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Inflammatory Arthritis and Younger Age of Lupus Onset are Associated with the Development of Neuropsychiatric Lupus

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Introduction

Neuropsychiatric Systemic lupus erythematous (NPSLE) refers to the various psychiatric and neurologic manifestations that develop secondary to involvement of the nervous system in patients with SLE [1, 2]. These clinical features occur either due to a diffuse neurological insult (e.g. encephalopathy, coma, depression, and psychosis) or a localized neurologic insult (e.g. stroke or seizure etc) [3]. Because of the varied diagnostic criteria associated with these manifestations, the American College of Rheumatology (ACR) has formulated case definitions, reporting standards, and diagnostic testing recommendations for the 19 neuropsychiatric SLE syndromes [4]. The prevalence of neurologic and psychiatric manifestations using the ACR case definitions follows the following order from most to least: cognitive dysfunction, headache, mood disorder, cerebrovascular disease, seizures, polyneuropathy, anxiety, and psychosis [5]. A psychiatric disturbance due to CNS lupus is a diagnosis of exclusion; all other possible causes of the observed symptoms must therefore be considered, including infection, electrolyte abnormalities, renal failure, drug effects, mass lesions, arterial emboli, and primary psychiatric disorders (such as bipolar disorder or severe stress disorder resulting from a chronic and life-threatening disease) [6]. One clue to the diagnosis is that majority of acute neuropsychiatric episodes occur during the first two years after the onset of SLE [7]. The timely diagnosis of these manifestations of lupus is necessary to start urgent immunosuppression therapy, and to avoid unnecessary antibiotic therapy and invasive workup [8].

Given the morbidity and mortality associated with the diagnosis of NPSLE, it is vital that timely diagnosis is made. Because of scarcity of manifestation, and lack of dedicated lupus centres, very little data is known as regards its prevalence and predictive clinical features among Pakistani lupus patients. Moreover, the data available to date in Pakistan mostly comes from non-rheumatology settings, and hence the diagnosis of lupus and NPSLE remains questionable. We sought to investigate this subset of lupus (NPSLE) in a more dedicated fashion through a prospective study. Our objectives were to determine the prevalence of neuropsychiatric SLE (NPSLE) among SLE patients attending a tertiary care rheumatology centre. Moreover, we aimed to evaluate any potential associations with demographics, systemic features and disease activity in comparison to a well characterized cohort of SLE with no neuropsychiatric features.

Materials and Methods

In this prospective cohort analysis, all SLE patients attending rheumatology department of Fatima Memorial Hospital during study period (January 2018 through to April 2019) were included. Association of demographic data and clinical manifestations of SLE with neuropsychiatric manifestations was studied, and the cohort of NPSLE patients was compared with a cohort of SLE with no neuropsychiatric features.

Material

In was a case control analysis of all SLE patients attending Rheumatology department of Fatima memorial hospital, Lahore, Pakistan from January 2018 through to April 2019. Fatima

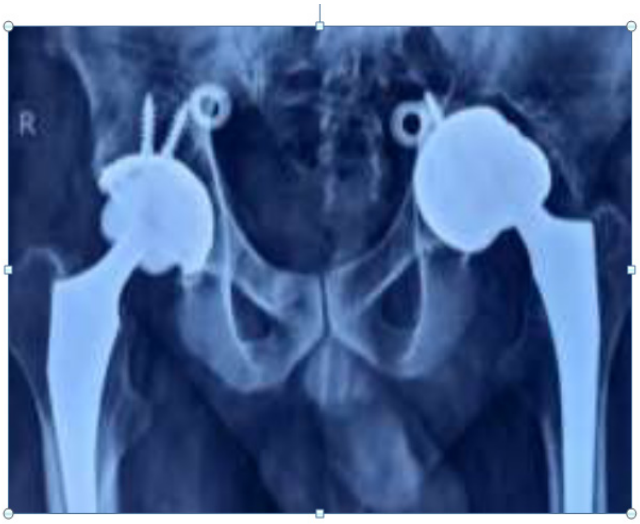

Figure 1 Xray pelvis showing B/L hip implants with displaced left implant.

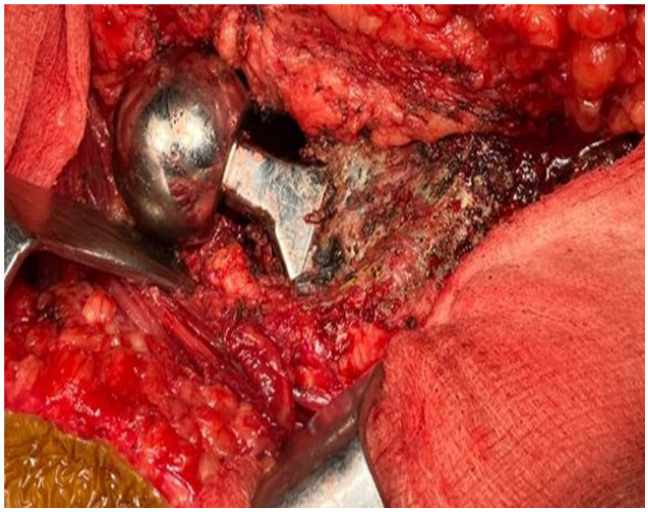

Figure 2 Shows implant deterioration and deposition in soft tissue.

memorial hospital is a tertiary care hospital and a referral center for complicated rheumatic diseases. This study was approved by ethical review committee of the institute (#: FMH-03-2020-IRB-750M) and informed consent was obtained from all patients. All patients with diagnosis of NPSLE were categorized into cases, while the control group was made after excluding patients with inadequate data of demographics and laboratory features, those who were lost to follow-up, and those with active central nervous infection to control bias.

We studied - by filling a preformed proforma - the demographic data, Clinical features, onset of the disease in the form of initial manifestation, time lapse between the onset of symptoms and diagnosis of NPSLE, clinical activity of SLE measured as Modified SLE Disease activity index 2000 (Modified SLEDAI-2K) at the time of neuropsychiatric manifestations, laboratory features including cerebrospinal fluid (CSF) analysis and radiological features - MRI brain in cases of central neurologic manifestations (stroke, seizures, psychosis, acute confusion). Laboratory parameters performed for excluding close differentials were also recorded. SLE-associated neuropsychiatric manifestations comprise of 19 syndromes categorised by American College of Rheumatology into central nervous manifestations and peripheral nervous manifestations. (REF). Headache was attributed to lupus after excluding infection (no history of upper respiratory symptoms and clear CSF analysis), mass effect (clear MRI) comprising of migranous type headache, resistant to narcotics. The case cohort was compared with a well characterized cohort consisting of 150 patients selected form the original 269 patients of Lupus patients with no neurological involvement.

Data analysis

Statistical analysis was performed using the SPSS software, version 23. Significance was defined as $p<0.05$ (two-tailed). A chi square (X2) statistic and Fisher's exact test was used to investigate the distribution of categorical variables, and continuous variables were analyzed using Student's t-test, which were not categorised. We applied odds ratios (OR) and associated confidence intervals (CI) to measure association between different variables. The association of different clinical variables with the diagnosis of NPSLE was determined using univariate and multivariate logistic regressions. The factors associated with NPSLE on univariate analysis with significance at the 0.25 level were entered into a multivariate model. The model was then reduced by backward elimination until the remaining effects were significant at the 0.05 level. Estimates of regression coefficients were obtained from this final model.

Results

During the study period, 269 SLE patients attended our rheumatology department. After detailed clinical assessment and follow up, 57 patients were diagnosed with NPSLE as per the American College of Rheumatology case definitions – prevalence of about 21.1% (57 out of 269 patients). All these patients underwent detailed clinical assessment as per the routine standard clinical practice and their demographics & clinical manifestations were recorded. The mean age of NPSLE cohort was 27.18±6.16 years; female comprised of 52 (92.5%) of the cohort, with 38 (70%) patients having low socioeconomic family status. The median duration of disease was 5 (5-Inter Quartile Range) years. Mean age at the onset of SLE was 20±6.21 years. Mean SLEDAI-2K at time of neurological manifestation was 21.63±6.7. About half of population (51%) has NPSLE at the onset of SLE. In remaining half, the mean duration between SLE diagnosis and NPSLE manifestation was 3.32±2.40 years.

Constitutional symptoms such as fever, fatigue, weight loss and loss of appetite were present in 40(77.5%), 28(50%), 21(37.5%), 17(30%) of the cohort respectively. Mucocutaneous manifestation like malar rash, oral ulcers, hair loss and photosensitivity were present in 46(82.5), 51(90%), 51(90%), 35(62.5%) of the cohort of NPSLE respectively. Systemic manifestations such as arthritis, serositis, nephritis and vasculitis were present in 46

(82.5%), 15(27.5%), 38 (70%) and 8 (15.0%) of the NPSLE cohort respectively (**Table 1**).

Among central neurological manifestations, seizures were present in 21(36.8%) patients, lupus associated headache in 12(21%) patients, stroke in 10(17.5%), and acute psychosis in 11(19.2%) of patients. Headache attributed to lupus in 12 patients comprised of Benign intracranial hypertension in 4 patients (papilledema, normal MRI, raised ICP and clear CSF), and migraine type headache in 8 patients (normal MRI, raised ICP and clear CSF, and absence of any head and neck infection, and raised SLEDAI score). Peripheral NS involvement comprising of Mononeuritis multiplex and cranial neuropathy occurred in 2(3.5%) and 1(1.7%) respectively. Rest of the neurological manifestations as elaborated in ACR nomenclature were not present in the cohort. Among demographic features, low educational status had near significant association with psychosis (p=0.09). Other demographic features did not show any significant associations (Table1). Analysing the association of central nervous manifestation of the cohort with clinical manifestations; among constitutional symptoms, weight loss and anorexia had significant associations with psychosis (p= 0.008, and 0.009 respectively), while APLS positivity also showed nearly significant association with stroke (p=0.07). No other demographic or systemic features among patients with NPSLE reach any statistical significance of <0.05. Table 2- Peripheral nervous manifestation, being scarce in the cohort were not included in this analysis).

Table 1. Demographic and clinical manifestation of NPSLE.

Characteristics	Total
Age	57(100)
BMI	27.18±6.16
Underweight	17(31%)
Normal-weight	16(28.6%)
Overweight	18(32.3%)
Obese	6(11.1%)
Educational status	-
Uneducated	7(12.5%)
Up-to secondary	12(22.5%)
Intermediate & above	35(65.1%)
Socioeconomic class	-
Lower S.E.C	41(70%)
Middle S.E.C	11(20%)
Upper S.E.C	5(10%)
Duration between SLE and NPSLE *	5(5)**
NPSLE presenting at onset of SLE	29(51.7)
SLEDAI at time of NPSLE	21.63±6.7
Age at onset of SLE	20±6.21 y
Constitutional symptoms	-
Fever	40(77.5)
Fatigue	28(50)
Weight loss	21(37)
Anorexia	17(31)
Mucocutaneous	-
Malar rash	46(82.5)
Oral ulcers	51(90)
Hair loss	51(90)
Photosensitivity	35(62.5)
Arthritis	46(82.5)
Serositis	15(27.5)
Nephritis	38(70)
Vasculitis	8(15.0)
Central Nervous manifestation	-
Seizures	21(36.8)
Lupus headache	12(21)
Stroke	10(17.5)
Psychosis	11(19.2)
Peripheral Nervous manifestation	-
Mon neuritis Simplex/multiplex	2(3.5)
Cranial neuropathy	1(1.7)

On comparison of NPSLE with non-neurological lupus cohort, univariate analysis showed the presence of inflammatory arthritis (OR 24.7, CI 8.8-68.8, P<0.001), episodes of pyrexia (OR 15, CI 5.8-38.5, P<0.001), Malar rash (OR 7.9, CI 3.0-20.2, P<0.001), serositis (OR 2.7, CI 1.04-7.43, P=0.04), age at the diagnosis of SLE (OR 0.87, CI 0.81-0.93, p<0.001) and raised creatinine (OR 0.33, CI 0.14-0.76, P=0.009) were significantly associated with the diagnosis of NPSLE. However, on multiple step-wise regression analysis (table-3), a significant association of NPSLE diagnosis was noted with the presence of inflammatory arthritis (OR 15.8, CI 4.7-53, P<0.001), younger age at the diagnosis of SLE (OR 0.89, CI 0.81-0.97, p=0.01) and pyrexia (OR 10.7, CI 3.2-36, P<0.001). The final regression model resulted in a statistically significantly improved prediction of NPSLE diagnosis (R-square=0.70), which means that this model accounted for 70% of the variation in the prediction of NPSLE diagnosis.

Discussion

NPSLE in our study comprised of seizures (36.8%) as the most common manifestation, followed by headache (21%), psychosis (19.2%), and CVA manifesting in 17.51% of the patients. Peripheral nervous manifestations manifested collectively in 7.5% patients. Interestingly, NPSLE was diagnosed at the onset of SLE in 50% of patients, and is associated with episodes of febrile episodes and inflammatory arthritis.

There are number of different clinically important findings of our study which are worth highlighting. For example, half of the NPSLE cohort (50%) had NPSLE as their first manifestation of SLE. In remaining half, neuropsychiatric symptoms happened after a short lag of only 3.32±2.40 years. This earlier occurrence of NPSLE during the disease course of SLE is concordant with the findings of earlier studies. Several plausible explanations can be put forth. For example, it is possible that NPSLE patients belong to different genotype group compared to the rest of SLE group. In different immune related diseases, genetic heterogeneity has been shown to explain the clinical phenotype variability; in other words, different disease/organ manifestations have probably different genetic basis [9].Contrasting genetic heterogeneity of skin psoriasis only and psoriatic arthritis is a nice example to explain this hypothesis. Additionally, a high lupus disease activity in earlier years of the disease is another explanation of NPSLE presenting in the earlier years of disease course. In comparison to Henley et al, who evaluated SLICC cohort for NPSLE at initial diagnosis of SLE, the overall prevalence of NPSLE in our cohort

was lower (21% vs 28%), however, a much higher percentage of our NPSLE cohort had neuropsychiatric manifestation at the onset of SLE (50% vs 28%).

High disease activity (SLEDAI-2K score) at the time of NPSLE is an important feature of NPSLE and helps in differentiation from other CNS insults such as infection. In concordance to our findings, Jiang M et al proposed both the high SLEDAI and hypocomplementemia to be the important features favouring NPSLE over infection, and can potentially be very helpful in the management. Similarly Fang Het al also reported high SLEDAI a feature favouring NPSLE over infection. Wu XY et al by studying NPSLE in paediatric population have concluded with fairly similar findings - prevalence of NPSLE (21% each), earlier onset of NPSLE in disease course (75% within first 2 years), and association with high disease activity, fever and skin rash.

Our study confirms the earlier findings that younger age of SLE onset has independent significant association with NPSLE features, even after controlling the confounders in a multivariate regression model. This further suggests that NPSLE patients perhaps belong to a genetically different cohort of patients. In our centre, through an international collaboration, we are collecting DNA for our entire cohort of SLE patients and in near future, we hope to have some early genetic data to better understand this hypothesis.

Compared to local studies, our study results are higher than the findings of Ishaq et al (prevalence of NPSLE 21% vs 14%), however, CVA was not included as a part of NPSLE in their study. Rabbani et al found a higher prevalence of NPSLE than our cohort (29% vs 21%), but they have included only the seizures and psychosis in their study. Similar to the study of Mumtaz et al, the neuropsychiatric manifestations occurred within 2 years of Lupus. They reported significantly higher prevalence of NPSLE than our cohort (84% vs 21%), however, the major central nervous manifestations attributed to lupus in the study (comprising of stroke, seizures and psychosis) were present only in 23.8% of the cohort. The prevalence of CVA (25% vs 17.5 each) was slightly higher in that study. Their study however showed a higher prevalence of seizures (65% vs 36.8%) and headache (40% vs 21%).

To conclude, NPSLE symptoms are present in 21.1% of patients with SLE. These neuropsychiatric manifestations occur either at the onset or early in course of disease. Presence of inflammatory arthritis, younger age of the development of SLE, and episodes of pyrexia are predictive of NPSLE features (**Tables 2-4**).

Table 2. Association of Central nervous manifestation with Demographic and clinical manifestation.

Variable	Seizures 21(36.8)	P value	Headache 12(21)	P value	CVA 10(17.5)	P value	Psychosis 11(19.2)	P value
Constitutional symptoms								
fever	18(85.7)	0.26	11(91.7)	0.23	6(60)	0.19	10(90.9)	0.39
fatigue	9(42.9)	0.53	5(41.7)	0.73	4(40)	0.72	7(63.6)	0.48
weight loss	6(28.6)	0.33	6(50)	0.31	2(20)	0.27	8972.7)	0.009
anorexia	5(23.8)	0.49	2(16.7)	0.29	3(30)	1.00	7(63.6)	0.008
Mucocutaneous								
malar rash	18(85.7)	0.69	11(91.7)	0.65	6(60)	0.05	10(90.9)	0.65
oral ulcers	19(90.5)	1.00	12(100)	0.30	8(80)	0.26	10(90.9)	1.00
Hair loss	20(95.2)	0.33	11(91.7)	1.00	7(70)	0.04	11(100)	0.56
Photosensitivity	14(66.7)	0.74	8(66.7)	1.00	4(40)	0.13	8(72.7)	0.48
Hypertension	2(9.5)	0.12	3(25)	0.68	3(30)	0.39	4(36.4)	0.18
Arthritis	19(90.5)	0.23	10(83)	1.00	6(60)	0.52	10(90.9)	0.6
Serositis	4 (19)	0.29	5(41.5)	0.25	2920)	0.69	4936.4)	0.46
Nephritis	17(81.0)	0.16	7(58.3)	0.45	6(60)	1.00	6(54.5)	0.26
Vasculitis	3(14.3)	1.00	2(16.7)	1.00	2(20)	0.63	3(27.3)	0.30
APLS positive	8(54.4)	1.00	5(45.5)	1.00	5(50)	0.71	2(18.2)	0.07

Table 3. Comparison of demographic characteristics and clinical parameters of NPSLE.

Variable	NPSLE cohort (n=57)	Non-NPSLE cohort (n=150)	p-value
Gender – Female	92.5% (n=37)	82.6% (n=124)	0.17
Pyrexia	77.5% (n=31)	18.6% (n=28)	<0.001
Inflammatory Arthritis	82.5% (n=33)	16% (n=24)	<0.001
Malar Rash	82.5% (n=33)	37% (n=56)	<0.001
Serositis	27.5% (n=11)	12% (n=18)	0.03
Anemia (Hb <10g/dL)	40% (n=16)	34.6% (n=52)	0.68
Leukopenia (TLC < 3x 10^9/L)	85% (n=34)	82.6% (n=124)	0.59
Thrombocytopenia (< 150 x 10^9/L)	75% (n=30)	80% (n=120)	0.63
Raised Creatinine (> 1.2 lab value)	27.5% (n=11)	53% (n=80)	0.01
Age - Years	27.6±7.4	28±9	0.83
Age at the diagnosis of SLE	20.6±6.2	27±7.4	<0.001
Serum Creatinine	1.05±0.53	1.7±1.8	0.006

Table 4. Univariate and multivariate (adjusted simultaneously for variables shown) associations of different clinical variables with the diagnosis of NPSLE.

	Univariate Model			Multivariate Model		
	OR*	95% CI	P value	OR	95% CI	P value
Age	0.99	0.95-1.04	0.83	-	-	-
Age at the diagnosis of SLE	0.87	0.81-0.93	<0.001	0.89	0.81-0.97	0.01
Gender	2.58	0.69-9.6	0.15	-	-	-
Pyrexia	15	5.8-38.5	<0.001	10.7	3.2-36	<0.001
Inflammatory Arthritis	24.7	8.8-68.8	<0.001	15.8	4.7-53	<0.001
Malar Rash	7.9	3.0-20.2	<0.001	-	-	-
Serositis	2.7	1.04-7.43	0.04	-	-	-
Anemia	1.25	0.56-2.77	0.57	-	-	-
Thrombocytopenia	0.75	0.30-1.86	0.53	-	-	-
Leukopenia	1.42	0.46-4.3	0.53	-	-	-
Raised Creatinine	0.33	0.14-0.76	0.009	-	-	-

Conclusion

NPSLE is present in 21.1% of patients with SLE. Presence of inflammatory arthritis, younger age of the development of SLE, and episodes of pyrexia are predictive of NPSLE features.

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