Influence of Psychological Stress on Headache in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To compare the prevalence and disability of headache in patients with systemic lupus erythematosus (SLE) with the general population and to assess the role of chronic psychological stress (CPS) in headache development.

Methods. One hundred seventy patients with SLE and 102 control subjects matched for age, sex, and level of education were included in this multicenter, cross-sectional study. CPS, headache-related disability, and chronic analgesic intake (CAI) were evaluated in all participants.

Results. No statistical differences in the prevalence of headache between both groups were observed but headache disability was significantly higher in patients with SLE. In addition, a higher average score in the Cohen Perceived Stress Scale (CPSS) and a higher prevalence of patients with CAI were observed in patients with SLE. In multivariate analysis, CPSS score was positively (OR 1.09; 95% CI: 1.03–1.14; p = 0.001) and CAI negatively (OR 0.43; 95% CI: 0.19–0.99; p = 0.049) associated with headache in patients with SLE.

Conclusion. Despite the prevalence of headache in patients with SLE and the general population being similar, headache-related disability may be higher in patients with SLE. Moreover, CPS might play a role in the pathogenesis of SLE headache, whereas CAI might have a protective effect against it. (First Release Feb 1 2014; J Rheumatol 2014;41:453–7; doi:10.3899/jrheum.130535)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ or system, including the central nervous system. Central neurological involvement is proteiform and frequent, occurring in up to 91% of patients with SLE[1]. One of the neurological symptoms most commonly referred to is headache, with a prevalence ranging from 23% to 68%[2,3,4,5]. However, the lack of specific criteria for headache in SLE has made the study of its prevalence and the factors involved in its pathophysiology difficult.

Most of the studies conducted to date suggest that the prevalence of headache in patients with SLE is similar to that observed in the general population[6]. Psychological factors, such as anxiety and depression, have been previously associated with headache in patients with SLE[7]. In addition, it is known that chronic psychological stress (CPS) may act as a predisposing, aggravating, and perpetuating factor for headache in the general population[8] and that the use of stress management therapies in healthy people are effective in the treatment of tension headache[9].

The aim of our study was to compare the prevalence of headache in a large cohort of patients with SLE with a healthy control group, as well as to assess the level of

headache-related disability and the possible influence of CPS in the development of headache in patients with SLE.

MATERIALS AND METHODS

Participants. One hundred seventy patients with SLE who fulfilled ≥ 4 of the American College of Rheumatology (ACR) criteria were recruited from 4 Spanish hospitals (Virgen de las Nieves University Hospital and San Cecilio University Hospital in Granada; Carlos Haya University Hospital in Málaga; Asturias Central Hospital in Oviedo). We excluded patients with SLE and less than 1 year of followup, and illiterate subjects. A control group of 102 subjects matched for sex, age, and level of education without a history of connective tissue disorder was recruited from hospital staff and relatives of patients with SLE. All participants were white and gave informed consent to participate. The local ethics committee approved the study.

Protocol and clinical assessment. This was a cross-sectional study conducted over a 6-month period. Patients and control subjects were assessed for demographic and educational data and current medications [including chronic analgesic intake (CAI)]. The participants were asked to recall any type of analgesic used at any dose when they suffered from headache or other types of pain, and the answers from patients with SLE were confirmed by consulting the medical records (a possible recall bias effect on the results, especially in the control group, was assumed). Headache status was defined as the presence of any type of headache during the last 12 months, regardless of the intensity or duration, and this information was confirmed by means of the medical records in the case of patients with SLE. The Migraine Disability Assessment (MIDAS) questionnaire was used to measure the level of headache-related disability. CPS was evaluated by means of the Cohen Perceived Stress Scale (CPSS). SLE-related information was obtained from the medical records of each patient. Disease activity and accumulated organ damage were measured with the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), respectively. Antiphospholipid syndrome (APS) was investigated and diagnosed according to revised Sapporo criteria[10] (Appendix 1).

Statistical analysis. The data are presented as the mean (SD) for continuous variables and as a percentage for categorical variables. Differences between continuous variables were tested for significance using the Mann-Whitney U test. Categorical data were analyzed using Pearson's chi-square test. A multivariate logistic regression analysis was used to identify independent determinants of headache (dependent variable) in patients with SLE. The independent determinants tested were age, sex, SLEDAI, SDI, chronic analgesic intake, APS, and CPS. All analyses used a 5% 2-sided level of significance. Statistical analyses were carried out using SPSS software for Windows (version 15.0; SPSS Inc.).

RESULTS

A total of 170 patients with SLE and 102 matched controls were included in our study. Their main characteristics are listed in Table 1.

Differences between patients with SLE and controls. No significant differences in age, sex, and level of education were found. The prevalence of headache was similar in both SLE and control groups (22.4% vs 22.5%, respectively; p = 0.988), but headache-related disability was significantly higher in patients with SLE (MIDAS score 11.9 ± 1.3 vs 6.8 ± 0.9; p = 0.007).

As expected, a significantly higher prevalence of CAI was found in the SLE group (61.8% vs 46.1%; p = 0.017). Lastly, a higher average score in the CPSS (25.7 ± 8.9 vs 21.4 ± 8.7, p < 0.001) was observed in patients with SLE.

Differences between patients with SLE with or without headache. Demographic and clinical data, as well as CPS assessment of patients with and without headache, are shown in Table 2. Patients with headache had a higher prevalence of APS (13% vs 5%, p = 0.023) and antiphospholipid antibodies (aPL; 13% vs 0%, p = 0.010). In addition, patients with headache had a higher average CPSS score (29.9 ± 8.9 vs 24.5 ± 8.7; p = 0.001). Lastly, patients without headache tended to have a higher chronic analgesic intake (65.9% vs 47.4%; p = 0.060). The type of analgesics used by patients with SLE were acetaminophen (75 patients, 71%), metamizole (37 patients, 35%), other nonsteroidal antiinflammatory drugs (NSAID; 44 patients, 42%; ibuprofen was the NSAID most frequently used, in 41 patients, 33%), and others (3 patients, 3%).

Multivariate analysis. The variables included in the multivariate analysis because of their significant association with headache in the univariate analysis or their clinical relevance were age, sex, SLEDAI and SDI scores, APS, chronic analgesic intake, and CPSS score. CPSS score was positively (OR 1.09; 95% CI 1.03–1.14; p = 0.001) and CAI was negatively (OR 0.43; 95% CI 0.19–0.99; p = 0.049) associated with headache in patients with SLE (Table 3).

DISCUSSION

The main findings of our study were (1) the prevalence of headache was similar in both SLE and control groups; (2) headache-related disability was significantly higher in patients with SLE; and (3) CPS was positively and CAI negatively associated with headache in patients with SLE.

Although the ACR described 5 types of headache as a clinical manifestation of SLE (migraine, tension headache, cluster headache, headache due to intracranial hypertension, and intractable nonspecific headache), precise classification criteria for them were not defined[11]. As a consequence of this lack of specificity in the criteria, the term "lupus headache" is recurrently identified in medical literature as headaches severe, disabling, persistent, and resistant to treatment, thus making it very difficult to establish a real causal relationship between SLE and headache. In line with this, Davey, *et al* compared the use of the International Headache Society (IHS) criteria with those given by ACR in 61 subjects with SLE, and found that, whereas IHS criteria enabled classification of all the headaches in the cohort, ACR criteria were not able to classify 22% of headache disorders[12]. Thus, they recommended using IHS criteria in all studies on headache in SLE until a revision of the ACR criteria was made.

The unspecific nature of the definition of lupus headache implies that the pathogenesis of headache in patients with SLE is mostly unknown. Circulating cytokines, vascular injury, or neural damage have been involved[13], but there is no current scientific evidence to support a particular mechanism for headache pathogenesis in patients with SLE[6]. However, we observed that CPS was higher and was associated independently from the presence of headache in patients with SLE, indicating the possible influence of CPS

Table 1. Main characteristics of patients with SLE and controls.

Characteristics	SLE Patients, n = 170	Control Group, n = 102	p
Age, yrs*	43.7 ± 13.5	43.8 ± 9.0	0.919
Female, n (%)	156 (92)	95 (93.1)	0.989
Level of education, n (%)			
Primary school or less	68 (40)	31 (30)	0.134
Junior school	60 (35)	21 (21)	
Secondary school/university studies	42 (25)	50 (49)	
Frequency of headache, n (%)	38 (22.4)	23 (22.5)	0.988
Headache disability (MIDAS)			
Group I, n (%)	20 (53)	16 (69)	0.542
Group II, n (%)	4 (11)	2 (9)	0.833
Group III, n (%)	7 (18)	2 (9)	0.237
Group IV, n (%)	7 (18)	3 (13)	0.586
Average score*	11.9 ± 1.3	6.8 ± 0.9	0.007
Chronic psychological stress			
Average score*	25.7 ± 8.9	21.4 ± 8.7	< 0.001
Chronic analgesic intake, n (%)	105 (62)	47 (46)	0.017
Organ involvement, n (%)			
Renal involvement	54 (20)		
Neurological involvement	15 (6)		
Anti-dsDNA + (> 30 IU/ml)	124 (73)		
APS, n (%)	12 (7)		
APL-positive, n (%)	17 (10)		
Age of SLE onset, yrs*	31 ± 12		
Duration of SLE, yrs*	12.4 ± 7.9		
SLEDAI*	2.4 ± 2.9		
SDI*	0.56 ± 1.03		

* Results are expressed as mean ± SD. aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI: SLE Disease Activity Index; ACR: American College of Rheumatology; MIDAS: Migraine Disability Assessment.

in the development of headache among patients with SLE for the first time in medical literature.

Currently, headache and stress are thought to be closely related. Stress can act as a predisposing factor that contributes to headache onset in people with preexisting vulnerability, as a trigger factor of attacks, and as a factor that accelerates progression to headache chronicity; lastly, the headache experience itself can induce stress[10]. Anxiety and psychological stress seem to be increased among patients with SLE[7] and our group previously found that CPS, and not stressful life events, worsens the clinical symptomatology perceived by patients with SLE[14].

Regarding therapeutics, stress reduction strategies can help prevent or break the cycle by which stress and headache exacerbate themselves reciprocally[8], and Holroyd, *et al*[9] described better results in the treatment of chronic tension-type headaches when stress management therapy was added to antidepressant therapy. Interestingly, it is known that patients with SLE usually have fewer and less effective stress coping strategies than the general population[15]. Coping with stress seems to favor an increased perception of well-being and good health, and the beneficial effects of different psychological strategies, such as self-help groups, counseling interventions, supportive-expressive group psychotherapy on a variety of symptoms or aspects of the disease have been documented[16]. In line with this, we previously reported that providing cognitive-behavioral therapy (Meichenbaum's stress inoculation therapy) to patients with SLE and high levels of CPS significantly reduced stress and other psychological effects related to it, such as anxiety and depression[17].

CAI, as we expected, showed a protective effect against the development of headaches in patients with SLE. This result may be because CAI in SLE may decrease or mask the presence of headache, especially mild ones. However, CAI may have been associated with a higher prevalence of medication overuse headache (MOH). Although we did not analyze the type of headache in each subject, we think the prevalence of MOH is probably low owing to the similarity found in the prevalence of headache in the general population and patients with SLE. Further, to develop, MOH requires not only an excessive use of analgesics, but also a certain level of genetic susceptibility. In line with this, Bahra, *et al* described that patients with arthritis and CAI did not show an increased incidence of MOH[18]. Moreover, diverse factors, such as low socioeconomic status and psychological comorbidities (depression and anxiety mainly), seem to increase the risk of MOH[19].

Table 2. Differences between SLE patients with or without headache.

Characteristics	SLE Patients without Headache, n = 132	SLE Patients with Headache, n = 38	p
Age, yrs*	45 ± 14	41 ± 11	0.109
Sex, female, n (%)	119 (91)	37 (97)	0.302
Level of education, n (%)			
Primary school or less	53 (40)	16 (42)	0.156
Junior school	41 (31)	17 (45)	
Secondary school/university studies	38 (29)	5 (13)	
Chronic analgesic intake, n (%)	87 (66)	18 (47)	0.060
Age of SLE onset, yrs*	31 ± 13	30 ± 10	0.641
Duration of SLE, yrs*	13 ± 8	11 ± 6	0.191
Renal involvement, n (%)	42 (32)	12 (32)	1
Neurological involvement, n (%)	10 (8)	5 (13)	0.330
Anti-dsDNA + (> 30 IU/ml), n (%)	100 (76)	24 (63)	0.182
APS, n (%)	7 (5)	5 (13)	0.023
aPL-positive, n (%)	0 (0)	17 (45)	0.010
Raynaud phenomenon, n (%)	12 (9)	3 (8)	0.300
SLE treatment, n (%)#			
Hydroxychloroquine	68 (52)	12 (32)	0.526
Prednisone	62 (47)	13 (34)	0.129
Azathioprine	7 (5)	2 (5)	0.864
Methotrexate	7 (5)	3 (8)	0.674
Mycophenolate mofetil	20 (15)	4 (10)	0.298
SLEDAI*	2.25 ± 2.53	3.11 ± 4.18	0.955
SDI*	0.58 ± 1.04	0.50 ± 1.03	0.443
Chronic psychological stress			
Average score*	24.5 ± 8.7	29.9 ± 8.9	0.001

* Results are expressed as mean ± SD. # Cumulative data. aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI: SLE Disease Activity Index; ACR: American College of Rheumatology.

Table 3. Variables associated with headache in patients with SLE, using logistic regression.

Explanatory Variable	OR	95% CI	p
Age	0.99	0.96–1.02	0.677
Sex, female	2.77	0.62–12.26	0.181
SLEDAI	1.09	0.98–1.22	0.129
SDI	0.92	0.63–1.35	0.672
APS	0.70	0.25–1.93	0.421
aPL	0.86	0.93–1.04	0.365
Chronic analgesic intake	0.43	0.19–0.99	0.049
Average CPSS score	1.09	1.03–1.14	0.001

aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; CPSS: Cohen Perceived Stress Scale; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ACR: American College of Rheumatology.

Like other authors, we did not find a link between headache and SLE activity[6]. In contrast, in the univariate but not in the multivariate analysis, both APS and positivity for aPL were significantly associated with headache. In this way, the role of Raynaud phenomenon in SLE headache is controversial. Mitsikostas, *et al* did not find any association[6], but subsequent studies have shown a risk of headache almost 3-fold higher in patients with SLE and Raynaud phenomenon[20]. APS is a known cause of headache and its implication in the pathogenesis of SLE headache has been the subject of much research. Among the possible mechanisms implicated in the pathogenesis of the headache of patients with SLE, the presence of aPL has been associated with multifocal cerebral infarcts and perivascular microgliosis[21]. Moreover, platelet activation and similar serotonergic involvement have been postulated as possible common pathogenetic mechanisms of both migraine and APS[22].

Despite a few studies previously describing a significant

link between headache and the presence of aPL[23], most of the research did not find such a correlation[6]. This disparity in the results may be due to the aforementioned lack of consensus regarding SLE headache criteria.

Some limitations affecting our study should be taken into account. Firstly, this is a cross-sectional study and no causal relationship between headache and CPS can be established. Secondly, some factors may have influenced the final results, such as the effect of an analgesics recall bias (especially in controls) or not considering the presence of anxiety or depression in the participants. Thirdly, we did not classify our patients according to their headache types, which could be of interest in the final results.

CPS could be a treatable factor in a patient with SLE headache. Further prospective studies that evaluate and confirm the association between CPS and headache and the efficacy of the stress control therapies are needed.

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APPENDIX 1. Definitions of measures.

Levels of educational were categorized as primary school (up to 8 yrs of education), junior school (8–12 yrs), and secondary school and/or university studies (> 12 yrs). Chronic analgesic intake was defined as the intake of analgesics due to headache or other types of pain during at least 10 days per month in the previous 3 months, a definition that coincides with the one established for Medication Overuse Headache[19]. The Migraine Disability Assessment questionnaire assesses the number of days in the previous 3 months in which activities were missed because of headache[24]. It is classified into 4 grades of severity: Grade I, score 0–5, minimal or infrequent disability with little or no treatment need; Grade II, score 6–10, mild disability with moderate treatment need; Grade III, score 11–20, moderate disability with urgent treatment needs; Grade IV, score > 21, severe disability with very urgent treatment needs. Cohen Perceived Stress Scale (CPSS) measures the degree to which situations in a person's life are appraised as stressful in the last month[25]. The scale consists of 14 questions with 5 possible answers that range from 0 (never) to 4 (always), with a final score from 0 (minimum perceived stress) to 56 (maximum perceived stress). Results of CPSS were presented as a continuous variable (CPSS score).