BMC Rheumatology

RESEARCH

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Headaches in SLE patients: a cross-sectional analysis of clinical, immunological, and Radiological Correlations

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Abstract

Background Systemic Lupus Erythematosus (SLE) is a multifaceted autoimmune disorder characterized by diverse clinical manifestations, including a significant prevalence of headaches. This cross-sectional study aimed to thoroughly explore the relationship between SLE and headaches by analysing their prevalence, types, and associated clinical, immunological, and radiological factors.

Method A comparative analysis was conducted on 179 SLE patients, who were categorized into two groups: those with headaches and those without. Data collection encompassed demographic details, disease activity levels, neurological assessments, immunological profiles, and brain imaging results. Headaches were diagnosed and classified following the International Classification of Headache Disorders (ICHD-3). Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Statistical analyses were performed to identify significant associations and correlations.

Results Headaches were observed in 55% of the SLE patients, predominantly presenting as tension-type headaches (65%) and migraines (27%). Notably, no patients met the criteria for a lupus-specific headache. The Headache Group exhibited significantly higher disease activity (SLEDAI scores). Tension-type and migraine headaches were particularly associated with increased muco-cutaneous manifestations. The presence of antiphospholipid (aPL) antibodies was significantly linked to migraines and cluster headaches. While neurological disorders such as ischemic stroke and venous sinus thrombosis were more prevalent in the Headache Group, these findings were not statistically significant. Brain MRI abnormalities were detected in 9.4% of patients with headaches, including venous sinus thrombosis (2.3%), ischemic stroke (5.8%), and white matter hyperintensities (1.1%).

Conclusion This study underscore es the complex relationship between SLE and headaches, suggesting that headaches may serve as an indicator of heightened SLE disease activity. Immunological factors, particularly aPL antibodies, show a strong association with specific headache types. MRI abnormalities further emphasize the intricate neurobiological aspects in SLE patients experiencing headaches. Continued research is essential to better understand biomarkers, genetic factors, and effective treatment strategies for managing headaches in SLE patients.

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Keywords Headache, SLE, Disease activity, Muco-cutaneous manifestations, Antiphospholipid antibodies (aPL), Magnetic resonance imaging (MRI)

Introduction

Systemic Lupus Erythematosus (SLE), a complex autoimmune disorder, presents with a wide range of clinical manifestations, among which headaches are particularly multifaceted [1]. The intricate relationship between SLE and headaches has become a key area of research, especially given the high prevalence of migraines among SLE patients [2, 3]. Various studies have investigated the prevalence of different headache types in SLE, including tension-type headaches, migraines, cluster headaches, and headaches related to increased intracranial tension (ICT) [4, 5]. The diverse findings across these studies highlight the complexity of the immune system's involvement in the development of headaches in SLE.

Neuropsychiatric manifestations such as ischemic stroke and venous sinus thrombosis have been observed in SLE patients experiencing headaches, though the consistent clinical significance of these findings remains an ongoing subject of research [3, 5]. To gain a comprehensive understanding, comparative studies, like that of Katsiari et al. (2011), have contextualized headaches in SLE by comparing them to those in other autoimmune conditions, such as multiple sclerosis, emphasizing the importance of examining headaches within the broader spectrum of autoimmune disorders [3].

Our study seeks to provide detailed insights into the various dimensions of headaches in the context of SLE. Several underexplored aspects represent a research gap in this area: the mechanisms linking headaches to SLE activity, particularly the role of the immune system, remain unclear; longitudinal studies are necessary to track the progression of headaches in SLE patients over time; comparative analyses should further distinguish SLE-related headaches from those in other autoimmune conditions; the clinical significance of the association between antiphospholipid (aPL) antibodies and specific headache types requires deeper investigation, as does the potential for headaches to serve as early indicators of severe neuropsychiatric complications. Additionally, the relevance of MRI abnormalities in SLE patients with headaches warrants further exploration. Addressing these gaps could significantly enhance our understanding of headaches in SLE.

Methods

A comparative cross-sectional study was conducted, involving 179 Systemic Lupus Erythematosus (SLE) patients aged 18 to 55, who met the 2012 Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) criteria for SLE [6]. The participants were selected from the rheumatology & immunology unit outpatient clinic at our institution between July 2022 and July 2023. The patients were categorized into two groups: Group I (SLE with Headache) and Group II (SLE without headache).

Exclusion criteria encompassed patients with any medical disorders not related to lupus, including other systemic autoimmune diseases, hereditary neurological disorders, and primary epilepsy, as these conditions could confound the neurological assessments and headache classification.

Demographic data, including age and gender, were collected. A thorough medical history was obtained, detailing the main clinical features, followed by a clinical examination by an experienced internist (EH) and a neurological examination by an experienced neurologist (ABT). Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [7].

Patients' sera were screened for positivity in antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and Antiphospholipid Antibodies (aPL). Additionally, a complete blood count, creatinine, and urinary protein/creatinine ratio measurements were conducted for all participants. Fundus examinations were performed on all patients.

The presence of headache was identified through an initial question regarding headaches within the past year, including the frequency and number of headache attacks. This information was crucial for evaluating the significance of headache characteristics in relation to the study's results.

Headaches were diagnosed and classified according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) [8], covering four primary headache types: migraine, tension-type headache (TTH), cluster headache, and secondary headaches such as those from idiopathic intracranial hypertension (IIH). IIH is characterized by moderate to severe headache, often with a pulsating quality, typically aggravated by straining (such as with coughing or bending over), and may be associated with nausea, vomiting, and visual disturbances. Diagnosis is based on specific criteria, including elevated intracranial pressure, normal neuroimaging (except for empty sella), and the absence of other underlying causes.

"Lupus headache" is one of the items in the SLEDAI-2 and has been defined as a severe, disabling, persistent headache that is not responsive to narcotic analgesics [9]. Headache severity was measured using the Visual Analog

Scale (VAS) [10], recorded by a mark on a 10 cm line ranging from "no pain" to "worst possible pain."

CT, MRI, MRV, and MRA brain imaging were performed when indicated based on clinical presentation, such as the presence of neurological deficits, severe or atypical headache patterns, or suspicion of secondary causes of headaches.

The study adhered to ethical standards, obtaining informed consent from all patients and controls following the local ethical committee guidelines. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of our institution in February 2023 (Reference number: INTM 13−2).

Data analysis was performed using SPSS software version 20 (IBM Corp, Armonk, New York, United States). Continuous variables were presented as mean ± standard deviation (SD). One-way ANOVA was employed for normally distributed data, while the Kruskal-Wallis test was used for non-normally distributed data. Qualitative variables were expressed as numbers and percentages, analysed using Chi-square or Fisher's exact test. Correlation between variables was assessed using the Spearman coefficient. The significance level was set at $P<0.05$.

Results

A total of 179 patients diagnosed with Systemic Lupus Erythematosus (SLE) were included in the study, with a predominance of females (162, 90.5%) compared to males (17, 9.94%). The female-to-male ratio was 9.5:1. SLE patients were categorized into two groups: Headache Group I (100 patients) and Non-Headache Group II (79 patients). The groups demonstrated comparability in terms of age, sex, and disease duration. No statistically significant differences were observed in clinical presentation and laboratory investigations between the two groups [Table 1].

A significant statistical difference was noted in disease activity between the two groups, with headache sufferers exhibiting a higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ($p<0.0001$) [Table 1].

Among SLE patients with headaches ($n=100$), 55.86% experienced primary headaches. Tension-type headache (TTH) was the most common type (65%), followed by migraine (27%). Notably, 5% of patients had headaches related to increased intracranial tension (ICT), which are classified as secondary headaches. The causes of ICT headaches among these patients included idiopathic intracranial hypertension (IIH), as there were no cases of space-occupying lesions such as brain tumors or brain abscesses. None of the patients met the SLEDAI criteria for lupus headache, and no patients experienced more than one type of headache simultaneously.

Table 1 Demography, clinical and laboratory data of the studied SLE patients

	Headache group ***n*** **= 100**		**Non headache group** ***n*** **= 79**		**Test**	***P*** **value**
	Mean ± SD		**Mean ± SD**			
Age (years)	29.45 ± 8.6		28.8 ± 9.7		0.5	0.6
Age of onset	26.8 ± 8.9		26.6 ± 8.7		0.3	0.9
Duration of the disease	2.6 ± 2.3		2.7 ± 2.1		0.2	0.8
Systolic BP	120.4 ± 15.5		122.9 ± 16.1		0.8	0.3
Diastolic BP	77.6 ± 10.5		79.3 ± 10.7		0.1	0.7
	n	%	n	%		
Female	91	91	71	73.2%	0.01	0.9
Male	9	9%	8	26.8%		
Mucocutenous	91	91%	79	100%	0.01	0.9
Serositis	26	26%	23	29.1%	0.2	0.7
Lupus nephritis	64	64%	43	54.4%	1.6	0.2
CNS affection (other than headache)	7%	7%	2	2.5%	1.8	0.3
Arthritis	59	59%	47	59.4%	0.04	0.9
aPL positivity	34	34%	28	35.4%	0.04	0.8
Anti-cardiolipins	31	31%	26	32.9%	0.07	0.7
ANA positive	100	100%	100	100%	…….	…….
Creatinine	1.1 ± 0.9		1.2 ± 1.0		0.7	0.4
Anti-ds DNA	256.5 ± 323.4		202.6 ± 201.8		1.2	0.1
UPCR (g protein\mg creat)	1.7 ± 2.6		2.1 ± 2.8		0.6	0.4
SLEDAI	6.1 ± 5.7		2.7 ± 1.3		5.1	< 0.0001*

SD = Standard Deviation, n = number, UPCR = urinary protein\creatinine ratio, ANA = Anti-Nuclear Antibodies, SLEDAI = Systemic Lupus erythematosus Disease Activity Index, CNS = Central Nervous System, aPL = Antiphospholipid, BP = Blood Pressure, dsDNA: Double-Stranded Deoxyribonucleic Acid

Approximately one-third of lupus patients experienced headaches prior to their lupus symptoms. Among them, 63% reported headaches lasting from over one to five years before diagnosis, while 37% experienced headaches for less than a year. Headaches were categorized as follows: 50% migraine with aura, 16.7% idiopathic intracranial hypertension (IIH), and 33.3% tension-type headaches (TTH). Half of these patients had a family history of headaches, predominantly migraines (90%) and 10% TTH. 60% had a headache history of 1–5 years, with 35% experiencing daily headaches. Headache duration without medication was: <1 h (48%), 1–4 h (21%), >4 h (31%). With medication, 73% had headaches < 1 h, 10% for 1–4 h, and 12% >4 h [Table 2].

Headache triggers included stress (75%), fatigue (5%), menstruation (5%), dietary factors (3%), sleep deprivation (2%), and other factors (10%). During lupus exacerbations, 32% reported worsened headaches. Pregnancy exacerbated headaches in 15% but improved them in 10% of patients. Regarding seasonal variations, 88% reported no changes, 7% increased headaches in summer, and 5% in winter. Steroid use for lupus exacerbation improved headaches in only 4% of patients [Table 2].

Statistical analysis revealed a significant association between headache type and mucocutaneous manifestations. Tension-type headache (TTH) and migraine were linked to higher occurrences of mucocutaneous manifestations. Additionally, Antiphospholipid (aPL) antibody

Table 2 Headache characteristics and modifying factors in the studied patients

Variable	number (%)
Headache prior to lupus symptoms	**30 (30%)**
Headache Type:	
Tension	65 (65%)
Migraine	27 (27%)
Cluster	3 (3%)
IIH	5 (5%)
Family history with headache	50 (50%)
Headache period	
< 1 year	37 (37%)
1–5 years	63 (63%)
Occurrence	
30–31 day / month	35 (35%)
15–29 days /month	35 (35%)
4–14 days /month	10 (10%)
< 3 days / month	20 (20%)
Duration with no medication	
< 1 h	48 (48%)
1–4 h	21 (21%)
> 4 h	31 (31%)
Duration with medication	
< 1 h	73 (73%)
1–4 h	10 (10%)
> 4 h	12 (12%)
Triggers	
Stress	75 (75%)
Fatigue	5 (5%)
Menstruation	5 (5%)
Food	3 (3%)
Sleep deprivation	2 (2%)
None of these	8 (8%)
Others	2 (2%)
lupus exacerbation	
Worse	32 (32%)
No change	68 (68%)
lupus medication (mainly steroids)	
Worse	0 (0%)
No change	96 (96%)
Improve	4 (4%)

positivity showed a statistically significant association with migraine and cluster headache (70.5% in migraine vs. 100% in cluster headache, vs. 16.9% in TTH, 20% in the IIH group, $p<0.000$) [Table 3].

Neurological disorders, specifically ischemic stroke (5/100) followed by venous sinus thrombosis (2/100), were more prevalent in the headache groups. These conditions are often associated with the hypercoagulable state linked to antiphospholipid syndrome or vasculitis in SLE patients. Nearly all the 7 patients with ischemic stroke and venous sinus thrombosis had seizures at presentation. Lupus headache was not included in this study, as none of our patients had a headache that met the criteria for lupus headache.

MRI brain results indicated that 90.6% of headache sufferers (from a total of 85 patients who underwent MRI) had a normal MRI, while the remaining 9.4% showed abnormalities, including venous sinus thrombosis in 2 patients (2.3%), ischemic stroke in 5 patients (5.8%), and white matter hyperintensities in 1 patient (1.1%). The two patients who had venous sinus thrombosis on MRI had history of tension-type headaches. Of the ischemic stroke patients, four had a history of migraines, and one had a history of tension-type headaches. The patient with white matter hyperintensities had a migraine headache. Notably, all patients with cluster headaches had normal MRI findings. Two of the patients without headaches had ischemic stroke (2.5%) [Figs. 1, 2 and 3].

The severity of headaches, as measured by the Visual Analog Scale (VAS), correlated with SLEDAI but did not reach clinical significance. No statistically significant difference was found between headache type and SLEDAI [Tables 4 and 5].

In the multivariate regression analysis examining the relationship between headaches and various factors, the intercept is highly significant, indicating a baseline likelihood of headaches when all other variables are zero. The SLEDAI score is also highly significant, showing that higher disease activity is strongly associated with an increased likelihood of headaches. Conversely, renal symptoms significantly reduce the likelihood of headaches. However, other factors, including age, sex, duration of the condition, mucocutaneous symptoms, arthritis, serositis, neuropsychiatric symptoms, anti-DNA antibodies, and antiphospholipid antibodies, do not show significant associations with headaches. Issues with the data for ANA and anti-DNA antibodies suggest that these variables may need further review. Overall, the SLEDAI score stands out as the most significant predictor of headache occurrence in this analysis [Table 6].

Discussion

Our comparative cross-sectional study advances the current understanding of the intricate relationship between SLE and headaches, integrating insights from various studies that explore different facets of this association [3–5, 10–28] [Table 7].

Table 3 Relation of headache to clinical and laboratory data

	Tension ***n*** **= 65**		**Migraine** ***n*** **= 27**		**Cluster** ***n*** **= 3**		**BIH** ***n*** **= 5**		**Test of sig.**	**Sig**
	Mean ± SD		**Mean ± SD**		**Mean ± SD**		**Mean ± SD**			
Age	28.5 ± 7.9		31.2 ± 9.8		32.3 ± 7.5		29.8 ± 10.4		0.7	0.5
Age of onset	26.2 ± 8.4		27.4 ± 9.7		30.5 ± 6.3		27.0 ± 9.7		0.4	0.7
Duration of disease	2.5 ± 2.2		3.2 ± 2.7		1.9 ± 1.8		2.8 ± 0.9		0.6	0.5
Haemoglobin	9.6 ± 1.1		10.1 ± 0.8		10.01 ± 0.9		10.01 ± 0.6		1.1	0.3
WBCs	4.9 ± 1.8		4.1 ± 1.1		5.1 ± 0.4		5.1 ± 1.4		1.4	0.2
Platelets	206.8 ± 104.2		225.1 ± 111.1		214.9 ± 138.3		182.1 ± 70.9		0.1	0.9
Creatinine	1.1 ± 0.9		1.2 ± 0.8		1.2 ± 0.7		0.7 ± 0.1		0.6	0.5
Proteinuria	1.8 ± 2.7		1.6 ± 2.1		3.3 ± 1.2		0.72 ± 0.19		1.1	0.3
SLEDAI	5.6 ± 5.7		7.2 ± 6		8.6 ± 3.1		4.0 ± 4.0		0.9	0.4
VAS	4.17 ± 1.1		4.8 ± 1.5		5.3 ± 2.1		4.2 ± 1.4		2.2	0.09
	n	%	n		n	%	n	%		
Male	5	7.7%	4	14.8%	0	0%	1	20%	1.9	0.5
Female	60	92.3%	23	85.2%	3	100%	4	80%		
Mucocutaneous	61	93.8%	25	92.5%	2	66.7%	3	60%	8.7	0.04*
Serositis	16	24.6%	10	37.03%	0	0%	0	0%	4.5	0.2
Arthritis	36	55.4%	18	66.7%	1	33.3%	4	80%	2.7	0.4
aPL	11	16.9%	19	70.4%	3	100%	1	20%	19.1	< 0.000*
ACL	9	13.8%	18	66.6%	3	100%	1	20%	19.1	< 0.000*

SD = Standard Deviation, n = number, Test of significance (One way ANOVA for quantitative data, Fisher exact for qualitative data). * significance. aPL = Antiphospholipid, ACL = anti-cardiolipin. VAS = Visual analog scale SLEDAI = Systemic Lupus erythematosus Disease Activity Index, WBCs = White Blood Cells, SD = Standard Deviation, BIH = Benin Intracranial Hypertension, n = number

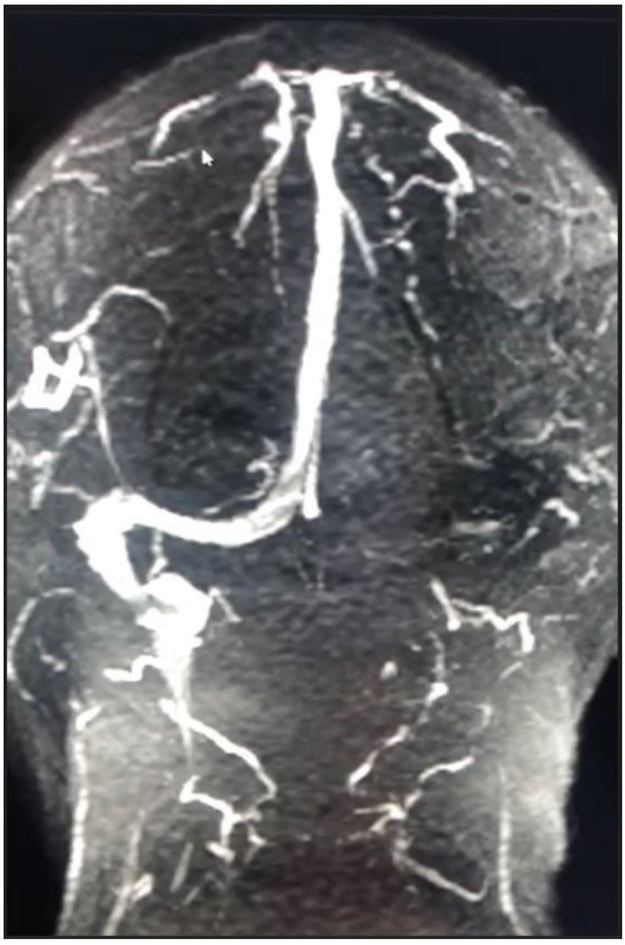

Fig. 1 25y female with SLE for 2 years presented with tension like headache, blurring of vision, repeated vomiting, fundus exam shows grade II papilledema, MRV show left transverse and sigmoid venous sinus thrombosis

The prevalence of headaches in SLE patients, ranging from 28.5 to 82% in previous studies [3–5, 10–28], aligns with our findings, where headaches were observed in 55% of our SLE cohort.

The prevalence of headaches in Egyptian patients with systemic lupus erythematosus (SLE) varies across studies from 55 to 38% [4, 28–35].

This significant variance in prevalence among studies can be attributed to methodological differences, varying patient numbers, and widely differing criteria for defining headache types. Despite observing a female predominance in our SLE cohort, consistent with established epidemiological patterns, we found no significant differences in age, sex distribution, or disease duration between SLE patients with and without headaches.

In a related study focusing on childhood SLE, Santos et al. examined a population of 1,463 SLE patients, revealing that 29.9% experienced 869 neuropsychiatric SLE events, averaging 2.48 events per patient. Headache was reported in 52.2% of these cases [27]. However, it is noteworthy that a meta-analysis conducted by Mitsikostas et al. presents a contrasting perspective. Pooled data from seven controlled studies in their analysis showed that the prevalence of all headache types, including migraine, did not differ significantly from controls [17].

Regarding headache subtypes, migraines (27%) and tension-type headaches (65%) emerged as the predominant subtypes, consistent with existing literature. None of our patients were found to have lupus headaches, in agreement with other studies where it was 1.5% in the study by Hanly et al. [22], and none in the study by Aloleimy et al. [4]. This questions the existence and clinical significance of lupus headache, emphasizing the need for a standardized classification system for lupus-related headaches to enhance diagnostic precision, as the available evidence does not strongly support the concept of a distinct entity known as 'lupus headache.

Our finding that 55% of SLE patients experience headaches, predominantly tension-type and migraine, contributes new data to the existing literature. Unlike previous studies that have reported varying prevalences, our study provides a detailed breakdown of headache types and their association with disease activity. Notably, none of our patients met the criteria for lupus-specific headaches. This absence challenges the clinical relevance of this classification, highlighting the need for a standardized diagnostic approach. This finding is crucial as it questions the concept of 'lupus headache' and suggests that such a classification may not be clinically significant.

In recent decades, researchers have explored the intersection of migraines and immunological/autoimmune disorders due to substantial evidence linking both conditions. Epidemiologically, both conditions predominantly affect females, with an onset typically at young ages [36, 37]. Pathologically, shared genetic components, particularly involving human leukocyte antigens (HLA) and cytokine polymorphisms [37], establish a connection between migraine pathogenesis and autoimmune disorders. This association is further underscored by elevated levels of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8 in migraines, indicative of a persistent pro-inflammatory environment [38]. Notably, during migraine attacks, there is an increase in IL-10 levels, suggesting a compensatory anti-nociceptive response [39]. Additionally, immune cell subset al.terations, involving natural killer cells, as well as CD4+and CD8+lymphocytes [40], hint at potential dysregulation contributing to the underlying pathophysiology of migraines.

Regarding lupus headache, its pathophysiology appears to involve two primary pathways. The ischemic-vascular mechanism involves antiphospholipid antibodies (aPL), immune complexes, and leuko-agglutination, contributing to focal neuropsychiatric manifestations. The inflammatory-neurotoxic mechanism includes complement

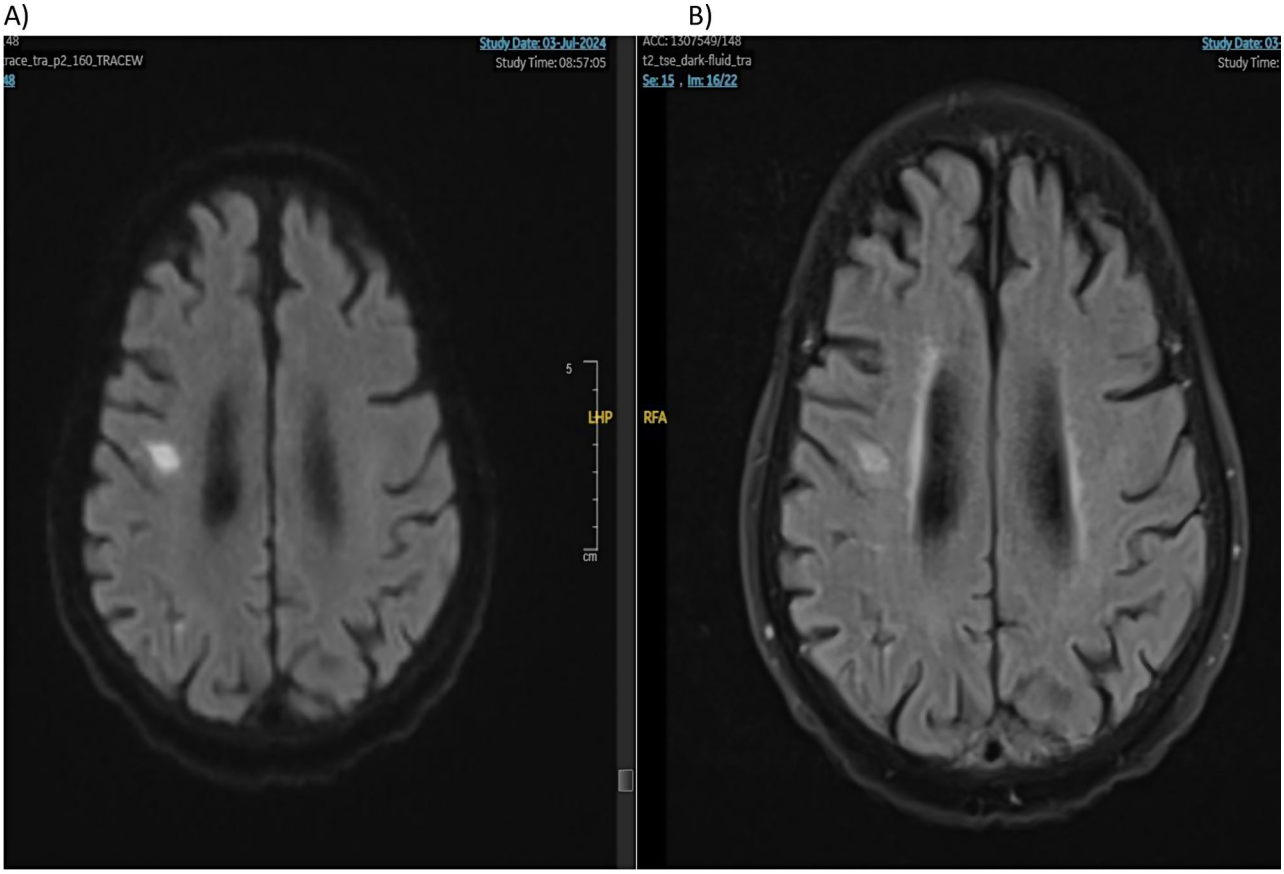

Fig. 2 32y, male, SLE for 4 years, presented with sudden onset left sided numbness with MRI brain DWI **(A)** show restricted diffusion and FLAIR **(B)** show hyperintense signals of Right parietal cortical and subcortical areas denoting recent infarction

activation, increased blood-brain barrier permeability, migration of intrathecal autoantibodies, and local production of pro-inflammatory cytokines, associated with diffuse neuropsychiatric manifestations [41].

Shifting focus to tension-type headaches, although they have received limited attention in terms of immune system derangement, there are indications of increased pro-inflammatory cytokines, particularly in the cerebrospinal fluid [42]. For cluster headaches, there is also evidence suggesting a role for immunological dysfunctions in the pathogenesis of this disorder, indicated by a negative association with HLA-B14, an increase in natural killer (NK) cytotoxicity, elevated receptor expression of classical neurotransmitters associated with pain, and elevated levels of pro-inflammatory cytokines such as IL-1β [43].

There appears to be an association between idiopathic intracranial hypertension (IIH) and systemic lupus erythematosus (SLE), although the exact relationship is not fully understood. IIH has been recognized as a complication in SLE, with a prevalence ranging from 0.7 to 1.5%. However, it remains an uncommon manifestation of SLE. IIH can occur as the initial presentation of SLE, even in the absence of other systemic symptoms. In one study, 17% of lupus patients with intractable headaches were found to have IIH on CSF studies. The pathophysiology linking IIH and SLE is unclear. Proposed mechanisms include immune-mediated injury within the arachnoid villi, disruption of the blood-brain barrier, and abnormal regulation of CSF production. Antiphospholipid antibodies may also play a role. Treatment of the underlying SLE with corticosteroids and immunosuppressants like cyclophosphamide has been effective in resolving IIH in some cases. However, more research is needed to establish optimal treatment guidelines [44, 45].

We noted that headache sufferers exhibited a higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score compared to SLE patients without headaches ($p<0.0001$). This finding is consistent with the conclusions drawn by Appenzeller et al. (2004), where migraines in SLE patients were linked to elevated MEX-SLEDAI scores [16]. Additionally, multivariate regression analysis revealed a strong link between the SLEDAI score and headache likelihood. This association highlights the potential clinical relevance of headaches as a marker for increased SLE disease activity.

Despite the lack of a significant correlation between headache severity and disease activity assessed by the Systemic Lupus Erythematosus Disease Activity Index

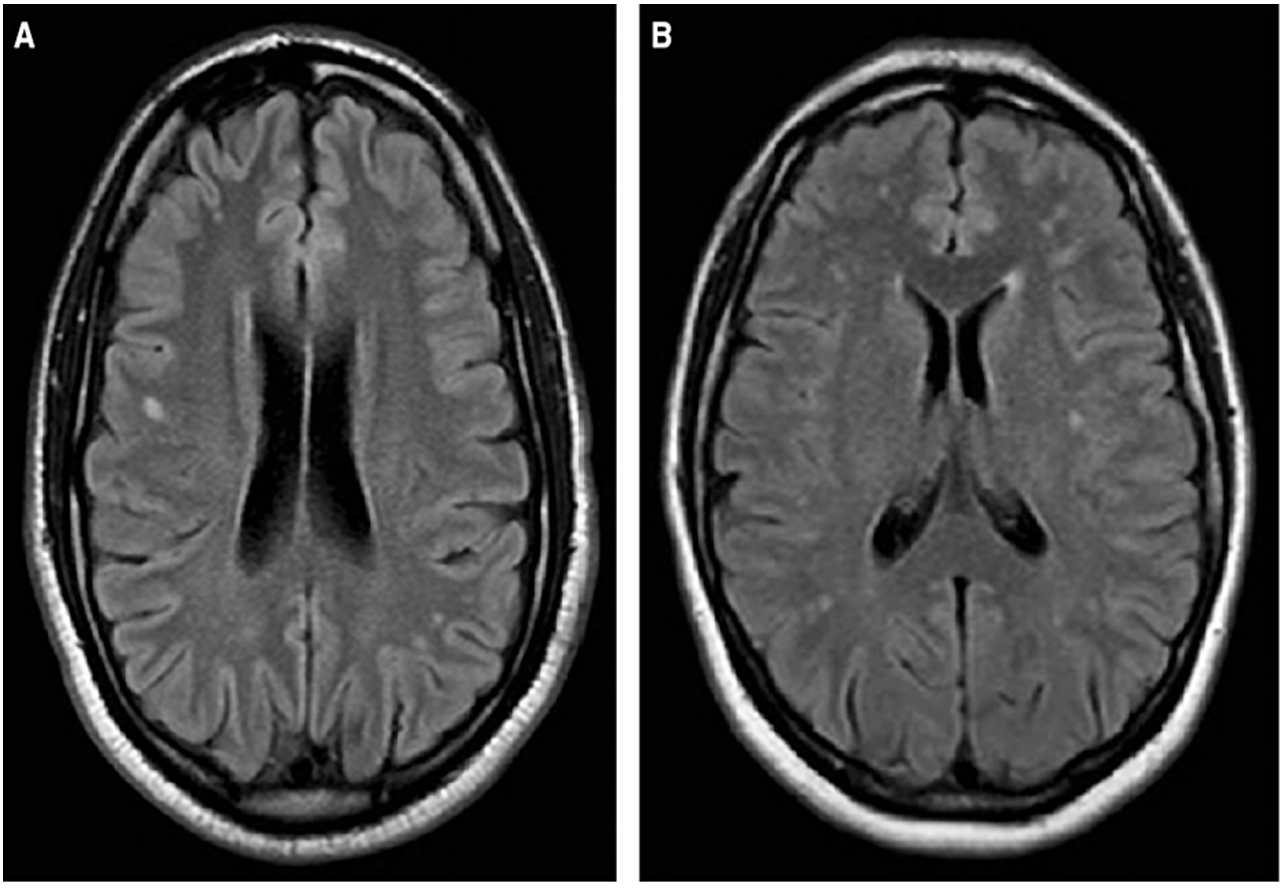

Fig. 3 30y female, SLE for 5 years with history of migraine 1y before lupus diagnosis, with MRI FLAIR show scattered foci of small white matter hyper intensities (WMH) concomitant with migraine

Table 4 Distribution of headache types across SLEDAI scores in SLE patients

Type of Headache	No Activity (*n* = 19)	Mild (0–5) (*n* = 23)	Moderate (6–10) (*n* = 29)	Severe (11–19) (*n* = 25)	Very Severe (> 20) (*n* = 4)	*P* value
Tension-Type	14 (73.7%)	15 (65.2%)	21 (72.4%)	12 (48%)	3 (75%)	0.3
Migraine	4 (21.1%)	4 (17.4%)	6 (20.7%)	12 (48%)	1 (25%)	
Cluster	0 (0%)	2 (8.7%)	0 (0%)	1 (4%)	0 (0%)	
BIH	1 (5.3%)	2 (8.7%)	2 (6.9%)	0 (0%)	0 (0%)	

SD = Standard Deviation, n = number, BIH = Benign Intracranial Hypertension, VAS = Visual analog scale, SLEDAI = Systemic Lupus erythematosus Disease Activity Index, P value significance: $P < 0.05$ indicates statistical significance

Table 5 Correlation of SLEDAI & VAS

Variable	*r*	*P* value
SLEDAI & VAS	0.008	0.9

VAS = Visual analog scale, SLEDAI = Systemic Lupus erythematosus Disease Activity Index, P value significance: $P < 0.05$ indicates statistical significance

(SLEDAI), our findings are consistent with those reported by Katsiari et al. (2011) and other researchers [3–5, 11–14]. Unexpectedly, our investigation did not uncover a substantial link between the existence of headaches and specific clinical manifestations. This finding contradicts certain studies that highlighted musculoskeletal and neuropsychiatric manifestations as prevalent in individuals experiencing headaches [4]. On the other hand, there was a notable correlation between migraine and tension-type headaches and mucocutaneous manifestations. Notably, Appenzeller identified a significant association between migraines and Raynaud's phenomenon as well as organ damage [16].

Additionally, aPL antibody positivity showed a statistically significant association with migraines and cluster headaches. Our findings are consistent with prior research that underscores the potential involvement of anti-phospholipid (aPL) antibodies in SLE-related headaches [4], aligning with previous studies that explored the role of autoantibodies in neuropsychiatric manifestations. Faust et al.'s investigation into neurotoxic lupus autoantibodies [46], and Toubi and Shoenfeld's identification of

Table 6 Multivariate regression analysis between headaches and clinical SLE variables

	Coefficients	Standard Error	t Stat	*P*-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	2.98328	0.586232	5.088906	9.67E-07	1.825848	4.140712	1.825848	4.140712
Age	-0.00299	0.004156	-0.71969	0.472725	-0.0112	0.005214	-0.0112	0.005214
Sex	0.057132	0.122144	0.467742	0.640582	-0.18402	0.298289	-0.18402	0.298289
Duration of illness	-0.02343	0.017009	-1.37756	0.170194	-0.05701	0.010151	-0.05701	0.010151
Mucocutaneous	0.146863	0.122204	1.201789	0.231157	-0.09441	0.388137	-0.09441	0.388137
Arthritis	-0.05335	0.075053	-0.71079	0.478214	-0.20153	0.094835	-0.20153	0.094835
Serositis	-0.14094	0.097637	-1.44352	0.15076	-0.33371	0.05183	-0.33371	0.05183
Neuropsychiatric	-0.20279	0.183713	-1.10384	0.271262	-0.5655	0.159926	-0.5655	0.159926
Renal	-0.17607	0.081209	-2.16807	0.031577	-0.3364	-0.01573	-0.3364	-0.01573
ANA	0	0	65,535	#NUM!	0	0	0	0
Anti-ds DNA	6.81E-05	0.000147	0.463646	#NUM!	-0.00022	0.000358	-0.00022	0.000358
SLEDAI	-0.06927	0.009016	-7.68335	1.28E-12	-0.08707	-0.05147	-0.08707	-0.05147
aPL	-0.17334	0.163704	-1.05885	0.291204	-0.49655	0.149872	-0.49655	0.149872

ANA = Anti-Nuclear Antibodies, Anti-ds DNA = Anti-double-stranded Deoxy Nucleic Acid, aPL = Antiphospholipid,, SLEDAI = Systemic Lupus erythematosus Disease Activity Index

the association of anti-P antibodies with neuropsychiatric symptoms [47], offer compelling evidence of a direct immunological link between SLE and neurological dysfunction. Yoshio et al.'s focus on IgG anti-NR2 glutamate receptor autoantibodies add another layer to our understanding, connecting inflammatory processes to neurological symptoms, including headaches [48].

In Fragoso-Loyo's study, patients with headaches displayed elevated cerebrospinal fluid (CSF) levels of IL-6, IL-8, IP-10, RANTES, and MIG compared to non-NPSLE and non-autoimmune disease patients [49]. Autoantibodies, such as anti-ribosomal-P, anti-DNA/NR2, antiphospholipid (aPL), and anticardiolipin (aCL), significantly contribute to neuropsychiatric systemic lupus erythematosus (NPSLE), contributing to neurotoxicity and blood-brain barrier (BBB) dysfunction [41]. Notably, associations of autoantibodies to β2-glycoprotein I (β2GPI) with non-specific intractable headaches, ischemic stroke, and seizures in NPSLE patients suggest their potential to surpass the predictive value of other autoantibodies like aCL or lupus anticoagulant [50].

Our study underscores the significant association between antiphospholipid (aPL) antibodies and specific headache types, particularly migraines and cluster headaches. This adds to the growing body of evidence linking autoimmunity and headache pathogenesis. The association with higher SLE disease activity scores in patients with headaches further supports the role of headaches as a potential marker for increased disease severity.

In our patient cohort, nearly 92% exhibited no abnormalities in brain MRI scans. Consistent with findings from other studies [1], we did not observe any significant association between cerebral lesions and headache characteristics, including types. Nevertheless, our investigation identified ischemic stroke followed by cerebral venous thrombosis as the primary MRI abnormalities. Both cases of CVT were associated with TTH, and 4/5 cases with ischemic stroke were migrainous. Only one case had hyperintensities on MRI.

Several studies have explored brain imaging findings in SLE patients, providing valuable insights. Nobili et al. (2006) noted focal hypoperfusion in 83% of SLE patients with migraines using brain SPECT [51]. Bicakci et al. (2008) established a correlation between abnormal MRI findings and prolonged disease duration, suggesting progressive neurological involvement in SLE [20]. In a study by Sarbu et al. (2015), brain abnormalities were identified in 59.3% of neuropsychiatric lupus patients, with small vessel disease predominantly correlated with lupus anticoagulant [24]. Zaky et al. (2015) reported brain abnormalities in 38.2% of SLE patients, with those diagnosed with NPSLE showing higher frequencies of white matter changes, ischemia, hemorrhage, and encephalopathy [52]. Tjensvoll et al. (2016) associated migraines in SLE with reduced cerebral grey matter volume [25], while Son et al. (2016) linked chronic daily headaches in SLE with neuronal dysfunction and neurometabolic changes [53]. Papadaki et al. (2018) explored cerebral perfusion abnormalities using perfusion-weighted MRI, emphasizing cerebral hypoperfusion in SLE patients with headaches and suggesting a potential vascular component [26]. A recent study by Aloleimy et al. (2021) found brain imaging abnormalities in 25.8% of patients, with white matter hyperintensities being the most frequent pathology [4].

The MRI findings in SLE patients with headaches highlight a convergence of structural, vascular, and immunologic aspects which can be explained by various molecular mechanisms. In approximately 30–40% of SLE patients, autoantibodies target the NR2A/B subunit of the NMDA receptor, leading to neuronal apoptosis and hippocampal damage, as demonstrated in both in vitro and animal models [54].

Additionally, matrix metalloproteinases (MMPs), especially MMP-9, play a crucial role in degrading

Table 7 Baseline characteristics of published studies investigating headache in systemic lupus erythematosus (SLE) patients: correlations with MRI and immunological investigations (1982–2023)

Study	Population	Headache prevalence	MRI findings	Key conclusions
1. Isenberg et al. (1982) [11]	30 SLE, 30 control	-Migraine: 40% vs. 13% control	Not included	No significant differences were found between the patients and controls, who had classical and common migraine or visual auras without headache, with regard to a family History of migraine, the age of onset of the migraine, Raynaud's phenomenon, or use of oral contraceptives. Increased activity of the lupus was not generally associated with an increase in migraine attacks.
2. Markus et al. (1992) [12]	90 SLE, 90 control	-Migraine: 35% vs. 16% control	Not included	Both migraine and non-migrainous headaches were more common in SLE patients and often responded to specific SLE treatment but no association with disease activity or antiphospholipid antibodies.
3. Sfikakis et al. (1998) [5]	78 SLE patients, 89 control	-All headache:32% vs. 30% control - TTH most frequent - Migraine: ¼ of headache	Not included	No specific association between headache and clinical, serological features of SLE, including Raynaud's phenomenon nor the presence of anticardiolipin antibodies.
4. Fernández-Nebro et al. (1999) [13]	71 SLE, 71 control	-all headache: 46.5% -Migraine: 23.9% -TTH: 22.5%	Not included	Patients with (SLE) show no significant differences from healthy controls in terms of headache presence and type. Additionally, there are no notable clinical or immunological distinctions among SLE patients with and without tension-type headache or migraine.
5. Glanz et al. (2001) [14]	186 SLE patients	-All headache: 62% -Migraine: 39% -Non migraine: 23%	Not included	There were no significant associations between headache type and other clinical, serologic, or treatment features of the disease.
6. Omdal et al. (2001) [15]	58 SLE patients	- All headache: 66% - Migraine: 31.9% -TTH: 15.3%	Not included	Headaches were not associated with disease activity or any other disease associated variable, including tests for antiphospholipid antibodies. Migraine and tension-type headaches associated with psychological distress.
7. Appenzeller & Costallat (2004) [16]	80 SLE patients, 40 RA patients, 40 controls	-Migraine: 42.5%	Not included	Active migraine was associated with higher disease activity, antiphospholipid antibodies, worsening of Raynaud's phenomenon and increased cumulative organ damage.
8. Mitsikostas et al. (2004) [17]	Pooled data from eight studies	-Migraine: 57.1% -TTH: 23.5%	Not included	No strong evidence for the concept of 'lupus headache,' and no identified neither pathogenetic mechanism nor an association between headache and the disease status, including CNS involvement.
9. Whitelaw et al. (2004) [18]	85 SLE patients, compared to 61 controls	-All headache:48% -Migraine:38% vs. 6%control -TTH: 10% vs. 66%control	Not included	Migrainous headaches more common in lupus patients than in healthy controls but not statistically associated with flares of systemic disease, the ACA syndrome, Raynaud's phenomenon or increased SLEDAI score
10. Lessa et al., (2006) [19]	115 SLE and 92 control	-All headache: 75.7% vs. 66% control - Migraine: 66.1% -TTH:13.9%	Not included	Both headache and migraine were associated with Raynaud's phenomenon in SLE patients
11. Bicakci et al. (2008) [20]	48 SLE patients	-All patients has headache with VAS > or = 4 -Migraine: 39.6% -TTH: 54.1%	Abnormal MRI in 37.5%, mostly as periventricular and subcortical focal lesions	Significant correlation found between abnormal MRI findings with advanced age and prolonged disease duration.
12. Katsiari et al. (2011) [3]	72 SLE/control pairs and 48 MS patients	-Migraine: SLE patients (21%), MS patients (23%), and controls (22%) - Chronic TTH:12.5% SLE vs. 1.4% control, 8.3 MS	Not included	No associations of any headache type with particular clinical manifestations, autoantibody, or disease activity, either in SLE or MS patient groups. Migraine should be no longer considered a neurologic manifestation of systemic or organ-specific autoimmunity. Increased migraine prevalence in these patients found in previous studies could be due to methodological weaknesses.

Table 7 (continued)

Study	Population	Headache prevalence	MRI findings	Key conclusions
13. Tjensvoll et al. (2011) [21]	67 SLE compared with 67 controls	-All headache: 82% vs. 72% control - Migraine: 36% vs. 19% control - TTH: 60% vs. 58% in controls	– 18% infarction vs. 3% in control - SLE patinets had more WMHs than control	Migraine is more prevalent in SLE patients, associated with depression like in the general population, but not associated with disease activity or abnormalities detected on cerebral MRI, in CSF, or any SLE characteristics except from SLE photosensitivity.
14. Hanly et al. (2013) [22]	1,732 SLE patients	-All headache: 17.8% at enrollment, increased to 58% after 10 years	Not included	Headache associated with other neuropsychiatric events, but not with specific SLE disease markers.
15. Hawro et al. (2015) [23]	57 SLE and 69 control	-All headache: 39%	Not included	Autoantibodies to β2GPI are linked to non-specific headaches, ischemic stroke and seizures, and show a better predictive value than aCL and LA.
16. Sarbu et al. (2015) [24]	108 newly diagnosed NPSLE patients	-All headache: 28.5%	Brain abnormalities in 59.3%, including small vessel disease, large vessel disease, and inflammatory-like lesions	Cerebrovascular syndrome correlated with LVD and microbleeds, cognitive dysfunction with WMH and myelopathy with inflammatory-like lesions. Low C4 and CH50 correlated with inflammatory-like lesions and lupus anticoagulant with WMH, microbleeds and atrophy.
17. Tjensvoll et al. (2016) [25]	67 SLE, 67 control	-All headache: 82% vs. 72% control -Migraine: 36% vs. 19% control	Larger GM volumes in SLE patients reduced the odds for headache in general and for migraine in particular No localized loss of GM was observed. Larger WM volumes in patients increased the odds for migraine. These findings could not be confirmed in healthy subjects.	SLE patients with migraine have a diffuse reduction in GM compared to patients without migraine. This finding was not observed in healthy subjects with migraine. Neither anti-NR2 and anti-P antibodies nor S100B were associated with headaches in SLE patients.
18. Papadaki et al. (2018) [26]	76 SLE (37 primary NPSLE, 16 secondary NPSLE, 23 non-NPSLE) and 31 healthy controls	Not specified	Lower cerebral blood flow and volume in normal-appearing white matter areas in primary NPSLE patients	Primary NPSLE is characterized by significant hypoperfusion in cerebral white matter that appears normal on cMRI. The combination of DSC-MRI-measured blood flow in the brain semioval centre with conventional MRI may improve NPSLE diagnosis.
19. Aloleimy et al. (2021) [4]	57 SLE	- All headache: 54.4% - Migraine: 48.4% - TTH:35.5	25.8% with brain imaging abnormalities, white-matter hyperintensities most frequent	Musculoskeletal manifestations, positive anti-phospholipid (aPL) antibodies, and SLEDAI score ≥ 13.5 were identified as predictors of headache.
20. Santos et al. (2021) [27]	1,463 childhood-onset SLE patients	-All headache:52.2%	Not included	Headache, along with various neuropsychiatric syndromes, is common in childhood-onset SLE.

Table 7 (continued)

Study	Population	Headache prevalence	MRI findings	Key conclusions
21. Tian et al. (2023) [28]	908 participants	Not specified	Not included	Meta-analysis suggesting a potential association between migraine and the risk of developing SLE.
22. Our study	179 SLE	-All headache:55% - TTH: 65% - Migraine: 27%	Brain MRI abnormalities were observed in 8% of headache sufferers, including venous sinus thrombosis (2%), ischemic stroke (5%) and white matter hyperintensities (1%).	Disease activity (SLEDAI) was significantly higher in the Headache Group. Muco-cutaneous manifestations were associated with tension-type and migraine headaches. APL antibody positivity showed a significant association with migraine and cluster headache. Neuropsychiatric manifestations, including ischemic stroke and venous sinus thrombosis, were more prevalent in the Headache Group, although not clinically significant.

SLE = Systemic Lupus Erythematosus, TTH = Tension Type Headache, MS = Multiple Sclerosis, VAS = Visual analog scale, SLEDAI = Systemic Lupus erythematosus Disease Activity Index, RA = Rheumatoid Arthritis, NPSLE = Neuropsychiatric Systemic Lupus Erythematosus, APL = Anti-Phospholipid, MRI = Magnetic Resonance Image, cMRI = conventional Magnetic Resonance Image, DSC MRI = Dynamic susceptibility contrast Magnetic Resonance Image, ACA = Anticardiolipin Antibodies, CSF = Cerebospinal Fluid, GM: Grey Matter, WM: White Matter

extracellular matrix components, which compromises the integrity of the blood-brain barrier (BBB) in neuropsychiatric SLE (NPSLE). Elevated levels of MMP-9 in the serum and cerebrospinal fluid (CSF) of NPSLE patients are associated with neurodegenerative markers, indicating its role in BBB disruption and central nervous system (CNS) involvement [55].

Furthermore, neutrophils in SLE exhibit increased granulopoiesis and enhanced formation of neutrophil extracellular traps (NETs), characterized by the release of histones and enzymes such as MMP-9. This contributes to heightened intravascular activation, cell death, and an exacerbated inflammatory response in NPSLE [56]. Concurrently, pro-inflammatory cytokines like IL-1, IL-6, and IFN-γ, produced by neurons and microglia, further intensify this response. Notably, elevated IL-6 levels in the CSF are associated with abnormal brain MRI signals and blood-brain barrier (BBB) dysfunction, fueling the inflammatory cascade that drives many of the neurological manifestations observed in NPSLE [57].

The management of headaches in Systemic Lupus Erythematosus (SLE) patients requires a nuanced approach, considering both the underlying autoimmune disease and the specific type of headache experienced. For primary headaches such as migraines and tension-type headaches, standard treatments are generally employed. Migraine management often includes triptans, such as sumatriptan, and preventive medications like beta-blockers, amitriptyline, or topiramate, tailored to the severity and frequency of the attacks [58]. Tension-type headaches may benefit from over-the-counter analgesics like ibuprofen or acetaminophen, with chronic cases potentially requiring tricyclic antidepressants (TCA) or other prophylactic agents [59]. For headaches associated with secondary causes like antiphospholipid syndrome or cerebrovascular events, addressing the underlying condition with anticoagulants or other specific therapies is crucial [60]. Overall, a multidisciplinary approach involving rheumatologists and neurologists is often required to tailor headache management to the unique needs of SLE patients, balancing efficacy and safety while minimizing drug interactions.

While the study has yielded valuable insights, it is crucial to recognize its limitations, including its single-center design, the cross-sectional nature of the investigation, potential selection bias, reliance on self-reported headache data, and limited neurological parameters. Future research avenues may involve exploring biomarkers associated with neuroinflammation or vascular dysfunction in SLE patients with headaches, conducting longitudinal studies to evaluate the impact of various SLE treatment modalities on headache prevalence and severity, investigating genetic factors contributing to the co-occurrence of SLE and headaches, and designing interventions to

assess the efficacy of headache management strategies in SLE patients.

Conclusion

Our study underscores the complex relationship between Systemic Lupus Erythematosus (SLE) and headaches, revealing that headaches are a common but multifaceted symptom in SLE patients, with tension-type headaches and migraines being the most prevalent. We observed a significant association between headaches and higher SLE disease activity, particularly in patients with antiphospholipid antibodies, which may serve as an indicator for increased vigilance in managing these patients. Notably, no cases met the criteria for "lupus headache," challenging the clinical relevance of this classification.

The findings emphasize the need for more precise diagnostic criteria and standardized approaches to managing headaches in SLE. Future research should explore the underlying mechanisms linking headaches to SLE, particularly the role of immune dysregulation, and further investigate the clinical significance of MRI abnormalities in this patient population. Longitudinal studies are also necessary to better understand the progression of headaches in SLE and to identify potential biomarkers for early intervention and tailored treatment strategies.

Abbreviations

SLE	Systemic Lupus Erythematosus
ICT	Intracranial Tension
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
ANA	Antinuclear Antibodies
dsDNA	Double-Stranded Deoxyribonucleic Acid
APL	Antiphospholipid Antibodies
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
MRV	Magnetic Resonance Venography
MRA	Magnetic Resonance Angiography
VAS	Visual Analog Scale
CSF	Cerebrospinal Fluid
IL	Interleukin
TNF-α	Tumor Necrosis Factor-alpha
HLA	Human Leukocyte Antigens
β2GPI	β2-Glycoprotein I
BBB	Blood-Brain Barrier
NPSLE	Neuropsychiatric Systemic Lupus Erythematosus
CVT	Cerebral Venous Thrombosis
SPECT	Single Photon Emission Computed Tomography

Acknowledgements

N/A.

Author contributions

E S: Study design, Manuscript writing, literature review. E Z: Study design, Data collection, Literature review, Manuscript writing M S: Data collection, Literature review, Manuscript writing. H E: Study design, Manuscript writing, literature review, editingAll authors read and approved the final manuscript.

Funding

No funding from any governmental or nongovernmental sources.

Data availability

"The data used or analyzed during the current study are available from the corresponding author on reasonable request."

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and approved by the ethical committee of Menoufia Faculty of Medicine dating February 2023. The committee's reference number [INTM13-2]. Informed consent to participate was obtained from all of the participants in the study after fully explaining the study and its aims to them.

Consent for publication

N/A.

Competing interests

The authors declare no competing interests.

Clinical trial number

not applicable.'

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Received: 18 July 2024 / Accepted: 26 September 2024
Published online: 31 October 2024

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