements such as saturated fat, protein, vitamin A & C, folic acid and iron.[58] This matter, regardless of making the patients fat or overweight and probably having a negative effect on disease course and more importantly on their QOL,[57] becomes a predisposing factor for development of fatigue; because obesity and that eating pattern including daily heavy meals could aggravate the fatigue syndromes, cause complications such as pressure sores or thrombosis or may worsen disabilities already existing.[57]

Meanwhile, an interesting point in fatigue diagram is lack of a direct path relation between depression and fatigue, since recent studies have confirmed over and over the relation between depression and fatigue.[10-12,59] This ambiguity could be answered considering the role of "*intermediary micro-variables*" to refer to effect on causal relation between depression and fatigue; like education level or type of occupation. Through this, we mean that even if upon results depression is not the direct causal factor resulting in fatigue, yet this is explainable taking individual differences of the patients into account. Recent subject is in line with study provided in 14th Meeting of European Neurological Society in Barcelona (2004). Recent research showed that those patients with an occupation and high education get better scores in "Functional Assessment of Multiple Sclerosis" (FAMS) in comparison to unemployed counterparts and those of low education.[60; p127] The reason is the important effect of education on QOL.[60] The referred situation might have been effective on mechanism of relation of these two variables. In fact, current thought could be interpreted as better knowledge of disease in those patients with higher education.[60] So that these patients prevented effect of fatigue or made it fade out despite of being exposed to a series of symptoms which are naturally physical and psychological Gruelings due to exercise and use of Favorable

cognitive mechanisms to control depression (indirect effect). Aforementioned matter could be generalized to presence of such other psychological variables in the research (e.g. anxiety, stress and MCS). Meanwhile, the role of other intermediary mechanisms are undeniable, which are not explicitly entered to the theoretical pattern but are needed to explain the affecting process of a complicated cause on a complicated effect in a set of causal relations (such as basic coping styles and appropriate ways of compatibility of patients) in a way that have prevented taking direct effect of depression from fatigue. Since the fatigue related to MS is probably multifactorial, it is probable that different contributors of biological and psychological factors in each of MS patients who experience fatigue would change. The fact is that psychological factors could contribute in fatigue report and are capable of stabilizing it.

Totally, our findings made clearly obvious the role of psychopathological symptoms and mental as well as physical dysfunctions related to QOL, in exacerbation of fatigue. Clinical usage of this result, useful for these groups of patients, is to propose some sort of rehabilitation interventions to upgrade qualitative aspects of life and decrease psychological destructive symptoms. In this respect, the tendency to concentrate on treatment strategies with aim of decreasing the risks of relapse and progression of disabilities is not enough. In fact, lack of effective pharmacotherapy on fatigue necessitates developing a therapeutic protocol consisting of various treatments for fatigue of these patients. To reach this aim, in addition to pharmacological treatments, we could take advantage of psychotherapies based on QOL which is a non-pharmacological, non-invasive and cost effective method to develop the physical and mental dimensions of life. In these psychotherapies, we can aim at anxiety resulted from disease progression in patients and improving their knowledge about nature of fatigue in MS and ways to manage it. Further, cognitive reconstruction programs, training compatibility to physical damages and cognitive behavioral therapy in patients can be conducted. It should be noticed that in these types of psychotherapy programs, MS patients should be encouraged to increase exercise and active pleasant physical behaviors. The fact is that (a) fatigue as a multidimensional structure is defined by those signs as decrease in activity, reduction of energy, and dullness of organs and; (b) greater extent of functional limitations predicts negative psychological symptoms overtime. It was shown that exercise programs[61] and aerobic[62] could end in decrease of fatigue, depression and weakness as well as improvement of positive attitude and contribution in social activities and eventually positive effect on QOL of the patients. At the end, results of the present study can help clinicians to determine those MS patients who are prone to highest risk of development of destructive psychological symptoms, disorders in physical and mental aspects related to QOL and also fatigue.

This study had some limitations, like lack of control on drug usage of the patients which could have a role in appearance of symptoms under evaluation especially fatigue. Moreover, the data of this research are self-reporting. This may probably increase bias and distortion of answers within numerous data collection tools. In addition, subjects under study were not equal in terms of hospital measures, type of social support, levels and quality of attention and care given to them after being affected by the disease (especially in family). Our results highlighted the importance of impact of depression, anxiety and stress as well as disorder in QOL dimensions on fatigue. Thus, we propose that researchers dedicate their efforts to longitudinal and experimental studies for a better understanding of nature of relations existing within variables of this research and determining whether changes in special psychological factors are related to the change in fatigue related to MS. In addition, future studies should more clearly aim at probable mechanisms engaged in increase of fatigue in MS patients such as immunomodulatory drugs, organic brain lesions stemmed from disease, social situation, and role of caregivers as well as spasticity and sphincter dysfunction which potentially are capable of influencing it. At last, subjects under study were mainly women (70.4%). Although MS is more frequent in women, it is proposed that in future studies, some factors such as eating behavior (effective in BMI) and employment (effective on QOL) in men be considered.

Conclusion

Results of this study unveiled a significant relation between fatigue severity and symptoms such as depression, anxiety, stress, PCS, and MCS in MS patients. Findings stemmed from path analysis showed that PCS is the only variable which directly affects fatigue severity. Moreover, the largest β also belonged to the causal relation between MCS and depression. According to these findings, we can refer to impact of the most obvious physical dysfunction related to life on fatigue. Thus, evaluating and monitoring problems related to physical dimensions of MS patients are recommended in addition to recognition of potential mechanisms effective on relations between psychological factors and fatigue.

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