

Headache in Multiple Sclerosis from A Different Perspective: A Prospective Study

Gökhan Özer¹, Ufuk Ergün², Levent Ertuğrul İnan³

¹ Sanko University Faculty of Medicine, Department of Neurology, Gaziantep, Turkey

² Kırıkkale University School of Medicine, Kırıkkale, Turkey

³ Bozok University School of Medicine, Yozgat, Turkey

E-mail: ufukergun@yahoo.com

E-mail: drlinan@yahoo.com

E-mail: primernordr@gmail.com

Corresponding author: Gökhan özer
Sanko University Faculty of Medicine
Neurology, Gaziantep, Turkey

E-mail: primernordr@gmail.com

Received: 31.01.2018,

Accepted: 03.03.2018

DOI: 10.5799/jcei.343509

ABSTRACT

Objective: It is known that patients with multiple sclerosis have a high incidence of headache. Although there is increasing evidence to suggest that periaqueductal gray matter (PAG) plays a role in the pathophysiology of migraine headache, it is not known whether the type of headache may be a predictor of a MS relapse.

Patients and Methods: The study enrolled 100 patients (68 females, 32 males) with clinically confirmed MS diagnosis established by McDonald diagnostic criteria. The type and duration of MS, MRI localization of lesions and cognitive status were recorded for all patients. Patients were questioned whether they experience headache during MS attacks.

Results: Sixty-eight percent of the patients had headache and 32% of the patients were free of headache. Of the patients with headache, 16% had tension -type headache (TTH), 14% had migraine, 11% had primary stabbing headache (PSH), 8% had TTH+ migraine, 6% had PSH+ migraine, 6% had medication overuse headache, 2% had medication overuse headache + migraine, 2% had paroxysmal hemicrania, 1% had cervicogenic headache, 1% had chronic TTH, and 1% had unclassified headache. There was a statistically significant relationship between the presence of headache and MS relapse ($p < 0.001$). We found a statistically significant relationship between the type of headache and the localization of plaques in all MS patients in a statistical analysis using chi-square test, ($p < 0.001$).

Conclusion: Headache may be the only symptom of a flare-up in MS patients. The relationship between stabbing headache and MS relapses merits further investigation.

Key words: Multiple sclerosis, relapse, stabbing headache

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of unknown etiology which is characterized by relapses and predominantly affects women in the second or the third decade of life. MS relapses may occur with visual disturbances, motor and sensory involvement, or cerebellar or spinal involvement. Initial and relapse symptoms of MS may include acute brachial pain, sore throat, hypoglossal nerve palsy, epileptic seizures, and headache. It is known that headache is very common in patients with MS [1,2,3]. However, there are few studies evaluating headache as a presenting symptom or a predictor of a MS attack [4]. MS lesions, particularly those found in the brainstem

have been reported to be more commonly associated with migraine-type headaches [5]. Idiopathic stabbing headache is a repetitive, sharp pain with a short duration. There are no data in literature to suggest that, stabbing headache may be a predictor of a MS relapse and little is known on the coexistence of stabbing headache and MS. In this study, we aimed to investigate the frequency and subtypes of headache in patients with MS and to determine whether stabbing headache predicts a MS relapse.

PATIENTS AND METHODS

The study sample consisted of 100 patients who were referred to and followed at the Multiple

Sclerosis Ambulatory Clinic of the Neurology Department at Ankara Research and Training Hospital. Patients were enrolled consecutively, and symptoms were evaluated via interviews. The study was approved by the Ethics Committee of our hospital. The study inclusion criteria of patients attending to the specific ambulatory clinic for multiple sclerosis were as follows:

1. Providing written informed consent before participating in the study
2. Verified diagnosis of MS
3. Sufficient cognitive ability to answer questions

Revised McDonald criteria were used for the diagnosis of MS. Functional disability scores of MS patients were calculated using the Kurtzke Expanded Disability Status Scale (EDSS). The Mini-Mental test was used for cognitive evaluation of the patients. Headache types were identified according to the criteria of the international headache society (HIS). The aims of this study were to determine headache prevalence and the most common types of headache in MS patients to explore the relationship between headache type and plaque localization and to investigate the co-existence of headache and MS attack. Furthermore, we aimed to investigate average disease duration in MS patients and to determine correlation between EDSS scores and MS duration, and to determine MS subtypes and the relationship between these subtypes and EDSS scores for these subtypes. Based on neuroimaging study results of the patients, distribution of plaque localizations were identified. Distribution of drugs used for the treatment of MS was also investigated.

Consequently, two separate forms were generate. The first one was a headache form used for collecting the following data: age, gender, marital status, the time of onset of pain, frequency and duration of pain, daily and seasonal periodicity, localization, characteristics of pain, intensity, accompanying and triggering symptoms, migraine aura and its characteristics, effects of pain on quality of life, therapies for attacks and for prophylaxis, type and amount of analgesic used, previous diagnosis and treatments, concurrent systemic illnesses, pain characteristics during childhood, neurological examination, neuroimaging data, and response to therapy at follow-up. The second form (MS and headache questionnaire) was used to obtain the following data in addition to the first form: MS type and duration, localization of MR lesions, previous and ongoing MS therapy, cognitive status, the association of MS relapse with headache, EDSS scores. After completion of both forms, the responses to questions were re-evaluated by a specialist physician from the MS-specific ambulatory clinic. Both the patients experiencing a MS attack and the patients in remission were asked about previous attacks and its temporal relationship with headache retrospectively.

Statistical Analysis

SPSS 13 (Statistical Package for Social Sciences) was used for statistical analyses. Comparisons between independent groups were performed by using the Student's t-test. Relationship between different variables was tested using parametric and non-parametric

correlation tests and Chi-square test. The statistical significance level was set at 0.05.

RESULTS

Newly or previously diagnosed MS patients (n=100) were included to the study. The study sample (mean age \pm SD, 33.9 \pm 9.0 years) consisted of 68 females and 32 males. Of the patients, 68 (68%) had headache, whereas 32 (32%) were free of headache. Headache-positive group consisted of 19 (27.9%) males and 49 (72.1%) females. The mean disease duration was 5.7 \pm 4.1 years. A statistically significant association was found between MS duration and EDSS scores ($p < 0.001$) and age ($p = 0.001$). MS subtypes were as follows: relapsing-remitting MS (78%), primary progressive MS (12%), secondary progressive (MS 7%), progressive relapsing MS (2%). The diagnosis of patients in the headache-positive group was relapsing-remitting MS in 75%, primary progressive MS in 9%, secondary progressive MS in 6%, and progressive relapsing MS in 2% of the patients. Statistically significant associations were found between the MS subtype and cognitive failure, treatment medication and EDSS scores ($p < 0.001$). According to neuroimaging studies of the brain and spinal cord, distribution of lesion localizations were as follows: only cortical lesions in 34 patients (34%), cortical and brainstem lesions in 43 patients (43%), cortical + brainstem + spinal cord lesions in 21 patients (21%) and cortical + spinal cord lesions in 2 patients (2%). A chi-square test performed for all MS patients showed a statistically significant association between headache types and plaque localizations ($p < 0.001$). Fifty-one headache-positive Relapsing-remitting MS (RRMS) patients showed plaque localizations as only cortical lesion in 18 patients (35.3%), cortical and brainstem lesions in 22 patients (43.1%) and cortical + brainstem + spinal cord lesions in 11 patients (21.6%). In RRMS patients, there was no significant association between headache types and plaque localizations ($p > 0.05$). In 9 primary progressive MS patients, plaque localizations were cortical and brainstem in 6 patients (66.7%) and cortical + brainstem + spinal cord in 3 patients (33.3%). Treatment modalities in the study patients were as follows: pulse treatment in 68%, interferon in 20%, immunosuppressive agents in 3%, and combined therapy in 9% of the patients. Mini-Mental State Examination (MMSE) results demonstrated cognitive impairment in 92% of the patients (MMSE < 24) whereas 8% of the patients were intact. Cognitive impairment was significantly correlated with EDSS scores ($p = 0.001$). Higher EDSS scores indicated more severe cognitive impairment in MS patients. There were no significant associations between cognitive impairment and MS duration ($p > 0.05$), age ($p > 0.05$) and gender ($p > 0.05$). Mean EDSS score was 2.26 \pm 2.23 in study group and 2.3 \pm 2.36 in the headache-positive group. There were positive relationships between EDSS scores and MS duration ($p = 0.00$), cognitive impairment ($p = 0.00$), and age ($p < 0.001$). EDSS scores showed no statistically significant association with gender ($p > 0.05$). Sixty-eight percent of the patients had symptoms of headache, whereas 32% did not have any type of headache. In headache-positive participants, the frequency distribution of headache types was:

Multiple Sclerosis-Stabbing Headache

TTH 16%, migraine 14%, primary stabbing headache 11% (PSB), TTH+ migraine 8%, PSB+ migraine 6%, medication overuse headache 6%, medication overuse headache+ migraine 2%, paroxysmal hemicrania 2%, cervicogenic headache 1%, chronic TTH 1%, unclassified 1%. There was a statistically significant positive correlation between the existence of headache and the occurrence of MS relapse ($p < 0.001$), however, there was not any significant correlation between the occurrence of headache and MS duration ($p > 0.05$) nor between headache types and MS types ($p > 0.05$). Clinically, all headache-positive MS patients ($n = 68$) were distributed as RR 75%, RP 13.2%, SP 8.8%, PR 2.9%. When we examined headache types according to the clinical MS subtypes, we found that there was an interesting distribution of headache in RRMS group. The number of patients in this group was 51, and headache subtypes in this group included TTH (23.5%, $n = 12$), migraine (19.6%, $n = 10$), PSH (19.6%, $n = 10$), TTH+PSH (11.8%, $n = 6$), medication overuse headache (9.8%, $n = 5$), PSB+ migraine (7.8%, $n = 4$), medication overuse headache+ migraine (3.9%, $n = 2$), cervicogenic headache (2.0%, $n = 1$) and unclassified (2.0%, $n = 1$). In RRMS patients, there was no significant correlation between headache types and MS plaque localizations ($p > 0.05$).

The types of headache among 9 patients diagnosed with primary progressive MS were TTH (22.2%, $n = 2$), migraine (22.2%,

$n = 2$), PSB (22.2%, $n = 2$), paroxysmal hemicrania (22.2%, $n = 2$), and chronic TTH (11.1%, $n = 1$).

Thirteen percent of MS patients presented with headache and all of them were relapsing at the time of headache ($n = 13$). These patients either reported a new type of headache or worsening of an existing headache. There was a statistically significant positive correlation between the timing of headache and MS attack ($p < 0.001$). Headache episode (exacerbation of existing headache or a new type of headache) and MS relapse occurred simultaneously in 23.6% ($n = 12$) of 51 RRMS patients, whereas in the remaining 76.4% ($n = 39$) of patients there was no relationship between MS relapse and headache episode. It was found that 19.1% ($n = 13$) of the patients with headache were having a MS relapse at the same time. The remaining 80.9% did not show this temporal relationship.

In RRMS patients, headache types occurring during an MS relapse included PSH (66.7%, $n = 8$), TTH+PSH (16.7%, $n = 2$), PSB+ migraine (8.3%, $n = 1$), and TTH (8.3%, $n = 1$). We found a positive association between the type of headache and MS attack ($p < 0.001$). A summary of the headache types during MS relapse, together with clinical and neurological/radiological findings are presented in Table 1.

Table 1. Summary of headache types during MS relapse and clinical and neurological/radiological findings.

Patient No.	MS Type	Headache Type	Neurological Examination	MRI Findings	Electrophysiological Evaluation (VEP)
1	RRMS	PSH (fep)	Limitation in looking to the right and horizontal nistagmus	Multiple lesions in the cortex and brainstem	P100 latencies are prolonged at left
2	RRMS	PSH (fep)	Bilateral intentional tremor	Disseminated contrast-enhancing lesions in the cortex, cerebellum and brainstem	Bilateral P100 values normal
3	RRMS	PSH (fep)	Normal	Disseminated contrast-enhancing lesions in the cortex and cerebellum	Left P100 latencies longer than normal
4	RRMS	PSH (fep)	Bilateral reduced stretch reflex	Disseminated cortical contrast-enhancing demyelinating plaques	Bilateral N75, P100 within normal limits
5	RRMS	PSH (fep)	Plantar response, dorsiflexion on the right	Disseminated cortical contrast-enhancing plaques	Bilateral VEP values normal
6	RRMS	PSH (fep)	Right NLO, indistinct paresis in the bilateral lower extremity	Contrast-enhancing active lesions in the cortex, cerebellum and pons	Left and right VEP P100 responses longer than normal
7	RRMS	PSH (fep)	4/5 paresis in upper right extremity and 2/5 in lower extremity and spasticity	Contrast-enhancing plaques in the cortex, pons and spinal cord	Bilateral VEP responses longer and amplitudes smaller than normal
8	RRMS	PSH (fep)	Abnormal tandem walking	Contrast-enhancing active lesions in cortex, pons, bulbous and cerebellum	Bilateral P100 latencies prolonged
9	RRMS	TTH (rec)	Left indistinct paresis	Active plaques perpendicular to corpus callosum in periventricular area	-
10	RRMS	TTH+PSH (rec)	3/5 Quadriparesis in the right upper extremity and 2/5 in lower extremity, cerebellar test impaired	Contrast-enhancing active plaques in the cortex, brainstem, and areas of the spinal cord	Bilateral VEP, posterior-tibial SEP responses longer than normal
11	RRMS	TTH+PSH (rec)	Right indistinct hemiparesis and hemihypoesthesia, increased deep tendon reflexes	Active plaques in the cortex and brainstem	-
12	RRMS	Migraine +PSH (rec)	Normal	Bilateral demyelinating plaques with contrast enhancement in cortical and subcortical areas	Right P100 latency longer than normal
13	PPMS	Migraine (rec)	Right hemihypoesthesia and dorsiflexor plantar response	Active disseminated demyelinating plaques in cortical and subcortical areas	Right P100 wave latency value longer than normal

TTH: Tension Type Headache, PSH: Primary Stabbing Headache, PPMS: Primary-Progressive Multiple Sclerosis, RRMS: Relapsing-Remitting Multiple Sclerosis, fep: First episode, rec: Recurrence

Treatments for headache included NSAIDs in 36.76% (n=25), antidepressants in 36.76% (n=25), antiepileptic drugs in 13.23% (n=9), tryptans in 8.82% (n=6) and indomethacin in 4.41% (n=3) of the patients. When all study patients were evaluated, 60% of the patients had no psychological disorder, while 36% had depression, 3% had bipolar disorder, and 1% had psychotic symptoms. On the other hand, 41.2% of RRMS patients had (n=22) depression, 2% (n=1) had bipolar disorder, and 2% (n=1) had psychotic symptoms. Fifty-four percent of the patients (n=28) did not have any psychiatric disorder. Of the PPMS patients, 66.7% (n=6) had no psychiatric illness, whereas 33.3% (n=3) showed depressive symptoms.

DISCUSSION

MS is two to three times more common in women than in men [1]. In our study group, 68% of the patients were female and 32% were male, giving a female/male ratio of 2.1. In the headache-positive group, 27.9% of the patients were male and 49% were female with an approximate female/male ratio of 2.5.

The mean age was 33.9±9.0 years in the study sample and 33.5±8.6 years in headache-positive patients. The mean MS duration was 5.7±4.2 years in the study sample and 5.8±4.4 years in the headache-positive patients. Patients were in the second or third decade of life, which is consistent with literature [6]. Most common MS types were relapsing-remitting (85%), primary progressive (10%), progressive relapsing (4%), and secondary progressive (1%) [6].

The distribution of the MS types was as follows: RR (78%), PP MS (12%), SP MS (7%), PR MS (2%). Our findings were consistent with those reported in previous studies.

Most common localizations of MS plaques were the cortex and brainstem [7]. Previous studies reported that migraine prevalence is high in MS patients with brainstem demyelinating plaques in the red nucleus [8,9].

When the whole study patients were evaluated, the most common plaque localizations were cortex (35.3%) and cortex plus brainstem (43.1%). Among headache-positive MS patients, there were 31 (45.6%) patients with cortical and brainstem lesions, 20 (29.4%) patients with cortical lesions, 16 (23.5%) patients with cortical plus brainstem and spinal cord lesions and 1 (1.5%) patient with spinal cord and cortical lesions. These results are correlated with previous findings.

Plaque distribution in RRMS subtype was as follows: 18 patients (35.3%) with cortical lesions, 22 patients (43.1%) with cortical and brainstem lesions, and 11 patients (21.6%) with cortical + brainstem + spinal cord lesions. In RRMS patients, we could not find any significant association between headache types and plaque localizations ($p>0.05$). Plaque localization distribution in 9 patients with primary progressive MS diagnosis was cortical and brainstem lesions in 6 patients (66.7%), and cortical + brainstem + spinal cord lesions in 3 patients (33.3%). Although we could

not identify findings from other studies for a direct comparison, it has been demonstrated in several studies that particularly demyelinating plaques located in the red nucleus, periaqueductal grey matter, and substantia nigra lead to migraine type headache [8,9].

The reported prevalence of cognitive dysfunction is around 5% during the initial period of MS and increases at the later stages and it was 8% in our study sample [10].

The mean EDSS score was 2.26±2.23 for all patients and 2.3±2.36 in headache-positive group. There were statistically significant positive correlations between EDSS scores and MS duration ($p<0.001$), cognitive impairment ($p<0.001$), and age ($p<0.001$). EDSS scores were not significantly correlated with gender ($p>0.05$). Previous studies reported a mean EDSS score of 2.5-3.4 in headache-positive MS patients [11].

In terms of comorbid psychological disorders, depression and emotional disorders are particularly common in MS [12,13]. In our study sample, 36% of all MS patients had depression, 3% had bipolar disorder, and 1% had psychotic disorder.

In a study by Gee et al., the most common types of headache in MS patients were migraine-like headache (61.7%), tension-type headache (25.3%) and tension-type headache coexisting with migraine (13%) and overall prevalence of headache was estimated at (55.6%) [8]. D'Amico, et al. reported an overall headache prevalence of 57.7% among MS patients which included tension-type headache (31.9%), migraine (25.0%), unclassified headache (8.6%) and cluster headache (0.8%) [11]. In the present study, the prevalence of headache was 68%, which was higher than average prevalence figures reported in other studies. In our study, migraine alone had a prevalence of 14% and total prevalence of mixed headache including other headaches such as migraine was 22%. Tension type headache occurred at a frequency of 16% and considering mixed headaches including TTH, the total TTH prevalence was 26%. These figures are lower than those reported in literature. In our study, PSH alone occurred at a rate of 11% but coexisted with migraine and TTH in 19% of patients. The high prevalence of PSH either alone or together with other types of headache as observed in this study is a remarkable finding.

In addition, there are published papers on migraine comorbidity in MS patients, and headache may occur during MS relapses. However, a definite comorbidity rate has not been reported in literature [15-18]. Another striking finding of our study was that the presenting symptom was headache in 13% of the patients diagnosed with MS according to the revised McDonald criteria along with clinical evaluation and neuroimaging findings. These patients either reported a new type of headache or an exacerbation of a previous headache. This patient group received pulse steroid therapy for 3 to 5 days for the treatment of MS attack depending on their clinical findings and headache symptoms improved partially or completely in 3 to 10 days. They were not given a specific therapy for headache. As it is known that lesion enhancement on MRI remains visible on average for 4 to 6 weeks for MS plaques, follow-up brain MRI was not performed in this patient group.

There was a statistically significant positive correlation between the occurrence of headache and simultaneous MS relapse. When headache-positive MS patients were considered separately, 19.1% of them were having a MS relapse at the time of headache. This is a novel finding because no such data was reported previously. Acute inflammatory process may contribute to the co-existence of a MS attack and headache.

This co-morbidity was particularly striking in RRMS type. Headache and MS relapse occurred concurrently in 23.6% of RRMS patients. Headache types observed during an MS attack in RRMS patients included PSH (66.7%), TTH+PSH (16.7%), PSH+ migraine (8.3%) and TTH (8.3%). In our study, a considerably high frequency of PSH headache was observed during a relapse in the RRMS group. Also, a positive relationship was found between headache types and the relationship of headaches with attacks. To our knowledge, there is no data on the co-occurrence of stabbing headache during a MS relapse.

As reported in previous studies, treatment of headache in MS patients involve NSAIDs (25% of patients) and tryptans (6.5%). In our study, MS patients were given NSAIDs (25%), tryptans (6%), antiepileptics (9%), antidepressants (25%), and indomethacin (3%). These results are consistent with relevant literature.

In conclusion, headache is a common condition both in general population as well as in patients with multiple sclerosis. Observed coexistence of stabbing type headache in MS disease or MS relapse is a very striking finding. Increased cytokine synthesis and specifically IL-10, an anti-inflammatory cytokine- has been demonstrated during both MS and migraine attacks [19,20]. Considering data, it can be suggested that headache may be a result of an inflammatory process during MS relapses and thus may be a symptom of a MS attack. Headache may be the only symptom of attack in MS patients and the relationship between stabbing headache and MS attacks necessitates further investigation. It may be argued that the timing and location of active lesions might be related with headache in MS patients because contrast enhancement of MS plaques remains visible for 4 to 6 weeks. Further studies may therefore focus on inflammatory process markers and immunologic parameters and headache occurrence in relation to MS relapses.

Headache may be a component of MS disease and also stabbing type headache may be a symptom of MS relapse. Therefore, we suggest that headache should be investigated during examination of MS patients and a concurrent MS attack should be suspected at the time of headache in MS patients.

Conflict of Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received

REFERENCES

1. WenJuan H, WeiWei C, Xia Z. Multiple sclerosis: Pathology, diagnosis and treatments. *Exp Therap Med.* 2017;13: 3163-6.
2. Yetimallar Y, Seçil Y, Inceoglu AK, et al. Unusual primary manifestations of multiple sclerosis. *N Z Med J.* 2008;121:47-59.
3. Ergun U, Özer G, Şekercan S, et al. Headaches in the Different Phases of Relapsing-Remitting Multiple Sclerosis A Tendency for Stabbing Headaches During Relapses. *Neurologist.* 2009;15):212-6.
4. Elliott DG. Migraine in multiple sclerosis. *Int Rev Neurobiol.*2007;79:281-302.
5. Kister I, Caminero AB, Monteith TS, et al. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. *J Headache Pain.* 2010;11:417-25.
6. Ropper AH, Samuels MA. Multiple sclerosis and allied demyelinating diseases. *Adams and Victor's Principles of Neurology.* New York: McGraw-Hill Medical. 2009; 771: 796.
7. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1988;38 (suppl 1):194.
8. Gee JR, Chang J, Dublin AB, Vijayan N. The association of brainstem lesions with migraine- like headache: an imaging study of multiple sclerosis. *Headache.* 2005;45:670-7.
9. Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. *Headache.*1993;33:452-5.
10. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Curr Opin Neurol.* 2003;16:283-8.
11. D'Amico D, La MAntia L, Rigamonti A, et al. Prevalence of primary headaches in people with multiple sclerosis. *Cephalalgia.* 2004;24:980-4.
12. Serafin DJ, Weisbrot DM, Ettinger AB. Depression and multiple sclerosis. *Depress. Neurol. Disord.: Diagn. Manag.* 2012;157-176.
13. Carlos R., et al. The varieties of psychosis in multiple sclerosis: A systematic review of cases. *Multiple Sclerosis and Related Disorders.* 2017;12: 9-14.
14. Srivastava S, Soma, et al. Headaches in multiple sclerosis: cross-sectional study of a multiethnic population. *Clin Neurol Neurosurg.* 2016;143:71-5.
15. Sandyk R, Awerbuch GI. The co-occurrence of multiple sclerosis and migraine headache: the serotonergic link. *Int J Neurosci.* 1994;76:249-57.
16. Evans RW, Rolak LA. Migraine versus multiple sclerosis. *Headache.* 2001;41:97-8.
17. Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. *Headache.*1993;33:452-5.
18. Mansoureh T, et al. Headache in relapse and remission phases of multiple sclerosis: A case-control study. *Iranian J Neurol.* 2016;15:1-5.
19. Munno I, Marinaro M, Bassi A et al. Immunological aspects in migraine: increase of IL-10 plasma levels during attack. *Headache.* 2001;41:764-7
20. Beebe AM, Cua DJ, de Waal Malefyt R The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS). *Cytokine Growth Factor Rev.* 2002;13:403-12.