



Research Paper: Prevalence of Tremors in Patients With Multiple Sclerosis: A Cross-Sectional Study in Isfahan, Iran



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Running Title: Tremor in MS Patients



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Bullet Points:

- The frequency of tremor in MS is relatively high.
- A strong correlation was found between tremor and patients' ataxia.

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ABSTRACT

Background: Multiple Sclerosis (MS) is a demyelinating disorder of the central nervous system. Tremors are a common problem in the patients suffering from MS which is mostly observed in the arms but can also affect the other body parts. There have been few studies on tremors among the MS patients.

Objectives: This study is the first to report the prevalence of tremor in a group of MS patients in Iran. We have also reported the possible associations between the presence of tremor and different forms of ataxia.

Materials & Methods: This study was performed on a group of MS patients in Alzahra hospital, Isfahan, Iran. Patients were interviewed, and a neurologist carried out the neurological examinations, including the evaluation of the type of tremor with the help of Expanded Disability Status Scale (EDSS); ataxia clinical scale for dysmetria, dysdiadochokinesia, dysarthria and gait ataxia. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3.15 to 3.17 was also used for tremor classification. Tremor-related disability and handicap were scored by using Disability and Handicap Questionnaires.

Results: Out of the 164 patients, 113 had tremor (69%) of which 23 were males (20%), and 90 were females (80%). A strong correlation between tremor and ataxia was reported while there were no correlations between tremor and patient's gender, type of MS or the first clinical presentation. Twenty-three of the 164 patients suffered from the incapacitating tremor and had serious problems doing certain tasks. We also reported tremor to greatly affect the daily activities.

Conclusion: The frequency of tremor in MS is relatively high. Strong correlation is between tremor and ataxia but not with the gender, the type of MS or the first clinical presentation. The tremor of MS greatly affected the activities of the daily living.

Keywords: Multiple Sclerosis, Tremor, Prevalence

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Introduction

Multiple Sclerosis (MS) is a demyelinating disease of the Central Nervous System (CNS), affecting mostly the young adults [1]. In patients with MS, tremor can be disabling [2], and it affects their quality of life. It is mostly observed in the arms but can also affect the legs, head, neck, vocal cords or trunk [3, 4]. MS prevalence has been assessed in rather a few numbers of studies, mainly because tremor assessment is not included in Kurtzke's scale for evaluating disability, which is the most used scale in the studies on MS patients [5-7]. Furthermore, assessing tremor incidence and prevalence in the MS patients is rather difficult and biased in its sampling; because the neurological symptoms of the patients are transient during the relapsing phase of MS [7, 8]. In this study, conducted in Isfahan, Iran, we aimed to report the prevalence of tremor among a group of patients with MS for the first time in this country.

Material and Methods

Patients

This cross-sectional study was prospectively performed on the patients with MS who fulfilled the following criteria: 1. Definite diagnosis of MS based on the McDonald 2010 criteria; 2. Age between 18 to 55 years; and 3. No other (concomitant disease) including Parkinson's disease, essential tremor, neuropathy and hyperthyroidism. The patients were recruited from an MS clinic in the Al-Zahra hospital, Isfahan University of Medical Sciences (IUMS), Isfahan, Iran between April 2016 to February 2017. Written informed consent was obtained from the patients. The ethical committee of the Medical School University of Isfahan had approved this study.

Examination and data collection

The patients were interviewed and a neurologist carried out the neurological examinations, including the evaluation of the type of tremor, Expanded Disability Status Scale (EDSS) [9] and ataxia clinical scale for dysmetria, dysdiadochokinesia, dysarthria and gait ataxia based on a previously approved checklist [8]. Tremor was evaluated at the three states of muscle activity based on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3.15 to 3.17 [10] which evaluated: Postural tremor of the hands, Kinetic tremor of the hands and Rest tremor amplitude. Patients were also asked to complete the two already approved questionnaires which assessed "tremor effects on the

activities in daily living" and "tremor-related handicap" [8, 11]. Demographic data and clinical characteristics were collected by a checklist with items including: age, gender, patient's dominant hand, disease duration, symptoms in the first attack and the type of MS.

Statistical analysis

All the data was analyzed using the SPSS 20 statistical software package. Quantitative demographic characteristics were expressed by mean±SD and qualitative data were shown as percentage. To compare the means of two normally distributed data, student's t-test was used and for non-normally distributed data, the Mann-Whitney test and U-test were used. For comparisons of correlations between the two groups, chi-square and Fisher's exact tests were used and Spearman's rank correlation coefficient was used to evaluate the associations among variables. A P value of <0.05 was deemed to be statistically significant.

Results

The study population characteristics

We recruited 164 patients in this study, of which 32 were males (19.5%) and 132 were females (80.5%). A total of 148 patients were right-handed and 16 were left-handed. The disease was classified as Relapsing-Remitting (RR) in 104, Secondly Progressive (SP) with or without relapses in 48 and Primarily Progressive (PP) in 12 patients. The average age was 36.35 years (SD=9.357), and at the time of study, the average EDSS was 2.732 (SD=1.7873). Blurred vision and weakness of the extremities were the first symptoms of MS in 23.8% and 20.1% of patients, respectively and were reported as the most prevalent first presentation of MS. Nineteen patients (11.6%) were under no medical treatment. Interferon beta-1a (48.8%) and Interferon beta-1b (11.6%) were the most prevalent medications taken by the patients.

Prevalence of tremor

A total of 113 patients (68.9%) had tremors of which 23 were males and 90 females. Action tremor was the most frequent type of tremor observed, affecting 64% of the patients. Rest and intention tremor also affected 30 and 44% patients. One hundred were right-handed and 13 left-handed. 59.3% patients affected by tremor had RR MS, 33.6% SP MS and 7.1% PP MS. Based on the chi-square test, there was no significant relationship between patient's gender, dominant hand or type of MS and the prevalence of tremor (P of 0.68, 0.39 and 0.18, respectively). There seemed to be no association between the

first symptom of MS and tremor either (P=0.8). In addition, 50 patients (30.5%) had resting tremor, 107(66.4%) had action tremor and 72(43.9%) had intention tremor.

Ataxia scale

Our data showed significant correlations between the presence of tremor and that of dysarthria, dysmetria and dysdiadokokinesia (P of 0.001, 0.002 and 0.05, respectively) (Table 1). We reported no significant correlations between the tremor and gait abnormalities (P=0.08). Thirty-eight patients (74.5%) who were not affected by tremor had no impairment in speech while only 52 patients (46%) of the tremulous group had completely normal speech. Mild dysarthria was seen in 42.5%, moderate dysarthria in 9.7% and severe dysarthria in 1.8% of the tremulous group while only 25.5% of the other group had mild dysarthria, and none had moderate or severe dysarthria.

The results of our questionnaires for dysmetria and dysdiadochokinesia were similar with most of the non-tremulous group having no impairments, 33% and 11% with mild forms of dysmetria and dysdiadokokinesia, respectively, and a small percent having moderate or severe impairments. As for the tremulous group, 35% of patients experienced no impairment in the case of dysmetria while 73 patients suffered from mild to severe forms. However, 70% of the patients did not suffer from dysdiadokokinesia while only 34 patients experienced mild to severe forms. We also reported 39% of the tremulous group to have no gait abnormalities and 47.7% with mild and moderate gait abnormalities. As for the non-tremulous group, 58.8% were completely normal while 37.2% experienced mild to moderate gait abnormalities. Also, seven tremulous patients (6.2%) and two (3.9%) of the other group were wheelchair bound.

Tremor effects on activities of daily living

Tremor effects on daily and personal activity were measured based on 25 factors such as the ability to use

a fork or the ability to brush the teeth. Based on our findings, patient's daily work was heavily impacted by tremor, although patient's ability to bathe, to do up a zip, to watch the TV, to make themselves understood on the phone and to insert an electric plug into a socket had no direct correlation with tremors (P>0.05) (Table 2).

Tremor-related disability

Disability caused by tremor was measured by 9 questions. Twenty-three (14%) of the 164 patients studied suffered from incapacitating tremor. Eight patients (4%) felt they were handicapped either because of the physical effects of the tremor or because they were embarrassed by the tremors or both. Patient's disability to work, to apply for a job or to promote, to shop, to travel, to drive a car, to do hobbies or sports, to eat out, to go on a holiday and to accept a party invitation was caused by tremors (P<0.05) (Table 3).

Discussion

In this study, we measured the prevalence of tremors among a group of patients with MS. We concluded that there was a correlation between the presence of tremor and dysarthria, dysmetria and dysdiadokokinesia. Patients' disability in performing certain tasks in life, such as applying for a job or to travel, was caused by tremors. Tremor had also affected patients' daily work. However, we reported that there was no apparent correlation between tremors and patients' ability to do some daily activities like to do up a zip or to bathe. There also seemed to be no correlation between the tremor and the presence of gait abnormalities, the patient's gender, the type of MS or the first clinical presentation.

Our study measured the prevalence of tremors among some of the MS patients for the first time in Iran. However, the patient group used in this study was small and not a definitive indicator for all the MS patients in the country. We suggest that for a more accurate prevalence

Table 1. The relationship between the presence of tremor and impairment associated with dysarthria, dysmetria and dysdiadokokinesia

Ataxia and Tremor	N (%) of Impairment			P
	No	Mild	Moderate to Severe	
Dysmetria/tremor	40(24.4)	44(26.8)	29(17.7)	0.002
Dysdiadochokinesis/ tremor	79(48.2)	22(13.4)	12(7.3)	0.057
Dysarthria/tremor	52(31.7)	48(29.3)	13(7.9)	0.001

N total=113

Table 2. The relationship between the presence of tremor and ability of personal and daily activities

Daily Activities and Tremor	N (%)			P
	Able With Little Effort	Able With a Lot of Effort	Completely Disable	
Cut with a knife/ tremor	30(26.5)	20(17.6)	10(8.8)	<0.001
Use a spoon/ tremor	25(22.1)	12(10.6)	4(3.5)	0.06
Hold a cup/ tremor	35(30.9)	18(15.9)	4(3.5)	<0.001
Pour milk/ tremor	36(31.8)	21(18.5)	4(3.5)	<0.001
Wash and dry dishes/ tremor	28(24.7)	9(7.9)	10(8.8)	0.001
Brush teeth/ tremor	23(20.3)	3(2.6)	2(1.7)	0.005
Use a tissue to blow your nose/ tremor	17(15)	2(1.7)	1(0.8)	0.049
Bath/ tremor	25(22.1)	26(23)	4(3.5)	0.074
Use the lavatory/ tremor	18(15.9)	11(9.7)	4(3.5)	0.024
Wash your face and hands/ tremor	18(15.9)	2(1.7)	1(0.8)	0.036
Tie up shoe laces/ tremor	24(21.2)	11(9.7)	7(6.1)	0.005
Do up buttons/ tremor	27(23.8)	15(13.2)	2(1.7)	0.009
Do up a zip/ tremor	15(13.2)	3(2.6)	0(0)	0.079
Write a letter/ tremor	31(27.4)	19(16.8)	5(4.4)	<0.001
Put a letter in an envelope/ tremor	25(22.1)	5(4.4)	0(0)	0.003
Hold and read a newspaper/ tremor	32(28.3)	8(7)	0(0)	<0.001
Dial a telephone/ tremor	20(17.6)	3(2.6)	1(0.8)	0.006
Make yourself understood on the phone/ tremor	7(6.1)	1(0.8)	1(0.8)	0.148
Watch the television/ tremor	17(15)	4(3.5)	1(0.8)	0.108
Pick up your change/ tremor	26(23)	3(2.6)	2(1.7)	0.001
Insert an electric plug/ tremor	16(14.1)	2(1.7)	1(0.8)	0.271
Unlock your front door with a key/ tremor	24(21.2)	7(6.1)	2(1.7)	0.001
Walk up and down the stairs/ tremor	46(40.7)	38(33.6)	13(11.5)	0.007
Get up out of an armchair/ tremor	25(22.1)	22(19.4)	10(8.8)	0.003
Carry a full shopping bag/ tremor	27(23.8)	24(21.2)	19(16.8)	0.006

N total=113

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rate of tremors and definitive reports for the correlations between tremor and the factors that we measured, more expansive studies should be performed.

Tremor has long been counted as a common problem in MS. Especially, in the upper limbs, tremors can be extremely disabling, embarrassing and affect the quality of life of the patient. The estimated prevalence of tremors

Table 3. Prevalence of disability related to tremor

Disability Related Tremor	N (%)			P
	Yes			
	Because Embarrassed by Tremor	Because of Physical Difficulties	Because of Both Embarrassed and Physical Difficulties	
Tremor working	4(3.5)	23(20.3)	4(3.5)	<0.001
Apply for a job or promotion	4(3.5)	17(15)	5(4.4)	<0.001
Shopping by yourself	3(2.6)	16(14.1)	6(5.3)	<0.001
Doing a favourite hobby or sport	10(8.8)	9(7.9)	6(5.3)	<0.001
Traveling by public transport	1(0.8)	15(13.2)	1(0.8)	0.004
Driving a car	1(0.8)	12(10.6)	2(1.7)	0.007
Eating out	6(5.3)	10(8.8)	2(1.7)	0.003
Going on holiday	6(5.3)	11(9.7)	3(2.6)	0.001
Accepting a party invitation	8(7)	7(6.1)	5(4.4)	0.001

N total=113



in the MS patients is said to be 25 to 60% in some studies. Tremor is typically difficult to manage. Use of some medications (such as propranolol, isoniazid or carbamazepine) has shown little beneficial effects [5]. In MS patients, tremor usually consisted of an action tremor of the upper extremities with the rest component being almost nonexistent. However, MS patients may have various types of action tremors associated with other movement disorders. It may be difficult to characterize tremor in this context, and the neurophysiological investigations can be helpful [4, 12].

Alusi et al. reported a 58% prevalence rate for tremors among the selected MS patients in their study. This rate is nearly 1.2 times smaller than the rate we reported. Furthermore, they reported a greater percentage of patients who were handicapped by tremor but a smaller percentage who experienced incapacitating tremors. Also, similar to our results, there was a strong correlation between tremor and dysarthria, dysmetria and dysdiadokokinesia among their patients [8].

In yet another study, Pittock SJ et al. reported 26% prevalence rate for tremors among their MS patients. Similar to what we reported, the presence of tremor and patients' gender had no correlations. However, they reported the patients' type of MS to be associated with the presence of tremor, and it was more prevalent among patients with SPMS. Pittock used a different tool for ex-

amining impairment, disability and handicap: Minimal Record of Disability for MS. Which consisted of Kurtzke EDSS for impairment evaluation, Incapacity Status Scale for disability evaluation and Environmental Status Scale for handicap evaluation [9, 13, 14]. Although, he similarly found out that these factors have a strong correlation with the presence of tremors [15].

In a study done in 2015, researchers examined 124 MS patients with clinical, neurophysiological and neuroimaging methods and identified five main variants of tremors: distal postural and postural-intention, distal intention, proximal and distal intention and postural-intention, Holmes and axial [16]. This study and several other studies done on MS patients support the fact that MS tremor is most likely caused by the damage of the cerebellar circuitry (especially the cerebellar peduncles) [17-19]. Feys et al., for example, found a strong correlation between tremor severity in one arm and the lesion load in the pons contralateral to it [17].

Conclusion

In conclusion, our findings suggested that the frequency of tremor in MS is relatively high and the presence of tremor in MS patients is highly correlated with the presence of cerebellar dysfunction. Presence of cerebellar dysfunction resulted in mild to severe disability to

do the daily activities or certain tasks in life as we also measured with the previously approved questionnaires.

Ethical Considerations

Compliance with ethical guidelines

The study was implemented in accordance with the tenets of the declaration of Helsinki. The study protocol was approved by the institutional ethics board and all participants signed informed consents for research.

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Conflict of interest

The authors have no conflict of interest.

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