

Migraine In Systemic Lupus Erythematosus in Rheumatological outpatients unit

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ABSTRACT

Background: Migraine is common in systemic lupus erythematosus. It is a significant source of patient disability.

Objective: To determine the rate of migraine in patients with systemic lupus erythematosus, to assess migraine type, severity, and the association between migraine and patient's characteristics.

Type of the study: Cross-sectional study.

Methods: 100 subjects were recruited and divided into two groups; fifty patients with the diagnosis of systemic lupus erythematosus were recruited from the Rheumatologic department of medicine, and another 50 normal subjects, then complete medical and drug history were taken from them.

Results: Fifty patients completed the questionnaire. Thirty percent of systemic lupus erythematosus patients and 12% of normal subjects had migraine. Of the patients with migraine 80%, 13.3% and 6.7% met criteria for migraine without aura, migraine with aura and retinal migraine respectively. The moderately severe migraine was commonly observed (53.3%). There were significant associations between migraine and systemic lupus

erythematosus patients who have Raynaud's phenomenon, and cardiolipin antibodies. There were no statistically significant associations between migraine, systemic lupus erythematosus duration and patient's age, sex, and anti-dsDNA.

Conclusions: A high rate of migraine in patients with systemic lupus erythematosus. Migraine associated with Raynaud's phenomenon, and cardiolipin antibodies.

Key words: SLE, migraine, antiphospholipid antibodies, anticardiolipin antibodies.

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Migraine is a familial benign disorder characterized by periodic, commonly unilateral alternating in site but could be bilateral; often pulsatile may be associated with nausea, vomiting, photophobia and phonophobia^(1, 2, 3). Migraine is a highly prevalent headache disorder that has a substantial impact on the individual, society, and the family. The prevalence of migraine is high; and is highest in women, migraine attacks occur in up to 17 percent of women and 6 percent of men each year^(4, 5). Migraine is most common in those aged 30 to 39, where prevalence in men and women reaches 7 and 24 percent, respectively⁽⁵⁾. Migraine is thus about three times more common in women than men. Migraine also tends to run in families. Migraine without aura is the most common type, accounting for approximately 80 percent of cases⁽⁵⁾. Because of comorbidity, once a diagnosis of migraine has been established, clinicians should have a heightened index of suspicion for epilepsy, stroke, and psychiatric disorders.

Systemic lupus erythematosus (SLE) is a chronic, occasionally life threatening, multisystem disorder. Patients suffer from a wide array of symptoms and have a variable prognosis that depends upon the severity and type of organ involvement. Due to the uncertain course,

effective treatment requires ongoing patient/doctor communication to correctly interpret laboratory tests, alleviate symptoms, prevent and treat relapses, and lessen side effects related to drug therapy. The prevalence of SLE was one case per 1867 of the population, one per 1127 of the total female population and for women aged between 10 and 49 years it was one per 616⁽⁶⁾. Central nervous system manifestations of SLE are highly diverse and often have major prognostic consequences. The incidence of CNS manifestations attributable to SLE is not entirely clear and variable⁽⁴⁴⁾.⁽⁷⁾

This divergence has several reasons, one being differences of opinion concerning the syndromes that constitute the neurology and psychiatry of SLE, whether or not a syndrome is directly attributed to SLE, may have consequences for therapeutic strategies. Neurologic and psychiatric symptoms occur in 10 to 80 percent of patients either prior to the diagnosis of systemic lupus erythematosus (SLE), or during the course of their illness.⁽⁸⁾ The proposed mechanisms include vascular occlusion due to vasculopathy; vasculitis; leukoaggregation or thrombosis and antibody-mediated neuronal cell injury or dysfunctions.⁽⁹⁾

The neuropsychiatric SLE includes neurological syndromes of the central, peripheral and autonomic nervous system and psychiatric disorders in which other causes have been excluded. These manifestations may occur as a single or multiple events that might be important in diagnosis.⁽¹⁰⁾ It has not been possible to determine a specific cause for the high prevalence of headache in SLE patients. Some of the proposed theories until now include: autoantibodies production, microangiopathic, intrathecal production of proinflammatory cytokines, atherosclerosis, SLE central nervous system (CNS)-activity and use of several drugs, such as non-steroid-anti-inflammatory (NSAIDs) drugs or prednisone.⁽¹¹⁾ On the other hand, some authors propose that there is no specific cause of headache in SLE, and that psychosocial factors and the presence of a chronic disease may be responsible for this high prevalence.⁽¹²⁾

Methods :

An observational case control study conducted on 50 patients with SLE who were seen at the Rheumatology Unit, Department of Medicine and in Neurological Department in Baghdad Teaching Hospital from October 2009 to October 2010. The diagnosis of SLE was made by a rheumatologist using the criteria developed by the

American College of Rheumatology.⁽¹³⁾ 50 healthy individuals were randomly selected and were not taking any medications, written consent was taken from all patients to participate in this study, the diagnosis of migraine was made by the International Headache Society (IHS) diagnostic criteria for migraine.⁽¹⁴⁾ Statistical Package for Social Sciences-Version 17 (SPSS v.17) used for data input and analysis. Pearson Chi square (test for Independence) and Fisher Exact test used for verifying the association (relationship) between discrete variables as appropriate. The significance of difference between two independent continuous variables was tested with t-test (t-test of two independent variables) when they were normally distributed and with Mann-Whitney test when they are not normally distributed.

Results:

Fifty patients with SLE, 43 females (86%) & 7 males (14%), their mean age (35.6 ± 12.0) years, and 50 healthy control group, 43 females (86%) & 7 males (14%), their mean age was (38.4 ± 10.8) years were included in this study. Migraine was present in 15 SLE patients (30%), and absent in 35 SLE patients (70%), while it was present in 6 (12%), healthy individuals and absent in 44 (88%) and is statistically significant.

Table 1: demographic data

Variables	SLE patients (50)	Normal subjects (50)	P value
Age (years) (mean \pm SD)	35.6 \pm 12	38.4 \pm 10.8	0.223
Gender	Male	7 (14%)	1.00
	Female	43 (86%)	

T test used for age, chi square test for gender and migraine
SD: standard deviation, SLE: systemic lupus erythematosus

Table 2: association between migraine and SLE

	SLE	Control	OR	95%CI	P value
Migraine	Present	15 (30%)	3.143	1.105 - 8.942	0.032
	Absent	35 (70%)			

Binary logistic regression

Table 3: migraine type and severity distribution

Variables	SLE patients	Normal subjects	P value
Type of migraine	Common	12 (80%)	0.5
	Classic	2 (13.3%)	
	Retinal	1 (6.7%)	
Severity of migraine	Moderate	8 (53.3%)	0.635
	Severe	7 (36.7%)	

Chi square used for type of migraine, fisher exact test used for severity

Variables	Migraine		P value	OR
	Present	Absent		
Continuous variables				
Age {years} (mean \pm SD)	26.6 \pm 8.3	35.2 \pm 13.4	0.716 ^a	-
SLE duration {years} mean \pm SD	3.6 \pm 3.2	6.2 \pm 6.7	0.195 ^b	-
Discrete variables	No (%)	No (%)		
Gender			0.062 ^d	-
	Male (7)	7 (100%)		
	Female (43)	15 (34.9%)		
SLE disease activity	Active	15 (30%)	-	-
Reynaud's phenomenon	Present (14)	8 (57.1%)	0.009 ^c	5.524
	Absent (36)	7 (19.4%)		
Anxiety/depression	Present (28)	11 (39.3%)	0.106 ^c	0.343
	Absent (22)	4 (18.2%)		
Anti-Ds DNA	Positive (46)	14 (30.4%)	0.82 ^d	0.762
	Negative (4)	1 (25%)		
Anti cardiolipin ab	Positive (10)	6 (60)	0.021 ^c	5.167
	Negative (40)	9 (32.5%)		

^a T test, ^b Mann Whitney test, ^c chi square, ^d Fisher exact test
 No: number, SD: slandered deviation, and SLE : systemic lupus erythematosus, ab: antibody

Discussion : In the present study we found significant association between migraine and SLE. The pathogenesis of migraine in SLE is not clearly understood but possible explanations are; there might be SLE central nervous system (CNS)-activity, use of several drugs, such as non-steroid-anti-inflammatory (NSAIDs) drugs or prednisone, or the antiphospholipid syndrome.⁽¹¹⁾ There is no specific cause of headache in SLE, and that psychosocial factors and the presence of a chronic disease may be responsible for this high prevalence.⁽¹²⁾

Up to the best of our knowledge this is the 1st case control study investigating migrainous headache in Iraqi SLE patients. The main finding of the present study is the high frequency of headache in our patient with SLE. The prevalence of migraine in SLE varies greatly among several published studies, mainly due to design problems or the criteria used to diagnose headache. Since the implementation of the IHS criteria⁽¹⁴⁾, it has been easier to standardize the presence of this common feature in a more accurate manner.

In this study, the rate of migraine was 30%, this finding agreed with previous studies done by Weder-Cisneros ND,⁽¹⁵⁾ D A Whitelaw,⁽¹⁶⁾ Dimos.Mitsikostas⁽¹⁷⁾, but contrasted with other studies done by Isenberg DA⁽¹⁸⁾ and Sanna G.⁽¹⁹⁾ in which the association was not significant; this can be explained by that it was studied before the standard protocol for IHS headache criteria. Comparisons are difficult, as some authors do not provide detail. Brey et al⁽²⁰⁾ does not comment further on the nature of the headaches experienced in his cohort, while others do not utilize the IHS criteria.⁽¹⁴⁾ A further complicating factor in interpreting data is the absence of control groups in a number of studies.⁽²¹⁾ Given the widely reported rates for various forms of headache these omissions make any interpretation of the frequency of headaches difficult.

Using fifty SLE patients and a validated questionnaire based on IHS migraine criteria, we identified migraine in 30% of patients with SLE. In the present study migraine occurred in (34.9%) females & (0%) males. These findings do not conform to the pattern described in the general adult literature. Estimates of the prevalence of IHS-defined migraine in the general adult population range from 12.9% to 17.6% for women, and 3.4% to 6.1% for men^(4,5). The prevalence of migraine in patients aged 16 to 40 years was 30.3% and in patients aged 41 to 48 years the prevalence was 29.4%. In the general adult population, the prevalence of migraine increases among both men and women until the age of 40 years, and then declines⁽²²⁾. The failure to find a similar age-related decline in the prevalence of migraine in patients with SLE suggests that migraine is an attribute of the underlying disease. Other explanation is that SLE is about nine times as common in women as in men, with a peak age of onset between 20-40 years⁽²³⁾. Lastly was the way in which the diagnosis of migraine was made, using questionnaires which raise the issues of ascertainment bias, validity of self-reporting and case definition.

In the present study migraine in SLE was severe in (46.75%) and moderate in (53.3%), while control group was severe in (66.7%) and moderate in (33.3%), which was not significant. This high percentage of less severe migraine in SLE patient might be explained by ingestion of non-steroidal and steroidal drugs that ameliorate headache.

In this study we did observe significant associations between migraine and Raynaud phenomenon, Raynaud's phenomenon is common in SLE. The severity of Raynaud's phenomenon did not correlate with the frequency and severity of classical or common migraine. It was considered that small-vessel disease might underlie the clinical phenomena of SLE, including

Raynaud's disease, and contribute to the cerebrovascular mechanism causing migraine⁽²⁴⁾. Despite the lack of correlation between exacerbation of lupus and Raynaud's phenomenon in the present study it seems reasonable to suggest that any young female patient with migraine and Raynaud's phenomenon should be further investigated to exclude SLE. This could mean that migraine in SLE could have avascular physiopathological mechanism among other different associated mechanisms⁽¹²⁾. Nevertheless, another study had not found association between headache and Raynaud's phenomenon in patients with SLE⁽²⁵⁾. At present, it is not possible to explain this discrepancy. This also applies to the conflicting findings on the possible association between the ACA syndrome and headaches. These data are complicated in that some studies report on the association between aPL antibodies,⁽²⁶⁻²⁸⁾ while others report on the ACA syndrome.⁽²⁹⁾ A recent study found an association between the ACA syndrome and headaches but not with migraine.⁽³⁰⁾ This discrepancy could be related to population or study design differences or to searching intensity considering that prevalence of Raynaud's phenomenon varies with the observer's specific questioning of the patient.

Also anticardiolipin antibodies significantly associated with migraine, this finding agreed with another previous studies done by Weder-Cisneros ND⁽¹⁵⁾, but contrasted with the study done by A Fernandez-Nebro⁽³⁰⁾. These discrepancies might be due to the technique of measuring these antibodies (we measure the positivity and not the titers) and may be the activity of SLE disease.

In present study the incidence of common migraine in present study was significantly increased in the lupus group. It has some acceptance with other studies as Bonnie I. Glanz study⁽³¹⁾, but in present study there is high percentage of common type in comparison to classical migraine which may be due to the small sample of our study in comparison to the Bonnie I study (440 SLE patient) which may decrease the detection level of classical type, but was comparable with A Fernandez-Nebro study.

The main limitation of our study the case control nature limiting conclusions regarding cause and effect relationship between migraine and SLE, also the small sample taken. Despite that our findings call attention to high frequency of migraine in SLE patients that need treatment and help in management of SLE patient to decrease morbidity. Due to the fact that headache may occur due to drugs such as steroid, on steroid drugs, and chloroquine we decided to include migrainous SLE and non migrainous SLE in comparison and we found no statistical deference regarding drugs use, so the presence of migraine could not be explained by recent corticosteroid, NSAID, anti-malarial, or immunosuppressive medication use.

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