Received: 24.11.2006 **Accepted: 8.6.2007**

Original Article

Anxiety disorders in multiple sclerosis: significance of obsessive-compulsive disorder comorbidity

Amir Shabani[*], *Jafar Attari Moghadam*[*], *Leily Panaghi*[**], *Arshia Seddigh*[***]

Abstract

BACKGROUND: Considering reports on the associations of symptoms of anxiety disorders with multiple sclerosis (MS), this study aimed to 1) further evaluate various anxiety disorders systematically presenting in patients with MS and 2) compare the results with a control group.

METHODS: To assess anxiety disorders in patients with MS in a case-control study, 85 registered patients in the Iranian Multiple Sclerosis Society (IMSS) were randomly selected according to the inclusion criteria. A group of healthy individuals whose age and gender were matched with the case group were also selected. Both groups underwent a clinical interview based on DSM-IV diagnostic criteria.

RESULTS: Frequency of diagnosis of all anxiety disorders in the two groups was 22.4% and 7.1%, respectively, indicating a statistically significant difference. Frequency of obsessive-compulsive disorder (OCD) was significantly higher in the case group ($P<0.05$). Relation of university education with the diagnosis of generalized anxiety disorder was significant too ($P<0.05$).

CONCLUSIONS: OCD in patients with MS was more frequently observed than in the control group.

KEY WORDS: Multiple sclerosis, obsessive-compulsive disorder, anxiety, neuropsychiatry.

JRMS 2007; 12(4): 172-177

Archive of SID

Anxiety disorders include panic disorder, agoraphobia, specific phobias, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder, acute stress disorder and generalized anxiety disorder [1]. Multiple Sclerosis (MS) is the most common demyelinating disease of the central nervous system mainly affecting the white matter [2]. A spectrum of neuropsychiatric manifestations including some cognitive, affective, and anxiety symptoms are seen in MS patients. The correlation of MS with anxiety symptoms and disorders in general [3-5] and with generalized anxiety disorder, panic attacks [6] and OCD [7], specifically, has been well documented. The frequency of anxiety symptoms according to the neuropsychiatry inventory (NPI) in 44 patients with MS reported to be 37% [3]; and the reported figure for the generalized anxiety disorder and panic attacks was 5% and 6%, respectively [7]. We were not able to find any large significant study assessing the prevalence of anxiety disorders in patients with MS even in the review article of Feinstein [8]. Lately in an

*Mental Health Research Center, Iran University of Medical Sciences, Tehran, Iran.
** Family Research Institution, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*** Institute of Psychiatry, King's College, London, England.
Correspondence to: Dr Amir Shabani, Mental Health Research Centre, Niayesh Street, Sattarkhan Avenue, Tehran, Iran.
e-mail: amirshabani@tehranpi.org

www.SId.ir

Iranian cross-sectional study on 40 MS patients with no control group [7], a frequency of 17.5% of OCD was reported based on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) cutoff point. Current study actually aimed to re-evaluate this finding using a diagnostic interview and a control group. Given no conclusive diagnostic finding based on controlled assessments in MS patients in Iran, we developed this study to determine the frequency of anxiety disorders in patients with MS.

Methods

This was a case-control study to examine the frequency of anxiety disorders diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revised (DSM-IV-TR) diagnostic criteria in MS patients recruited from the Iranian MS Society Registry and compare it with that in the control group. This study was conducted during 2003 and 2004. From the 2,025 registered MS patients at the Iranian MS Society, 85 subjects who met the inclusion criteria (see below) were randomly selected using a random number table, which allowed each member of the population to have an equal chance of being selected as part of the sample. People in this society had a definite diagnosis of MS made by different neurologists. The neurologists used different instrumental tools to diagnose MS disease for registration in the society, including the McDonald criteria [9], the Poser criteria [10] and the Schumacher criteria [11]. Inclusion criteria were age between 18 and 65, Tehran residency and willingness to give informed consent to enter the study. Exclusion criteria were history of other neurologic disorders, serious head trauma and systemic diseases and substance dependence (based on DSM-IV-TR criteria). The control group included 85 people who were either teachers of a high school or employees of a production company. Sampling continued as necessary until study investigators achieved an age and gender matched control group to the case group. People in the control group gave an informed consent prior to study participation. Assessments took place in the office of the MS society or the office of the probands in the control group and included demographic data such as age, gender, marital status and level of education that were collected using a written questionnaire. After obtaining a written consent, a third-year psychiatry resident conducted a face-to-face clinical interview using a checklist prepared from DSM-IV-TR diagnostic criteria. The interview continued until the resident obtained sufficient information to make a diagnosis. Interviews covered all anxiety disorders mentioned in DSM-IV-TR. A complementary interview with the patients' family was also done as necessary. Each interview lasted approximately 40 to 90 minutes. If the interview length became intolerable for the subject, he or she was given a rest after which the interview continued until completion. To assess the validity of the clinical interview, the psychiatry resident interviewed 23 people from another project. These people were also evaluated by two other psychiatrists (interviewing the patient by one psychiatrist in the presence of another psychiatrist) using the semi-structured clinical interview (based on the DSM-IV-TR diagnostic criteria) with the patients and their families and the patients' hospital records. The diagnostic sensitivity and specificity of the study's interviewer in anxiety disorders in these patients were both 100%, with a significant Kappa coefficient of 1 ($P<0.001$). The clinical interview of MS patients had appropriate validity. Paired Student's t-test and Chi square were used for data analysis. The study was approved by the Research Committee of the department of psychiatry and medical school, Iran University of Medical Sciences, Tehran, Iran.

Results

Table 1 includes demographic features for both the study population and the control group. Mean ages in the MS and the control groups were 47.6 ± 10.2 and 47.5 ± 10.4, respectively.

Archive of SID

www.SId.ir

Neither age nor other demographic variables showed any significant difference. The overall frequency of anxiety disorders in the two MS and control groups were 22.4% (n = 19) and 7.1% (n = 6), respectively, indicating a statistically significant difference ($P<0.001$, df = 1, $\chi^2 = 7.93$). Table 2 shows the distribution of all the observed anxiety disorders in the two groups. Given that only 6 MS patients (7.1%) had a single anxiety disorder and the rest had comorbidity with other anxiety disorders, the total frequency of anxiety disorders (22.4%) should be less than the sum of the frequency of each of the anxiety disorders displayed in table 2. Although generalized anxiety disorder, OCD, panic disorder and specific phobia were more frequent in MS patients, only the OCD proved to be significantly higher. In the other three, however, due to the low power of the study (39%, 17%, and 30%, respectively), one cannot deduce lack of statistically significant differences between the two groups. In none of the cases with anxiety disorders, had it begun before the first manifestations of MS. Further evaluation of demographic data in MS patients revealed significant and close to significant association of having university education with a diagnosis of generalized anxiety disorder ($P<0.05$, df = 1, $\chi^2 = 13.99$) and OCD. Frequency of generalized anxiety disorder in people with and without university education was 40.0% and 5.7%, respectively. The figures for the diagnosis of OCD in these patients were 26.7% and 8.6%, respectively.

Table 1. Demographic features of the study (multiple sclerosis) (n = 85) and the control (n = 85) groups.

Variables		Multiple Sclerosis group Frequency (%)	Control group Frequency (%)
Gender	Male	40 (47.1)	39 (45.9)
	Female	45 (52.9)	46 (54.1)
Marital status	Single	36 (42.4)	35 (41.2)
	Married	42 (49.4)	46 (54.1)
	Widowed	2 (2.4)	2 (2.4)
	Divorced	5 (5.9)	2 (2.4)
Education	Illiterate	3 (3.5)	0 (0)
	Primary school	19 (22.4)	12 (14.1)
	Secondary school	23 (27.1)	25 (29.4)
	College	25 (29.4)	28 (32.9)
	University	15 (27.6)	20 (23.5)

Table 2. Distribution of various anxiety disorders in the multiple sclerosis (n = 85) and control (n = 85) groups.

Anxiety disorder	Multiple Sclerosis Frequency (%)	Control Group Frequency (%)	χ2	df	P value
Generalized anxiety disorder	10 (11.8)	4 (4.7)	2.80	1	ns*
Panic disorder	1 (1.2)	0 (0)	1.00	1	ns
Specific phobias	6 (7.1)	2 (2.4)	2.09	1	ns
Obsessive- compulsive disorder	10 (11.8)	2 (2.4)	5.73	1	0.05

*ns = non-significant.

Archive of SID

www.SId.ir

Discussion

In this study, we compared the frequency of anxiety disorders in MS patients with a group of control subjects. This study showed a high frequency of anxiety disorders, in general, and OCD, specifically, in MS patients. High rates of anxiety symptoms and disorders in MS patients are in agreement with and a confirmation to findings of Diaz-Olavarrieta et al. [3], Zorzon et al. [4] and Janssens et al [5]. Some features of the current study overcame the limitations of the previously mentioned studies. These include (1) applying a set of defined symptoms and disorders instead of taking an account of independent symptoms alone; (2) making the diagnosis by the use of a clinical interview by a senior psychiatry resident; (3) using a complementary interview with the patient's family; (4) making a comparison with a control group; and, (5) using a larger sample size compared to previous studies. Finding a relationship between obsessions and MS, according to the authors' knowledge, dates back to Philippopoulos [12] who reported a 45% frequency of hysterical, anxiety, or obsessive-compulsive symptoms in patients with MS. There are also case reports of MS patients affected by OCD [13]. The first evaluation of MS patients regarding specifically obsessive-compulsive symptoms involved 40 of them assessed by two psychometric scales (including Y-BOCS) [7]. In that study, 17.5% OCD comorbidity was found based on Y-BOCS measuring cutoff points. The figure is even higher than the frequency of OCD that we measured in the current study in patients with MS. The observed difference in the figures might result from different sampling methods and scales used. Sampling in the above-mentioned study had not been on a simple random basis. Moreover, the applied scale was basically used for screening obsessive-compulsive symptoms and not meant for diagnostic purposes. However, what these two studies are both suggesting is a significantly higher than expected frequency of OCD in MS. Obsessive-compulsive disorder has been reported to be associated with subcortical brain disorders like Parkinson's disease [14] and autoimmune disorders such as Sydenham's chorea [15]. An autoimmune mechanism has also been linked to OCD [16]. Multiple Sclerosis, as a demyelinating disorder, can also be considered a white matter and autoimmune disorder [1]. Given these facts, one can suggest the appraisal of the etiologic relations of these two disorders in future studies.

In the previously mentioned study [7], authors have reported the appearance of OCD in MS patients (7 out of 40 MS patients) all before the very first manifestations of MS. The study presented in this article, however, illustrates that all identified of OCD (10 cases of OCD comorbidity) were documented after the appearance of MS. The latter finding favors an association between OCD and MS. Findings of the previous study regarding the occurrence of all cases of OCD before the presentation of MS does not rule out an association between the two, as the psychiatric manifestations of some subcortical neurologic disorders can appear before the motor manifestations (e.g. appearance of depression in the course of Parkinson's disease [2]). The presence of generalized anxiety disorder and, to some extent, OCD proper in patients with MS was associated with having university training in our study. Frequency of having university training was actually higher in MS patients compared to those without these disorders. The direct relation between the level of education and OCD in MS patients was reported in another study as well [7]. It is noteworthy that a negative relationship between the level of education and depressive symptoms has been found in patients with MS or other medical conditions [17]. Findings of this study must be addressed in the light of its limitations, such as lack of applying a standard interview for DSM-IV-TR diagnosis like SCID (Structured Clinical Interview for DSM-IV-TR). We, however, took many measures to overcome this weakness including the complementary interviews conducted with patients' fami-

Archive of SID

www.SId.ir

lies, using a checklist to consider full DSM-IV-TR diagnostic criteria for anxiety disorders, and continuation of the clinical interview to further diagnose the comorbidities in anxiety disorders. Another limitation of the study was the number of non-consenters in MS patients regarding our simple random sampling method to participate in the study. Additionally, We had unfortunately no access to this excluded population of non-consenters. Sampling was limited in selecting the patients only from the registered members of the Iranian MS Society who were dwelling in Tehran, and in selecting the control subjects from the two specific centers (mentioned earlier in Methods). This would not let us generalize our results. It is also important to point out that using the different criteria to diagnose MS for registering patients at the MS Society may be another limitation of the study, although this was out of our control. Overall, findings of this study once again emphasize the association of anxiety disorders and especially OCD with MS. Careful evaluation of anxiety symptoms in these patients is thus further warranted. Based on these findings, assessing the effects of OCD on the course and response to treatment in patients with MS, relation of OCD with different biologic markers of MS, OCD response to anti-obsessive treatment in patients with MS, and the effect of OCD treatment on the course of MS are all suggested.

Acknowledgments

Running this study would be impossible, shouldn't there be the great and sincere help of all the authorities and members of the Iranian MS Society and other respectful people who helped us as our control group. We hereby thank all of them.

References

1. American Psychiatric Association. **Diagnostic and Statistical Manual of Mental Disorders. Text Revised**. 4th ed. Washington DC: American Psychiatric Association; 2000.
2. Sadock BJ, Sadock VA. **Kaplan and Sadock's comprehensive textbook of psychiatry**. 8th ed. Philadelphia: Williams and Wilkins; 2005.
3. Diaz-Olavarrieta C, Cummings JL, Velazquez J, Garcia dlC. **Neuropsychiatric manifestations of multiple sclerosis**. *J Neuropsychiatry Clin Neurosci* 1999; 11(1):51-57.
4. Zorzon M, de Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G et al. **Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects**. *J Neurol* 2001; 248(5):416-421.
5. Janssens AC, van Doorn PA, de Boer JB, van der Meche FG, Passchier J, Hintzen RQ. **Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression, and disease-related distress**. *J Clin Epidemiol* 2004; 57(2):180-186.
6. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. **Mood disorder and multiple sclerosis**. *Arch Neurol* 1987; 44(4):376-378.
7. Shabani A, Nikravesh S, Panaghi L. **Obsessive-Compulsive Disorder: Is It Common in Multiple Sclerosis?** *Iranian Journal of Psychiatry & Clinical Psychology* 2006; 46:209-215.
8. Feinstein A. **The neuropsychiatry of multiple sclerosis**. *Can J Psychiatry* 2004; 49(3):157-163.
9. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. **Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis**. *Ann Neurol* 2001; 50(1):121-127.
10. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC et al. **New diagnostic criteria for multiple sclerosis: guidelines for research protocols**. *Ann Neurol* 1983; 13(3):227-231.
11. Schumacker GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, Mcdowell F et al. **Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis**. *Ann N Y Acad Sci* 1965; 122:552-568.
12. Lishman WA. **Organic Psychiatry**. 3rd ed. Oxford: Blackwell Scientific Publications; 1998.
13. Miguel EC, Stein MC, Rauch SL, O'Sullivan RL, Stern TA, Jenike MA. **Obsessive-compulsive disorder in patients with multiple sclerosis**. *J Neuropsychiatry Clin Neurosci* 1995; 7(4):507-510.

Archive of SID

www.SId.ir

14. Aouizerate B, Guehl D, Cuny E, Rougier A, Bioulac B, Tignol J et al. **Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology**. *Prog Neuro-biol* 2004; 72(3):195-221.
15. Swedo SE, Rapoport JL, Cheslow DL, Leonard HL, Ayoub EM, Hosier DM et al. **High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea**. *Am J Psychiatry* 1989; 146(2):246-249.
16. Roy BF, Benkelfat C, Hill JL, Pierce PF, Dauphin MM, Kelly TM et al. **Serum antibody for somatostatin-14 and prodynorphin 209-240 in patients with obsessive-compulsive disorder, schizophrenia, Alzheimer's disease, multiple sclerosis, and advanced HIV infection**. *Biol Psychiatry* 1994; 35(5):335-344.
17. 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(11):1862-1868.

Archive of SID

www.SId.ir