Headache in multiple sclerosis

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Aim: Although multiple sclerosis (MS) can cause almost any neurological symptom, headaches are considered unusual. Studies investigating the relationship between the 2 conditions have produced conflicting results. The primary aim of this study was to test whether there was a difference between patients with MS (Group 1) and the control group (Group 2, patients with psoriasis and myasthenia gravis, diseases not affecting the central nervous system) in terms of the prevalence and types of primary headache.

Materials and methods: A total of 139 patients with MS and 59 patients in the control group were included. The patients underwent a complete neurological examination and functional systems were assessed according to the functional system scores of Kurtzke. A semistructured interview guided by a questionnaire about headache was applied.

Results: We found the life-long prevalence of primary headaches as 74.8% in patients with MS and as 71.2% in the control group. The prevalence of migraine and tension-type headaches did not show a significant difference between the 2 groups before the disease (P = 0.43), after the onset of disease (P = 0.18), or during the attack (P = 0.097).

Conclusion: MS does not increase the prevalence of headaches, and headache types do not show any difference between MS patients and the control group.

Key words: Multiple sclerosis, headache, prevalence, migraine, tension-type headache

1. Introduction

Multiple sclerosis (MS) is an immune-mediated chronic disorder of the central nervous system (CNS) in young people, characterized by a spatial and temporal dissemination of the pathological process. Multiple areas of inflammation, demyelination, and glial sclerosis are observed in the white matter. Various symptoms and signs occur due to the affected areas in the brain and the spinal cord (1).

Headaches are not a symptom of MS. The first article on the relationship between MS and headaches was published in 1952 (2). The life-long prevalence of headaches in patients with MS has been reported as ranging from 4% to 64% (3–10). The rate of migraine and of tension-type headaches in all MS patients with headache has been reported at 20%–70% and 21%–48% , respectively (4–11).

Despite the presence of publications reporting that the onset of headaches could be concomitant with the onset of MS symptoms and that headaches can show recurrence during the attack period in patients with relapsing remitting MS (RRMS), there are opposite suggestions in English-based literature (3–5,11–22). Moreover, although some studies showed that RRMS could be correlated with migraines, this issue could not be confirmed with other studies (3–5,8–22). In another study, it was suggested that deregulation of the serotonergic system may also be involved in the pathogenesis of MS as well as migraines (13). It was emphasized in a recent study that a stabbing headache was more common during the attack, and migraine and tension-type headaches were more common during remission in patients with RRMS (9). There are publications suggesting that the frequency of headaches and occurrence of new headaches is increased by the use of interferon-β in the treatment of MS (6,7,23–25).

It was not known if headache frequency and characteristics are similar in patients with MS (which is an inflammatory disease of the CNS) to headaches in patients with other chronic diseases that do not involve the CNS. Knowing this may provide clues about the pathogenesis of headaches in MS.

The primary aim of this study was to test whether there was a difference between patients with MS (Group 1) and the control group (Group 2, patients with psoriasis and myasthenia gravis, diseases not affecting the central

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nervous system) in terms of the prevalence and types of primary headache. We also compared the relationship between the onset of primary headaches and of the diseases between the groups, as well as the relationship between the onset of primary headaches and of the attacks. The second aim of this study was to find whether headaches in various types of MS (RRMS, secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS)) were similar; if the migraines in patients with RRMS were more frequent; if the headache types during the remission period and during attacks were similar; and if the presence of depression had any impact on these parameters.

2. Materials and methods
Patients presenting to the Multiple Sclerosis Clinic of the Ankara University Faculty of Medicine, Department of Neurology, from June 2005 to June 2008 were enrolled in this study (Group 1). Patients with the diagnosis of psoriasis and myasthenia gravis who were administered to our hospital in same period constituted the control group (Group 2). The study was approved by the Ethics Committee of the Ankara University Faculty of Medicine. All patients gave written consent for the study.

The inclusion criteria were: having a definitive diagnosis of MS, age between 18 and 55, and giving consent. The exclusion criteria were: having any disease which mimics MS (including systemic lupus erythematosus and Behçet's disease) and administration of megadoses of steroids prior to the assessment.

The date of diagnosis, other acute and chronic diseases, and types and duration time of all medications were recorded. Furthermore, the patients were questioned regarding the onset of the headache, i.e. whether it began before the onset of symptoms of the disease, after the diagnosis of the disease, or during attacks of the disease. A neurological examination was performed for each patient. Functional system involvement was assessed using the Kurtzke Functional System Scale for each system and the expanded disability state score (EDSS) was calculated. A detailed structured questionnaire on headaches was given to all patients in face-to-face interviews. Headaches were classified using the 2004 diagnostic criteria of the International Headache Society (26). All patients were examined with the Mini Mental State Test. The patients were then asked to complete the Hamilton Anxiety Scale and the Hamilton Depression Scale.

2.1. Statistics
The group rates were compared using the chi-square test, and the means were compared using the Student t-test. Multiple logistic regression analysis was used to determine the independent risk factors. All variables with a P-value of <0.25 in univariate analyses were included in the multiple logistic regression analysis. P < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

3. Results
In our study, 139 patients with MS and 59 patients in the control group (52 patients with psoriasis and 7 patients with myasthenia gravis) were included. Of the patients with MS, 96 (69.1%) were female and 43 (30.9%) were male. Of the control group, 37 (62.7%) were female and 22 (37.3%) were male (Table 1); there was no significant difference

Table 1. Demographic features and disease-related parameters in the MS and control groups.

	MS n = 139	Control n = 59	P
Age, years, mean ± SD	37 ± 10.2	37 ± 11.4	0.878
Sex, n (%)			
Female	96 (69.1)	37 (62.7)	0.384
Male	43 (30.9)	22 (37.3)	
Disease duration, median (min–max)	6.7 (1–29)	13.8 (1–41)	0.001*
Relapsing-remitting type, n (%)	129 (92.8)	55 (93.2)	0.917
Number of the diseases' attacks, median (min–max)	4 (1–20)	7.6 (1–30)	0.001*
EDSS median (min–max)	2 (0–9)	0	0.000*
HDS, mean ± SD	4.36 ± 4.5	3.30 ± 4.4	0.245
HAS, mean ± SD	3.49 ± 3.6	2.2 ± 3.2	0.073

SD: Standard deviation. HDS: Hamilton Depression Scale. HAS: Hamilton Anxiety Scale. *: Statistically significant.

between the groups (P = 0.4). The mean age of patients with MS was 37 ± 10 years (range = 18–64). The mean age in the control group was 37 ± 11 years (range = 17–55). The difference between the 2 groups was not significant (P = 0.88). The mean number of attacks in patients with MS was 4 ± 3 (range = 1–20), while in the control group it was 7.6 ± 6.7 (range = 1–30). The difference was significant (P = 0.001). The median EDSS score for patients with MS was 2 (range = 0–9) (Table 1).

Among the patients with MS, 109 (78.4%) cases were RRMS, 15 (10.8%) were SPMS, 10 (7.2%) were PPMS, and 5 (3.6%) were PRMS. Of the patients with psoriasis, 48 (81.4%) patients had activation with intervals, and 4 (6.8%) had continuous lesions. Of the patients with myasthenia gravis, all were in remission (11.9%). Of the patients with MS, 64 (46%) were in the attack period and 75 (54%) were in remission; of the patients in the control group, 27 (45.8%) were in the attack period and 32 (54.2%) were in remission. There was no difference between the 2 groups in terms of having attacks (P = 0.97). There was other chronic disease in 47 (33.8%) patients with MS and in 13 (22%) patients in the control group (P = 0.01).

Of the patients with MS, 16 (11.5%) were using interferon beta-1a (44 µg), 11 (7.9%) were using glatiramer acetate, 15 (10.8%) were using interferon beta-1b, 17 (12.2%) were using interferon beta-1a 6 MIU, and 80 (57.6%) were not using any immunomodulator drugs. The mean score of the Hamilton Depression Scale was 4.36 ± 4.54 (range = 0–23) and 3.30 ± 4.19 (range = 0–17) in Groups 1 and 2, respectively; the difference between the groups was not significant (P = 0.25). The mean score of the Hamilton Anxiety Scale was 3.49 ± 3.61 (range =

0–23) and 2.2 ± 3.26 (range = 0–10) in Groups 1 and 2, respectively; the difference between the groups was not significant (P = 0.07). Patients with a score of ≥8 on the Hamilton Depression Scale were accepted as having depression; 17.4% of patients in Group 1 and 20% of patients in Group 2 had depression; the difference between the groups was not significant (P = 0.72).

Of the patients with MS, 35 (25.2%) did not have headache before or after the disease; the same was true for 17 (28.8%) of the patients in the control group. Of the patients with MS, 69 (49.6%) had the onset of headache before the disease, and 35 (25.2%) had the onset of headache after the disease. In the control group, 20 (33.9%) patients had the onset of headache before the disease and 22 (37.3%) had the onset of headache after the disease, and the difference between the groups was not significant (P = 0.1). Of the patients with MS, 47 (33.8%) described headaches during the attack, and in the control group, 18 (30.5%) described headaches during the attack, and the difference between the groups was not significant (P = 0.7).

We compared the headache types in the MS group and the control group before the disease, during the disease, and during the attack (Table 2). As the number of patients with probable migraines was few, we included these patients in the migraine group. As the number of patients with stabbing headache was few, we did not include them in the statistical analysis. Therefore, statistical analysis was performed only for migraine and tension-type headaches (Table 3). The prevalence of migraine and tension-type headaches did not show a significant difference between the 2 groups before the disease (P = 0.43), after the onset of disease (P = 0.18), or during the attack (P = 0.097).

Table 2. Headache types in the MS and control groups.

	Headache types					
	TTH,	Migraine,	Probable migraine,	Stabbing Headache,	No headache,	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	
Before the disease						
MS	34 (24.5)	30 (21.6)	4 (2.9)	1 (0.7)	70 (50.4)	139
Control	8 (13.6)	11 (18.6)	1 (1.7)	-	39 (66.1)	59
During the disease						
MS	50 (36.0)	35 (25.2)	8 (5.8)	-	46 (33.1)	139
Control	16 (27.1)	21 (35.6)	2 (3.4)	2 (3.4)	18 (30.5)	59
During the attack						
MS	22 (17.1)	18 (14)	5 (3.9)	-	92 (66.2)	139
Control	4 (7.3)	12 (21.8)	-	-	41 (69.5)	59

TTH: Tension-type headache.

Table 3. Prevalence of migraine and tension-type headache in the MS and control groups.

Headache types	TTH, n (%)	Migraine*, n (%)	Total	P
Before the disease				
MS	34 (50)	34 (50)	68	0.43
Control	8 (40)	12 (60)	20	
During the disease				
MS	50 (53.8)	43 (46.2)	93	0.182
Control	16 (41.0)	23 (59)	39	
During the attack				
MS	22 (48.9)	23 (51.1)	45	0.097
Control	4 (25)	12 (75)	16	

TTH: Tension-type headache. *: Including probable migraine.

The onset time of the headaches regarding MS course is presented in Table 4. As the number of patients in each progressive course of MS (including SPMS, PPMS, and PRMS) was few, we grouped all of them under the title of "progressive MS" and compared them to the RRMS group (Table 5). The prevalence of tension-type headaches before and after the onset of disease did not show a significant difference between RRMS and progressive MS groups

Table 4. The onset time and types of headache in different MS subtypes.

Headache types	TTH, n (%)	Migraine, n (%)	Probable migraine, n (%)	Stabbing Headache, n (%)	No headache, n (%)
Before the disease					
RRMS	26 (23.9)	28 (25.7)	3 (2.8)	1 (0.9)	51 (46.8)
SPMS	3 (20)	-	-	-	12 (80)
PPMS	2 (40)	1 (20)	-	-	2 (40)
PRMS	3 (30)	1 (10)	1 (10)	-	5 (50)
During the disease					
RRMS	39 (50.6)	32 (29.4)	6 (5.5)	-	32 (29.4)
SPMS	6 (40)	1 (6.7)	1 (6.7)	-	7 (46.7)
PPMS	2 (40)	1 (20)	-	-	2 (40)
PRMS	3 (30)	1 (10)	1 (10)		5 (50)
During the attack					
RRMS	16 (14.7)	17 (15.6)	5 (4.6)	-	71 (65.1)
SPMS	4 (26.7)	-	-	-	11 (73.3)
PPMS	2 (40)	1 (20)	-	-	2 (40)

TTH: Tension-type headache.

Table 5. The onset time of migraines and tension-type headaches in the RRMS and progressive MS groups.

Headache types	TTH, n (%)	Migraine*, n (%)	Total	P	OR
Before the disease					
RRMS	26 (45.6)	31 (54.4)	57	0.1	3.18 (0.8–13)
Progressive MS	8 (72.7)	3 (27.3)	11		
During the disease					
RRMS	39 (50.6)	38 (49.4)	77	0.1	2.14 (0.8–13)
Progressive MS	11 (68.8)	5 (31.3)	16		
During the attack					
RRMS	16 (42.1)	22 (57.9)	38	0.047*	8.25 (0.9–75.4)
SPMS+PRMS	6 (85.7)	1 (14.3)	7		

*: Including probable migraine.

(P = 0.1 and P = 0.1, respectively). Migraines were more prevalent during the attack in the RRMS group compared to the group with progressive MS with attacks (P = 0.047).

We tested whether there was similarity between types of headache that began after the onset of MS and that began during relapses (if it was seen also in relapses). In cases where patients had tension-type headaches after the onset of MS as well as during MS attacks, 90.9% of MS patients had tension-type headaches during their relapse periods, too. Only 9.1% of those patients had migraines during relapse periods. All patients with migraines that began after the onset of MS, if they had headaches during their relapse period, had migraines. There was a significant relationship between types of headaches that began after the onset of MS and types seen during relapses, too (P = 0.000). A similar relationship was also found in the control group (P = 0.000).

In the multiple regression analysis, it was found that the age, sex, and immunomodulatory drug use in the MS group did not have any effect on headaches; it was found that the presence of depression was an independent risk factor for headache (OR = 5.9, 95% CI (1.7–20.6), P = 0.002). There was no significant relationship between headaches and depression in the control group (P = 1).

4. Discussion

In their prospective study with no control group, D'Amico et al. found that the life-long prevalence of primary headaches in 137 patients with MS was 57.7% (3). In another prospective study with no control group, Villani et al. reported that the life-long prevalence of primary headaches in 102 patients with MS was 61.8% (12). In

yet another prospective study without a control group undertaken by Boneschi et al., the life-long prevalence of headache was found to be 35.5% in 428 patients with MS (24). Ergün et al. found that the prevalence of primary headache was 73.5% in 44 patients with RRMS during remission (9).

In the majority of controlled studies published to date, the prevalence of headaches has been found to be higher in patients with MS compared to the control group (4,6,15). There has been only one study stating that the prevalence of headaches in patients with MS is equal to that of the general population (7).

We found the life-long prevalence of primary headaches to be 74.8% in patients with MS and 71.2% in the control group. Our prevalence was the highest in the literature. Even more striking was the fact that the headache prevalence in the control group was also as high as that of the MS group. Our control group was made up of patients with no disability, having psoriasis or myasthenia gravis, and having relapse and remission periods like MS. The high headache prevalence in the control group suggested that the life-long prevalence of primary headaches is high not only in MS, but in other chronic conditions as well. Further studies with larger patient numbers are needed to clarify this issue.

Freedman and Gray reviewed the records of 1113 patients with MS who were followed-up with for 20 years, and they found that 17 cases out of 44 with vascular-type headaches began after the onset of MS (5). Boneschi et al. reported in their study with 428 patients with MS that 62.5% of patients with tension-type headaches and 77.6% of patients with migraines had these headaches before the

onset of MS (24). Doi et al. reported that 32.3% of patients had the onset of headaches after the diagnosis of MS (8). In our patients with MS, 49.6% experienced headaches before the onset of clinical signs of disease; this rate was 33.9% in the control group. The onset of headaches occurred after the onset of disease in 25.2% of patients with MS and in 37.3% of the control group patients. The onset of headache before disease was more frequent in the MS group compared to the control group (P = 0.042; OR = 1.9). In conclusion, MS does not increase the prevalence of headaches after the onset of MS.

The prevalence of migraine and tension-type headaches in MS patients has been reported as being similar to that of control groups in previous studies (4,6–8). The type and onset time of headaches in patients with MS and the control group were similar in our study, too. We suggest that the headache types do not show any difference between MS and control groups, a finding consistent with the literature.

We found a significant relationship between types of headaches that were attack-related and headaches that were seen in the remission phase in both the MS patients and the control group (Table 2). Thus, we can conclude that the type of headache seen during the exacerbations of MS, and of other diseases that do not affect the CNS, is the same type as the headache seen during remission.

There are publications suggesting that migraines are more prevalent in patients with RRMS, and that tension type of headache is more prevalent in patients with progressive MS (3,12). However, there are also publications suggesting the lack of such an association (8,15). Consistent with these publications, the prevalence of migraine and tension-type headaches that began before or after the onset of MS did not show any difference between RRMS and progressive MS groups. However, the prevalence of attack-related migraines during relapse periods was 57.9% and 14.3% in patients with RRMS and progressive MS, respectively; the prevalences were 42.1% and 85.7% for attack-related tension-type headaches, respectively; and the difference between the 2 groups was significant (P = 0.047). In another study from Turkey, it was reported that a stabbing-type headache was common in the attack period; however, we could not find a similar result (Table 2). We concluded that migraines were more prevalent in patients with RRMS, and tension-type headaches were more prevalent in patients with progressive MS during relapse periods.

Rolak et al. reported that headaches began 7 years before the onset of MS, and that in 7 patients, the headaches started (tension-type headache in 3 patients, migraine in 4 patients) with the first symptoms of MS; however, the headache did not occur during the next attacks in the patients except in 1 patient (15). Freedman and Gray reported in their study that migraines began concurrently with MS in 12 of 44 patients with MS; hence, neurological signs in some of these patients were attributed to migraine vasospasm, and in 6 patients in whom there was an already existing migraine, the migraine was said to have accompanied the first MS attack. These authors suggested that there was vascular headache in 4% of patients with MS, which could be attributed to demyelination (5). Gee et al. reported that in 27% of 154 patients with headaches and MS, the headache occurred during the first MS symptoms or during an attack (16). Vacca et al. stated that in 69.67% of 122 patients, the headache began before MS, and that the onset of MS did not change the headache and that the severity of the headache increased following the onset of MS only in 13 patients (4). In a study by Ergün et al., it was found that in 44 patients with RRMS, migraines (41.2%) and tension-type headaches (20.6%) were common in remission, whereas stabbing headaches (27.8%) were common in the relapse period (9). We did not have any patient with MS in whom a headache was seen as a first attack. In 33.8% of our patients with MS, there was a headache during the MS attack. In 30.5% of the control patients, there was a headache during the exacerbation of their diseases. We concluded that the presence of headaches during the exacerbation was not specific for MS; there was a similar finding for the other diseases.

In our study, we found that the presence of depression in patients with MS increased the risk for headache 6-fold. We found no significant relationship between the other parameters (sex, age, chronic drug use, immunomodulator drug use, other chronic diseases, functional system involvement, EDSS, duration of disease, and age at onset of disease) and headache. Contrary to MS, there was no relationship between depression and headache in the control group. The life-long prevalence of depression in patients with MS was reported as 22% to 54% (27). In our patients with MS, 17.4% had depression, whereas 20% of the control patients had depression. We think that headaches are more common in MS patients with depression than in MS patients without depression.

Our study has some limitations. Although the groups were homogeneous in terms of age, sex, and disease duration and course, the higher number of attacks in the control group compared to the MS group may have caused a higher prevalence of headache in the control group and thus no difference between the groups. It was suggested that the proinflammatory immune response may be responsible for the pathogenesis of headache (28,29). Patients with psoriasis were the majority of the patients in the control group. Proinflammatory immune response is predominant in patients with psoriasis, similar to MS (30–37). Based on our finding that headaches were frequent in the control group, we can suggest that if this was to be related to the proinflammatory immune response, then the

headaches in MS would not be related to demyelination plaques. Therefore, further controlled studies are needed with larger samples in which patients with MS would be compared to patients with diseases not affecting the CNS (such as psoriasis) as the control group, and in which the frequency of attacks are homogeneous between the groups.

In conclusion, we could not find a significant difference for the frequency of headaches between MS and control groups; we think that the previous hypothesis suggesting that demyelination in the CNS in MS may be the cause of headache is invalid. There was no significant time relationship between the onset of headache and the onset of disease either in patients with MS or in the control group. The similarity between the types of headache in patients with MS and in the control group and the lack of any significant relationship between the disease course and headache type suggests that there is no type of headache that is specific to MS or its course. Contrary to previous publications, we can say that migraine is not more common in the remission period of RRMS. The probability of headache during the attack period of MS is high; however, this is not specific for MS; the same high rate is also current in the control group. Furthermore, the type of headache seen during the attack period is not different from that seen during remission. Finally, depression increases the risk of headache in patients with MS.

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