Clinical and Experimental Rheumatology 1999; 17: 467-470.

Headache in systemic lupus erythematosus and its relation to other disease manifestations

M. Amit[1,3]
Y. Molad[2,3]
O. Levy[1,3]
A.J. Wysenbeek[1,3]

[1]Department of Medicine B and Rheumatology Service, Assaf Harofeh Medical Center, Zerifin; [2]Department of Medicine D and Rheumatology Unit, Rabin Medical Center, Beilinson Campus, Petah Tiqva; [3]Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel

Mirit Amit, MD, Instructor in Internal Medicine; Yair Molad, MD, Lecturer; Ofer Levy, MD, Instructor in Internal Medicine; Arjeh J. Wysenbeek, MD, Clinical Associate Professor.

Please address correspondence and reprint requests to: Dr. M. Amit, Department of Internal Medicine B, "Assaf Harofeh" Medical Center, Zerifin 70300, Israel. E-mail: vazinam@post.tau.ac.il

Received on November 19, 1998; accepted in revised form March 17, 1999.

This manuscript was presented as an abstract in the 1997 annual meeting of the American College of Rheumatology (Amit M, Molad Y, Wysenbeek AJ. Headache in systemic lupus erythematosus and its relation to other disease manifestations. Arthritis Rheum 1997; 40: S256).

Key words
Systemic lupus erythematosus, headache.

ABSTRACT

Objective

To investigate headache in systemic lupus erythematosus (SLE) and its relation to other disease manifestations.

Methods

Clinical and laboratory variables of 148 SLE patients were prospectively recorded in a computed data base.

Results

The patients were divided into two groups. Group A consisted of patients who reported moderate to severe headache on at least two consecutive encounters, and Group B consisted of the remainder of the patients, with mild or no headache. The two groups did not significantly differ in age or in sex distribution.

Patients in Group A suffered from more severe joint pain and inflammation, muscle pain, photosensitivity, mouth ulcers, fever and fatigue. They also had higher disease activity scores, and a higher number showed central nervous involvement. There were no significant differences between the two groups in any of the laboratory variables examined, nor in the proportion of patients with renal involvement. The prevalence of non-thromboembolic central nervous system (CNS) manifestations was 7.2%. The sensitivity of headache for the diagnosis of non-thromboembolic CNS manifestations was 90.9%, and the specificity was 29.2%. On logistic regression analysis, the total arthritis score, muscle pain, fatigue and photosensitivity were each found to be significantly independently related to headache.

Conclusions

Headache is common in SLE, and in the majority of patients is related to musculoskeletal and constitutional disease manifestations.

Introduction

Headache is a common complaint in systemic lupus erythematosus (SLE), affecting up to 68% of patients (1). Various types of headache have been described in SLE. Migrainous headache (either classical or common migraine) is the most common type. Its prevalence is 10% to 40% (1-3), and it appears to be more common than in the general population (4). Tension headache, which is associated with muscular contraction, is also common. It affects up to 30% of SLE patients (1, 5).

Headache in SLE patients has frequently been suspected to result from serious central nervous system (CNS) involvement. Since the diagnosis of such involvement is sometimes not easy and requires advanced imaging techniques and invasive diagnostic procedures, it is important to study the significance of headache in SLE. Several studies in the past (most of them retrospective) have addressed the question as to whether headache in SLE patients indicates central nervous system (CNS) involvement and requires a change in therapy (1, 2, 5-7). Most of these studies failed to reveal such an association, however. Moreover, no association has been found between the presence of headache and other disease manifestations.

The association between migraine headache and the presence of anti-phospholipid antibodies in SLE patients has also been tested. While some of the studies suggested such an association to exist (8, 9), in other studies it has not been described (4, 10).

In the present cohort study we prospectively investigated the incidence of headache in SLE patients and the relationship of headache to serious CNS involvement, disease activity, the presence of anti-phospholipid antibodies and to other clinical and laboratory manifestations of SLE.

Patients and methods

Included in the study were 148 SLE patients, diagnosed according to the ARA criteria (11), who were followed at the Beilinson Medical Center and the Assaf Harofeh Medical Center rheumatology outpatient clinics in Israel between 1988 and 1996. At each encounter a patient history was taken and a physical examination was performed. The data were immediately transformed by the examining physician into 25 history and 29 physical examination variables on a scale of 0 - 3 (0-none, 1-mild, 2-moderate, 3-severe), and were prospectively recorded in a computed database, as previously described (12). All patients were assessed by one of four physicians in the

above clinics. Headache, which was defined according to the ARA dictionary of rheumatic diseases (13), was monitored in all patients and scored according to its severity: 0 = none; 1 = mild headache, not affecting daily life activities and not requiring any treatment; 2 = moderate headache, causing some interference with daily life activities; and 3 = severe headache, causing significant interference with daily life activities and requiring the use of analgesics and/or corticosteroids.

Laboratory data, where available, were also recorded at each encounter. Patients were divided into two groups. Group A consisted of patients who reported moderate to severe headache on at least 2 consecutive encounters, while Group B comprised the remainder of the patients. For each encounter a modified SLE Disease Activity Index score (SLEDAI) (14) was calculated, excluding the variable headache from the calculation.

Statistical analysis

Group interval data and ordinal data were compared by Wilcoxon's rank sum test and nominal data were compared by the χ^2 test. The correlations were tested by Spearman's rank correlation test. Multiple logistic regression analysis was used to investigate the relationship between variables. Data are presented as mean ± SE (standard error of the mean) for group interval data, and as percentages of the study groups for the nominal and interval data. Adjustment for multiple comparisons was not carried out.

Results

The study population consisted of 148 patients, of whom 136 (91.9%) were female. Their mean age was 41.5 ± 1.23 years (range 17.5 - 84.7 years). Fifty- two patients (35.1%) belonged to Group A and the remainder to Group B. Table I shows the demographic data of the two patient groups.

Table I. Comparison of demographic data for Group A and Group B patients.

	Group A	Group B	p-value
Number	52	96	
Age (yrs.)	43.19	40.63	NS
Female pts.	94.2%	90.6%	NS
Education (yrs.)	10.2	12.0	0.013

Table II. Comparison of Group A and Group B for major clinical (history and physical examination) and laboratory variables.

	Group A		Group B		p-value
Joint inflammation [a]	1.42 ± 0.2	[70.0]	0.92 ± 0.1	[51.0]	< 0.001
Fatigue [a]	2.79 ± 0.1	[98.1]	1.73 ± 0.1	[61.1]	< 0.001
Muscle pain [a]	1.84 ± 0.1	[76.0]	0.96 ± 0.1	[38.5]	< 0.001
Joint pain [a]	2.36 ± 0.1	[94.1]	1.66 ± 0.1	[78.1]	0.004
Photosensitivity [a]	1.68 ± 0.2	[74.5]	1.10 ± 0.1	[46.9]	0.005
Fever [a]	1.31 ± 0.2	[60.8]	0.81 ± 0.1	[39.6]	0.005
Mouth ulcers [a]	0.48 ± 0.1	[30.8]	0.18 ± 0.1	[14.5]	0.02
CNS involvement [b]	48.0%		22.9%		< 0.01
Nephritis [c]	48.1%		44.8%		NS
SLEDAI [d]	13.3 ± 1.0		9.8 ± 0.6		0.002
Prednisone [e]	11.9	[84.0]	10.3	[68.8]	NS
Hydroxychloroquine [f]	75.0%		71.8%		NS

[a] Score 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Prevalence of positive recordings for both groups is shown in parentheses;
[b] Percentage of patients with any of the following: seizures, psychosis, cerebritis, cerebral infarction, dementia;
[c] Percentage of patients with nephritis;
[d] SLE Disease Activity Index (headache excluded from calculation);
[e] Average dose of prednisone (mg/d);
[f] Percentage of patients treated with hydroxychloroquine.

The two groups did not significantly differ in age or in sex distribution, but the educational level was significantly lower in Group A. The mean duration of headache complaints was 430 ± 92 days. Data on the major clinical and laboratory variables examined in the two groups are shown in Tables II and III. Compared to Group B, patients in Group A suffered from more severe joint pain and inflammation, muscle pain, photosensitivity and mouth ulcers, as well as constitutional symptoms such as fever and fatigue. Patients in Group A also had higher modified SLEDAI scores and a higher proportion of patients with a history of CNS involvement (including psychosis, seizures, other non-thromboembolic CNS manifestations, and cerebral infarction). The two groups did not significantly differ in the proportion of patients treated with prednisone and its dosage, nor in the proportion of patients treated with anti-malarials and non-steroidal anti-inflammatory drugs. There was no significant difference between the two groups in any of the laboratory variables examined, such as anti-DNA, complement levels, anti-phosholipid antibodies, nor in the proportion of patients with renal involvement.

Table III. Comparison of major laboratory variables for Group A and group B.

	Group A	Group B	p-value
Anti-DNA [a]	32.5 ± 3.5	36.5 ± 3.2	NS
C3 mg/ml	71.6 ± 4.7	69.1 ± 3.4	NS
C4 mg/ml	15.2 ± 1.3	13.3 ± 0.9	NS
Anti-cardiolipin IgG [b]	2.56 ± 0.6	2.93 ± 0.6	NS

[a] Farr's method (%); [b] test result divided by the upper limit of the normal range.

A significant correlation was found between headache severity and the severity of joint pain ($R = 0.34$, $p < 0.001$), fatigue ($R = 0.39$, $p < 0.001$), fever ($R = 0.33$, $p = 0.03$) and photosensitivity ($R = 0.22$, $p < 0.001$). Non-thromboembolic CNS manifestations, including acute psychosis, seizures or change in consciousness, accompanied by abnormalities in cerebrospinal fluid and in CNS imaging, were rare events in our study population (7.2%), but they also correlated with the severity of headache.

The sensitivity of headache for the diagnosis of non-thromboembolic CNS manifestations was 90.9%, but its specificity was only 29.2%. On multiple lo-

Table IV. Relationship between headache and other clinical variables tested by multiple logistic regression analysis.

Covariate	Coefficient	S.D.	p-value
Intercept	-3.054	0.145	< 0.0001
Total arthritis score[a]	0.128	0.031	< 0.0001
Fatigue[a]	0.643	0.069	< 0.0001
Muscle pain score[a]	0.323	0.110	0.003
Photosensitivity[a]	0.279	0.080	0.0005
Raynaud's phenomenon[a]	0.180	0.107	NS
Fever[a]	0.097	0.132	NS

[a] Variables are expressed as a score of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe).

gistic regression analysis, using headache as the dependent variable, the total arthritis score, muscle pain, fatigue and photosensitivity were each found to be significantly independently related to headache (Table IV).

Discussion

In this study 35% of our SLE patients suffered from chronic or recurrent headache. Headache was not classified according to its type (migrainous or tension headache), but its frequency resembled the overall frequency of headache (migrainous and non-migrainous) reported in other studies (1, 3).

Headache can be a manifestation of many CNS diseases such as meningitis, brain vasculitis or infarction. Migrainous headache is thought to result from abnormal blood vessel reactivity (6, 15), which may be common to migraine and Raynaud's phenomenon (1 ,2 ,6). The role of antiphospholipid antibodies (APLA) in its pathogenesis has not been clearly defined (4, 8-10). Tension headache in SLE patients is thought to be related to reactive psychological mechanisms caused by chronic disease (1). Headache can also be caused by rare CNS events, such as superior sagittal sinus thrombosis (16).

In this study, we addressed the question as to whether the presence of severe and protracted headache in SLE patients is associated with other disease manifestations and to what extent it indicates serious CNS involvement. In our cohort patients who suffered from severe and protracted headache had more severe musculoskeletal as well as mucocutaneous manifestations than SLE patients not suffering from clinically significant headache. They also had more severe constitutional symptoms such as fever and fatigue.

There was no difference between the two groups in any of the laboratory variables examined, nor in the frequency of renal or other organ involvement. Other studies also failed to find any association between the presence of headache and other clinical and laboratory disease manifestations, including renal, pulmonary or cardiac involvement, or anti-dsDNA titers (1, 6). In several studies an association between migrainous headache and the presence of APLA was reported (7, 8), but other studies failed to find this association (4, 10). We also found no such association. In our study, patients who suffered severe and protracted headache had higher modified SLEDAI scores. This finding is in accordance with some studies which found headache to be related to disease activity (2, 4); other studies, however, did not find such a relationship (1, 17). It should be noted, however, that none of the above studies used the SLEDAI system to assess the activity of the disease. Therefore, our results cannot be directly compared to theirs.

In our cohort, patients who suffered from severe and protracted headache had a significantly lower educational level. Socioeconomic status has been implicated as a factor influencing the severity of SLE, as well as of other chronic diseases (18). Therefore, the differences in the SLEDAI score between the two groups in the present study may be, at least in part, attributable to differences in socioeconomic factors.

We found a higher proportion of patients with a past history of CNS involvement among those suffering from chronic or recurrent headache. In other studies in which the frequency of CNS involvement concomitant with the presence of headache in SLE patients was tested, no such difference was reported (2, 5, 7). The sensitivity of headache for the diagnosis of non-thromboembolic CNS manifestations was high but its specificity was low.

In multivariate analysis, using headache as the dependent variable, the total arthritis score, muscle pain, photosensitivity and fatigue were each independently related to headache. This is in agreement with the results of a factor analysis previously published by our group (19), in which headache was associated with fibromyalgia symptoms of nervousness and joint and muscle pain. The issue of fibromyalgia in SLE has recently been addressed (20, 21). It appears to be common in SLE patients, and is not associated with increased SLEDAI scores.

As mentioned above, in the present study we did not classify headache according to its type. It is possible that such a classification would result in smaller differences between patients suffering from any one of the types of headache and those without headache.

We conclude that headache is a common feature of SLE. In the majority of patients it is related to musculoskeletal and constitutional disease manifestations and is not specific for the diagnosis of serious neurological involvement.

References

1. VAZQUES-CRUZ J, TRABLOUSSI H, RODRIQUEZ A, GELI C, ROIG C, DIAZ C: A prospective study of chronic or recurrent headache in systemic lupus erythematosus. *Headache* 1996; 30: 232-5.
2. BRANDT KD, LESSELL S: Migrainous phenomena in systemic lupus erythematosus. *Arthritis Rheum* 1978; 21: 7-16.
3. OMDAL R, MELLGREN SI, HUSBY G: Clinical neuropsychiatric and neuromuscular manifestations in systemic lupus erythematosus. *Scand J Rheumatol* 1988; 17: 113-7.
4. MARKUS HS, HOPKINSON N: Migraine and headache in systemic lupus erythematosus and their relationship with antibodies against phospholipids. *J Neurol* 1992; 239: 39-42.
5. ATKINSON RA, APPENZELLER O: Headache and small vessel disease of the brain: A study of patients with systemic lupus erythematosus. *Headache* 1975; 15: 198-201.
6. MIZUTANI WT, HUTCHINSON M, OUISMORIO FP: Association of migraine headache and Raynaud's phenomenon in systemic lupus ery-

thematosus. *Arthritis Rheum* 1985; 28: S.63 (abstr. B47).

7. SFIKAKIS PP, MITSIKOSTAS DD, MANOUSSAKIS MN, FOUKANELLI D, MOUTSOPOULOS HM: Headache in systemic lupus erythematosus: A controlled study. *Br J Rheumatol* 1998; 37: 300-3.
8. LEVINE SR, DEEGAN MJ, FUTRELL N, WELCH KMA: Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. *Neurology* 1990; 40: 1181-9.
9. HOGAN MJ, BRUNET DG, FORD PM, LILLICRAP D: Lupus anticoagulant, antiphospholipid antibodies and migraine. *Can J Neurol Sci* 1988; 15: 420-5.
10. MONTALBAN J, CERVERA R, FONT J *et al.*: Lack of association between anticardiolipin antibodies and migraine in systemic lupus erythematosus. *Neurology* 1992; 42: 681-2.
11. TAN EM, COHEN AS, FRIES F *et al.*: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
12. WYSENBEEK AJ, LEIBOVICI L, WEINBERGER A, GUEDJ D: Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. *Br J Rheumatol* 1993; 32: 633-5.
13. AMERICAN RHEUMATISM ASSOCIATION: *Dictionary of the Rheumatic Diseases*. New York, Contact Association International Ltd., 1982; 1:7.
14. BOMBARDIER C, GLADMAN DD, UROWITZ MB, CARON D, CHANG CH and the COMMITTEE ON PROGNOSIS STUDIES IN SYSTEMIC LUPUS ERYTHEMATOSUS: Derivation of the SLEDAI, a disease activity index for lupus patients. *Arthritis Rheum* 1992; 35: 630-40.
15. KOSTER KING K, KORNREICH HK, BERNSTEIN BH, SINGEN BH, HANSON V: The clinical spectrum of systemic lupus erythematosus in childhood. Proceedings of the conference of rheumatic diseases of childhood. *Arthritis Rheum* 1977; 20: 287-94.
16. FLUSSER D, ABU-SHAKRA M, BAUMGARTEN-KLEINER A, FLUSSER G, SUKENIK S: Superior sagittal sinus thrombosis in a patient with systemic lupus erythematosus. *Lupus* 1996; 5: 334-6.
17. ISENBERG DA, MEYRICK-THOMAS D, SNAITH ML, MCKERAN RO, ROYSTON JP: A study of migraine in systemic lupus erythematosus. *Ann Rheum Dis* 1982; 41: 30-2.
18. WYSENBEEK AJ, LEIBOVICI L, WEINBERGER A, GUEDJ D: Expression of systemic lupus erythematosus in various ethnic Jewish Israeli groups. *Ann Rheum Dis* 1993; 52: 268-71.
19. WYSENBEEK AJ, LEIBOVICI L, AMIT M, WEINBERGER A: Disease patterns of patients with systemic lupus erythematosus as shown by application of factor analysis. *J Rheumatol* 1992; 19: 1096-9.
20. GLADMAN DD, MACKINNON A, GOUGH J UROWITZ MB: Fibromyalgia is a major contributor to quality of life in lupus. *J Rheumatol* 1997; 24: 2145-8.
21. MIDDLETON GD, LIPSKY PE, MCFARLIN JE: The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. *Arthritis Rheum* 1994; 37: 1181-8.