

Somatic and Psychological Features of Headache in Systemic Lupus Erythematosus

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ABSTRACT. Objective. Headaches — especially of migrainous type — have been considered part of the disease spectrum of systemic lupus erythematosus (SLE). We wished to characterize prevalence and types of headaches in SLE and find out if headache is associated with disease, personality traits, or other psychological factors.

Methods. Fifty-eight consecutive Caucasian patients with SLE were given a clinical examination. We recorded SLE disease activity according to the SLE Disease Activity Index, types of headache according to International Headache Society criteria, and personality traits and emotional status according to Minnesota Multiphasic Personality Inventory-2 and Beck Depression Inventory (BDI).

Results. Thirty-eight SLE patients (66%) were headache sufferers; of these, 22 patients (38%) had migraine and 21 (36%) had tension-type headache. Headaches were not associated with disease activity or any other disease associated variable, including tests for antiphospholipid antibodies. Migraine was associated only with a tendency to social isolation and anxiety, while tension-type headache was associated with psychological distress, such as anxiety, somatic complaints, reduced energy, mental tension, social discomfort and withdrawal, and depressive mood according to the BDI.

Conclusion. Migraine and tension-type headaches occur frequently in patients with SLE. Migraine shows the same clinical presentation as in a non-SLE population, and may not be part of a neuropsychiatric disease spectrum. This also applies to tension-type headache, which in contrast to migraine shows some associations with emotional and personality traits, and could represent components of a chronic pain syndrome. (J Rheumatol 2001;28:772–9)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

HEADACHE

MIGRAINE

NEUROPSYCHOLOGY

Systemic lupus erythematosus (SLE) is a disease characterized by a broad clinical spectrum and an array of immunological abnormalities. Involvement of the nervous system is reported to occur in up to 50% of patients, preferentially as manifestations of the central nervous system often termed neuropsychiatric SLE (NPSLE). These may be of both neurological and psychological nature^{1,2}. Headache of mainly migrainous or tension-type has for many years been considered important, in some studies occurring in almost

70% of patients³⁻⁶. Some speculate that there exists a genuine “lupus headache,” which is severe, disabling, persistent, and not responsive to narcotic analgesics^{2,7,8}. This form of headache has even been included in the criteria for assessing disease activity of SLE⁹. Notably, the American College of Rheumatology (ACR) ad hoc Committee on Neuropsychiatric Lupus Nomenclature recently judged this headache not to be specific enough to warrant inclusion among the criteria for NPSLE¹⁰.

International criteria to characterize and quantitate headache¹¹ have recently been more widely applied, and have facilitated comparative studies of prevalence and presentation. Such studies have not been able to confirm any influence on headache presentation by disease activity or severity^{3,12}. It is still unclear, however, whether headache in general — or only certain types of headaches like migraine, or perhaps only migraine with aura — represent part of the SLE disease spectrum. An alternative may well be that these phenomena are related to unspecific factors related to systemic or chronic disease, precipitating headache in susceptible individuals¹³.

Although migrainous headaches have traditionally been associated with SLE, evidence has emerged that tension-type headache in SLE might be at least as frequent as the migrainous type^{3,12,14}. Both migraine and tension-type

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Dr. Omdal was supported as a Postdoctoral Research Fellow by the Norwegian Research Council for Science and the Humanities and the Norwegian Foundation for Health and Rehabilitation.

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Submitted June 5, 2000 revision accepted October 19, 2000.

headaches are known to be influenced by affective or other psychological conditions, as well as sociodemographic and genetic factors^{15,16}. Some evidence also indicates that migraine with and without aura constitute 2 separate entities, where the former category is largely dependent on genetic factors, thus representing a more “biological” based headache¹⁶.

On the basis of these considerations, as well as recent publications that question if headache in SLE is actually more prevalent than in the general population^{12,14}, we wished to characterize types and prevalence of headache in an unselected Caucasian SLE population, and to investigate to which degree headache was associated with disease or other relevant factors.

MATERIALS AND METHODS

All the medical records of in- and outpatients with a diagnosis of SLE seen at the University Hospital of Tromsø from 1979 to 1995 were reviewed. This hospital offers local hospital service to roughly 150,000 inhabitants of Troms county, and central and regional hospital service to Troms, Finnmark, and part of Nordland counties, with a total of 450,000 inhabitants. Ninety-four patients fulfilled the 1982 revised ACR criteria for SLE¹⁷. Seventeen patients were dead, 3 had moved to another part of the country, and 4 patients were excluded due to foreign language, Down syndrome, or terminal cancer. Of the remaining 70 patients, 58 (83%) gave informed consent to be included in the study, which was approved by the regional research ethics committee. Of the 58 patients, all but one were outpatients, and the majority of these were recruited on local or central hospital basis. Fifty-one (88%) of these were women and 7 (12%) were men. Ages ranged from 23 to 73 years, mean 47.2 ± 12.8 years. Mean disease duration was 14.9 ± 8.9 years (range 2–36). Disease activity was measured by SLE Disease Activity Index (SLEDAI)⁹, excluding the item of “lupus headache” when testing for correlations between disease activity and headache variables (modified SLEDAI).

Headache was assessed according to a structured interview and diagnostic algorithm by one of the authors (WK) and classified according to the International Headache Society (IHS) criteria¹¹. This classification system details which clinical features must be present to establish a precise diagnosis of headaches, cranial neuralgias, and facial pain syndromes. It is most useful for grouping patients for scientific purposes, but more cumbersome in daily use. Prevalence was defined as one or more headache attacks during the last 6 months. When in doubt, a neurologist (SIM) was consulted.

Emotional status and personality traits were assessed by the revised version of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), which has been widely used as an objective descriptive measure of psychological functioning¹⁸ and was also used in the study of psychological problems associated with medical disorders¹⁹. The Beck Depression Inventory (BDI) was used for assessing mood²⁰. It is a self-completed questionnaire of 21 items in multiple choice format and assesses current levels of symptomatic depression with good reliability and validity²¹.

In addition to routine hematological, biochemical and immunological tests in all patients at the hospital laboratory, the lupus anticoagulant test (LAC) was performed by a commercial lupus anticoagulant sensitive activated partial thromboplastin time (APTT) reagent (PTT-LA; Diagnostica Stago). In cases of ≥ 6 seconds prolongation of clotting time, confirmation assays were done at the Hematological Laboratory, Ullevål University Hospital, Oslo, as described²². Anticardiolipin antibodies (aCL) of IgG and IgM isotypes were tested by a commercial ELISA (Shield, Dundee, UK) according to the manufacturer. Values above 30 GPL and 30 MPL U/ml were considered positive. Tests for anti- β_2 -glycoprotein 1 antibodies (β_2 -GPI) of IgG and IgM isotypes were by ELISA (Imtec Immundiagnostica,

Berlin, Germany). Values > 7 U/ml were considered positive according to the manufacturer’s recommendations.

Statistics. Results are presented as means. Unpaired t tests (2 tailed) or analysis of variance (ANOVA) were used to test differences between 2 or more groups of quantitative data, and chi-square tests for categorical data. Fisher’s protected least significance difference (PLSD) was applied for post hoc analysis of significant effects found in ANOVA. For calculation patients with SLE were grouped in 3 different ways: Group A consisted of the 2 categories “headache, no headache” ($N = 38, N = 20$), where the first category comprised all kinds of headache. Second, all patients with SLE were grouped into 4 categories (Group B): “pure migraine” (with and without aura), “pure tension-type headache” (episodic and chronic), “combination headache” (migraine and tension-type), and “no headache” ($N = 16, N = 15, N = 6, N = 20$). Finally, Group C, with 3 categories: “migraine with aura” ($N = 8$), “pure tension headache” ($N = 15$), and “no headache” ($N = 20$). In this group migraine without aura and combinations of tension-type and migraine without aura were removed from analysis to determine if migraine with aura was more closely associated with somatic features of SLE.

RESULTS

At the time of examination 12 of the 58 patients (21%) were not taking any drug for SLE. Thirty-five patients (60%) were taking prednisolone, 25 (43%) antimalarials, 13 (22%) azathioprine, or combinations of these drugs. Two patients were undergoing intravenous cyclophosphamide pulse therapy. Mean SLEDAI score was 5.7 ± 5.3 , and for modified (23 item) SLEDAI 5.1 ± 4.4 .

Headaches (Table 1 and Figure 1). Thirty-eight of the 58 patients (66%) were found to be headache sufferers. Two patients had lupus headache according to SLEDAI definitions⁹. According to the IHS criteria¹¹ 22 patients (38%) had migraine, 8 patients with aura and 14 without aura (14% and 24%, respectively, of all SLE patients). If only SLE patients with migraine were considered, 8 of these 22 patients had migraine with aura (36%), and 14 had migraine without aura (64%).

Twenty-one patients (36%) had tension-type headache, of whom 17 had episodic and 4 chronic tension-type headache (29% and 7% of all SLE patients, respectively). One patient had a headache impossible to classify. This patient is omitted from the calculation when the different types of headache are analyzed statistically (Groups B and C). If only headache sufferers were considered ($N = 38$), migraine occurred in 22 (58%) of these, tension-type in 21

Table 1. Number of patients (%) with different types of headache in 58 patients with SLE.

Headache	Single-type Headache	Combination Headache	Total
Migraine	16 (28)	6 (10)	22 (38)
With aura	7 (12)	1	8 (14)
Without aura	9 (16)	5 (9)	14 (24)
Tension-type	15 (26)	6 (10)	21 (36)
Episodic	12 (21)	5 (9)	17 (29)
Chronic	3 (5)	1	4 (7)

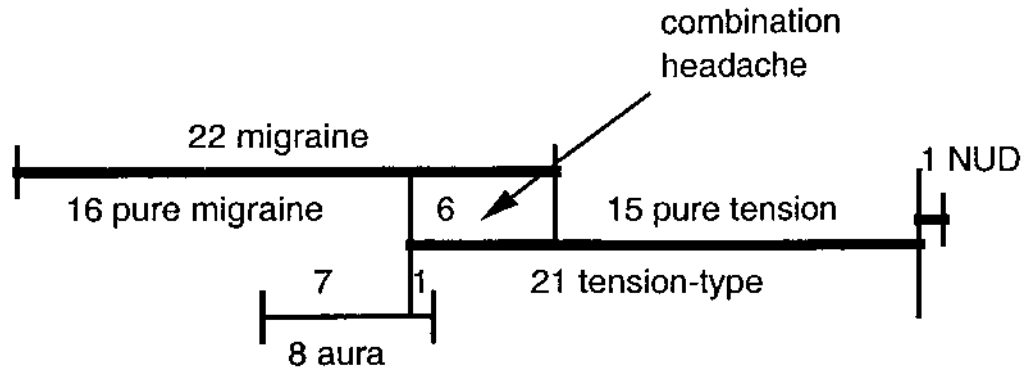


Figure 1. Types of headache reported by 38 out of 58 patients with SLE.

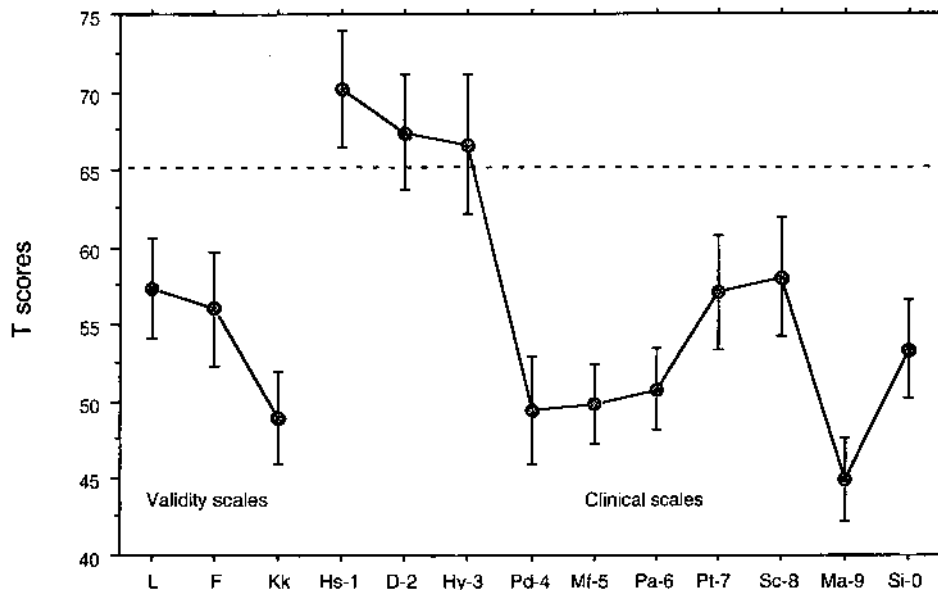


Figure 2. MMPI-2 profile of 51 patients with SLE. Mean T scores, 95% confidence interval, and normative cutoff score (broken line) are shown.

patients (55%), and both migraine and tension-type in 6 (16%).

MMPI-2. MMPI-2 was completed by 51 of the 58 patients (88%). The t scores for validity and clinical scales are graphically presented with means and confidence intervals in Figure 2. The standard procedure is to focus on those scales with T score values ≥ 65 as having clinical psychopathological significance. The mean profile of the SLE patients presented scale elevations for T scores ≥ 65 for clinical scale 1, Hypochondriasis (Hs-1), scale 2, Depression (D-2), and scale 3, Hysteria (Hy-3). Thirty-eight patients (75%) had a score ≥ 65 on scale 1 (Hs-1), which is associated with vague and nonspecific complaints about physical function¹⁸. Twenty-seven patients (53%) had abnormal scores (≥ 65) on scale 2 (D-2), consistent with significant depressive mood in a considerable number of the SLE patients. Further, 29 patients (57%) had a score of ≥ 65 on scale 3 (Hy-3). Similarly, 7 patients (14%) had abnormal

scores on scale 4, Psychopathic deviate (Pd-4), 3 (6%) on scale 5 Masculinity-femininity (Mf-5), 5 patients (10%) had abnormal scores on scale 6, Paranoia (Pa-6), 11 (22%) on scale 7, Psychasthenia (Pt-7), 13 (26%) on scale 8, Schizophrenia (Sc-8), and 9 (18%) on scale 0, Social introversion (Si-0).

Beck Depression Inventory. Fifty patients (86%) completed the BDI questionnaire. The group mean scores (9.7 ± 7.3) were within normal range. Eleven of the SLE patients (22%) were classified as depressive since they achieved scores > 13 , which is defined as the cutoff score in BDI²¹.

Laboratory tests. Positive tests for LAC were found in 3 out of 56 patients (5.3%), aCL IgG in 6 (10.3%), and aCL IgM in 3 patients (5.2%) out of 58. β_2 -GPI IgG was positive in 35 patients (60%) and β_2 -GPI IgM in 14 patients (40%), both out of 58 patients.

Relationship of headache to other variables. Age, sex, hypertension, disease duration, or modified SLEDAI did not

differ between patients with or without headache, or between those with different kinds of headache and those without (all groups A, B, or C). Neither were any associations observed between any category of headache to current use of, or number of months treated with, prednisolone, anti-malarials, azathioprine, cyclophosphamide, or to no current drug treatment, or number of months without treatment, for SLE. This also applied for spontaneous abortions, thromboembolic episodes, LAC, both aCL and β_2 -GPI of IgG and IgM isotypes, and for routine immunological and biochemical tests like antinuclear antibodies, anti-DNA, complement factors C3 and C4, erythrocyte sedimentation rate, hemoglobin, leukocytes, platelets, etc.

MMPI-2. In Group A (headache, no headache) significant differences in scores between SLE patients with and without headache were only found for hypochondriasis (Hs-1), for psychasthenia (Pt-7), and for social introversion (Si-0). For hysteria (Hy-3), it was close to significance (Figure 3).

In Group B (migraine, tension-type, combination, no headache) significant differences were only observed for social introversion (Si-0). Post hoc (subgroup) analysis revealed that this was due to significantly higher scores in SLE patients with tension-type headache and also migraine compared to SLE patients with no headache ($p = 0.02$ and $p = 0.04$, respectively), and a trend for combination type headache compared to no headache ($p = 0.05$) (Figure 4).

In Group C (migraine with aura, tension-type, no headache), significant differences were found between the various headache categories and hypochondriasis (Hs-1), hysteria (Hy-3), psychasthenia (Pt-7), and social introversion (Si-0) (Figure 5). Post hoc analysis revealed these differences to be due to the following. For hypochondriasis (Hs-1): higher scores in tension-type compared to no headache ($p = 0.004$), and a trend between migraine with aura and no headache ($p = 0.05$). In hysteria (Hy-3): higher scores in patients with tension-type headache compared to

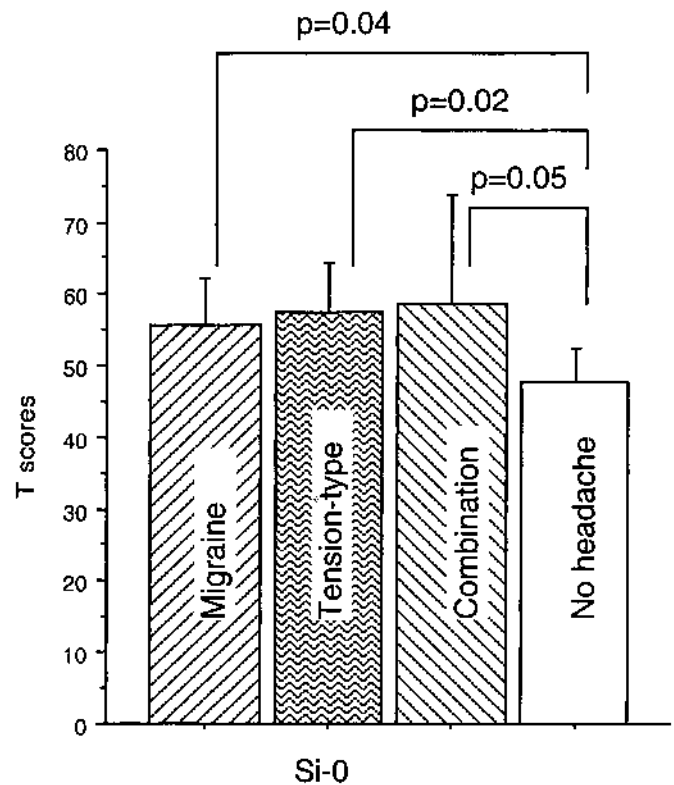


Figure 4. MMPI-2 scores in patients with SLE; Group B: Migraine, tension-type headache, combination headache, no headache (N = 51). Significant differences observed only in scale Si-0.

no headache ($p = 0.02$). In psychasthenia (Pt-7): higher scores both in patients suffering from migraine with aura and patients with tension-type headache compared to patients with no headache ($p = 0.02$ and $p = 0.04$, respectively). In social introversion (Si-0): higher scores in tension-type compared to no headache ($p = 0.01$).

Beck Depression Inventory. In Group A (headache, no headache) there were significantly higher scores for SLE patients with headache (11.3 ± 8.0) versus patients without headache (6.9 ± 4.9 ; $p = 0.04$). No such differences in depression were observed in Group B (migraine, tension-type, combination, no headache), while in Group C (migraine with aura, tension-type, no headache) the differences between headache categories were due to significantly higher BDI scores in patients with tension-type headache compared to those with no headache ($p = 0.007$) (Figure 6).

DISCUSSION

We found that the prevalence of any kind of headache in patients with SLE is 66%. For all practical reasons we estimate our 0.5 year prevalence is equal to the 1 year prevalence, which is a frequently used prevalence measure for headache. This means that 2 out of 3 patients with SLE were headache sufferers, a figure compatible with other reports³. In accord with recent studies^{3,14} these headaches were

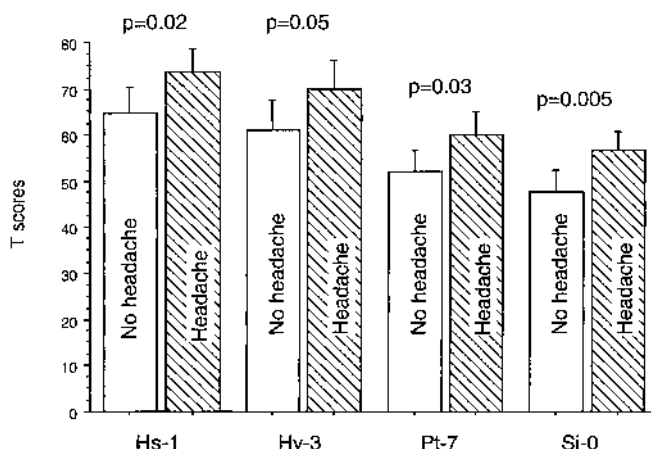


Figure 3. MMPI-2 scores in patients with SLE; Group A: Headache, no headache. Significant differences were observed only in scales Hs-1, Hy-3, Pt-7, and Si-0 (as shown).

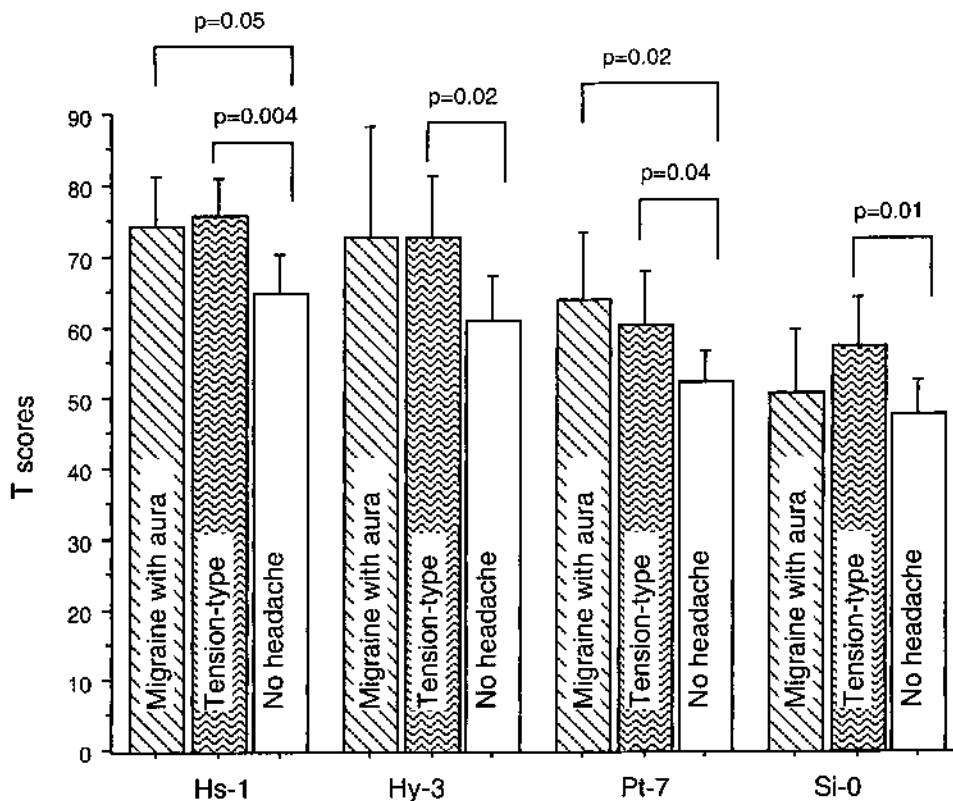


Figure 5. MMPI-2 scores in patients with SLE; Group C: migraine with aura, tension-type headache, no headache (N = 38). Patients with more than one type of headache were excluded. Significant differences were observed only in scales Hs-1, Hy-3, Pt-7, Si-0 (as shown).

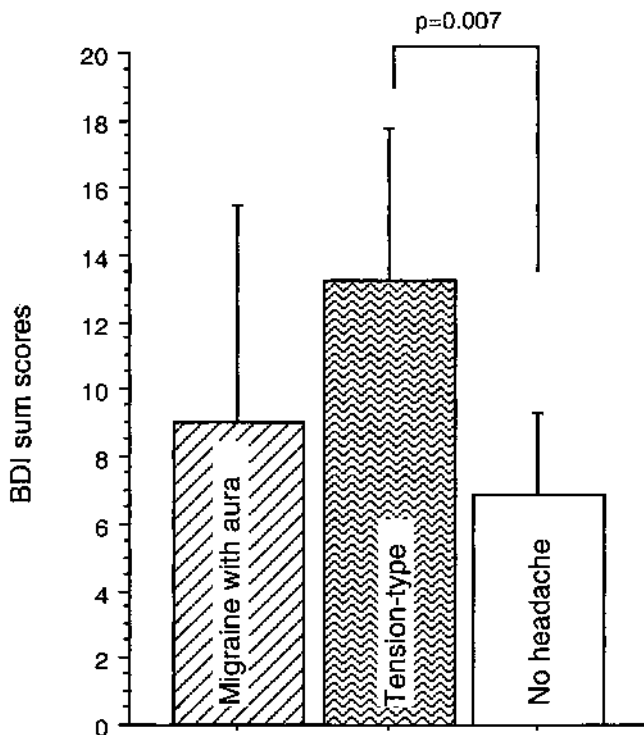


Figure 6. Beck Depression Inventory sum scores in patients with SLE; Group C: migraine with aura, tension-type headache, no headache (N = 38). Patients with more than one type of headache were excluded.

almost exclusively migraine with or without aura (38%) and episodic or chronic tension-type headache (36%). Combination of headaches were seen in 10% of patients. This pattern of more or less equally distributed tension-type headache and migraine was also noted in other studies in SLE^{3,4,14,23}. Notably, our study is short of a control group, a fact that limits the conclusions regarding the relative prevalence of headache in the cohort.

Migraine. With the above considerations in mind we found the prevalence of migraine comparable to the controlled study on SLE by Markus, *et al*⁴ and the prospective study by Vazquez-Cruz, *et al*³, but regrettably neither of these studies applied IHS criteria¹¹. In SLE studies where these criteria were used, there were somewhat smaller prevalences of migraine (Sfikakis, *et al*¹² 26%; Fernandez-Nebro, *et al*¹⁴ 22.5%). Because of missing controls, we are unable to compare the figures with the prevalence in the normal population, but the Copenhagen population study by Rasmussen, *et al*²⁴ found the 1 year overall prevalence to be 15% in women and 6% in men.

A possibly overlooked phenomenon regarding migraine and SLE is the large age and sex variations of migraine. Several population based studies on migraine show that the prevalence of migraine varies considerably with age and sex, and there is a maximum prevalence around age 40¹⁵,

with a prevalence in women of about 25%. One study found migraine in women was 3–4 times more frequent than in men²⁵. In the USA the 1 year overall prevalence of migraine in women was 17.6% and in men 5.7%, but it was considerably higher in age groups 35–45 years for both sexes, reaching almost 40% for women in low income groups of this age²⁶. Our hypothesis is therefore that in studies of migraine in SLE, it is important to know that because of sex and age of SLE patients, these patients will tend to be in the upper risk group for migraine, and this may explain the reportedly high prevalence for migraine in the SLE literature. The most recently published controlled study of migraine in SLE supports this view, as the overall prevalence of migraine was similar in patients with SLE and controls¹⁴. This is also supported by a Greek study, where equal frequencies of headache were seen in patients with SLE and controls, although subgroups of headache were not stated¹². On the other hand, 2 studies found lower migraine prevalence in the control groups, but IHS criteria were not applied^{4,27}.

We found migraine with aura to constitute 1/3 of all migraine in patients with SLE. This is the same ratio as observed in population based migraine studies²⁸, as well as in recent SLE studies^{3,12}, although one SLE study (not applying IHS criteria) observed “classical migraine” (migraine with aura) somewhat more frequently than common migraine⁴.

In agreement with most recent studies, the presentation of migraine with or without aura was not related to any SLE disease associated variable. There are hypotheses that migraine with aura constitutes a more biological entity on a genetic basis¹⁶. We could not confirm this subgroup to show any comorbidity to SLE. Notably, there were no associations to disease activity, disease duration, thromboembolic episodes, medication for SLE, or any routine biochemical or immunological test including tests for antiphospholipid antibodies. Although such antibodies have been associated with several neurological disorders, our findings do not support a role for them as a pathogenic factor for migraine, in accord with other reports^{4,14,23}.

On a group basis the emotional status and personality profile of all the SLE patients both with and without migraine indicate psychological dysfunctions such as excessive bodily concern, depressive symptoms, reduced energy, and somatic complaints. This is similar to the pattern found in patients with chronic pain, who show characteristic “neurotic profiles” with elevations of MMPI scales Hs-1, D-2, and Hy-3. Nevertheless, statistically significant associations to migraine were found only for social isolation, and for migraine with aura only for anxiety. This is in accord with one population study, where migraine with aura was more closely associated with anxiety than migraine without aura²⁹, but this study was confined to evaluating more severe psychiatric aspects. Anxiety is also known to be an

important factor in migraine¹⁵ and is a characteristic psychological feature of patients with SLE¹³. Most MMPI studies on migraine conclude that migraine patients fall within the normal ranges in contrast to the abnormalities of personality traits found in tension-type and combination headaches³⁰.

Depression as evaluated by MMPI-2 and BDI was notably not increased in the SLE patients with migraine, a finding apparently in contrast to population studies of migraine showing major depression to be an important association^{15,29,31}. Notably, these studies were confined to investigating the more severe psychiatric aspects and not minor depression as evaluated by our instruments. The influence of minor affective disturbances on migraine is therefore less well known, and this also applies for such influence on migraine in SLE.

Taken together, and with the lack of a control group in mind, these observations of prevalence, clinical presentation, and lack of associations to disease variables indicate that migraine is not comorbid with SLE, but the reported high frequency is due to methodological artifacts related to the peak prevalence of both diseases among women in middle age. Migraine may therefore not be a part of the neuropsychiatric disease spectrum in SLE.

Tension-type headache was found as frequently as migraine in our SLE patients (Table 1) and matches the data for tension-type headache in SLE found by Vasquez-Cruz, *et al*³, and the prevalence was slightly higher than those reported in 2 other studies (23.9% and 27%)^{4,14}. As in the general population, the episodic-type dominated³². In surveys of the general population, the prevalence of tension-type headache shows a considerable variation in prevalence (30–80%), seems to be more prevalent in women than in men, and shows a decline with increasing age. Socio-economic background does not seem to influence the prevalence, in contrast to what is seen in migraine^{32,33}. The occurrence of this type of headache is, like migraine, seemingly not increased in our SLE patients, and was not related to any SLE disease variable, laboratory test, or medication for SLE. It was, however, significantly associated with psychological distress, such as anxiety, somatic complaints, reduced energy, mental tension, and social discomfort and withdrawal (Figures 4 and 5), although some caution is needed in interpretation of significance due to multiple comparisons without correction. This is the same pattern observed in other studies showing patients with tension-type headache or combination headache to be more emotionally disturbed than patients with migraine, according to MMPI assessment^{30,34,35}. Such observations may strengthen a hypothesis that migraine possesses a more biological basis than tension-type headache, the latter more influenced by psychosocial factors and stress. In such a context, tension-type headache would be regarded as one of the several features of chronic pain syndromes.

Depressive mood according to BDI was a prominent

feature of the SLE patients with tension-type headache (Figure 6). This was not observed for the D-2 scale in the MMPI-2, which also evaluates depression, although it was more prevalent on a group basis in the patients with SLE. The D-2 did not pick up differences between headache groups or between those without headache compared to headache sufferers. This implies that BDI and D-2 in the MMPI-2 evaluate different spectrums of depressive symptoms. Our results thus are in agreement with BDI studies in chronic daily headache, which has many characteristics of tension-type headache³⁶, but do not comply with findings in MMPI studies where patients with tension-type headache have more depression than those with migraine³⁷⁻³⁹. A confounding factor here might be the influence of mood status on the ability to recall number of headaches.

We conclude that migraine and tension-type headaches might be as prevalent in patients with SLE as they are in the general population when corrected for age and sex. Migraine shows no association with disease associated factors, and has the same clinical presentation as in a non-SLE population. It is therefore not likely to be part of a NPSLE disease spectrum. This also applies to tension-type headache, which in contrast to migraine shows some associations with emotional and personality traits and could represent the components of a chronic pain syndrome.

ACKNOWLEDGMENT

The authors thank Dr. Bjørn Straume for statistical advice.

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