Rheumatology International (2019) 39:1689–1695
https://doi.org/10.1007/s00296-019-04423-4

Rheumatology
INTERNATIONAL

COHORT STUDIES

Mental disorders in systemic lupus erythematosus: a cohort study

Heidi Fernandez[1,2] · Andrea Cevallos[1,2] · Ruth Jimbo Sotomayor[2] · Fernando Naranjo-Saltos[1] · Diego Mera Orces[2] · Efrain Basantes[1]

Received: 21 April 2019 / Accepted: 10 August 2019 / Published online: 20 August 2019

Abstract

Currently, the evaluation of mental disorders in patients with Systemic lupus erythematosus (SLE) is essential in the management of the illness because of their impact in morbimortality. The main purpose of this study was to determine the prevalence of mental disorders in a group of patients with SLE in a tertiary referral hospital in Quito-Ecuador. The main diffuse central nervous system psychiatric syndromes in SLE (psychosis, anxiety and mood disorders) and cognitive dysfunction were evaluated with the MINI International Neuropsychiatric Interview and the Montreal scale, respectively. This was a descriptive, cross-sectional study which included patients 15 years and older diagnosed with SLE in a tertiary referral hospital in Quito, Ecuador. 85 patients diagnosed with SLE attending the internal medicine outpatient clinic during October 2017–May 2018 were included. A bivariate analysis of possible associations between these mental disorders with corticosteroid use, antiphospholipid syndrome (APS), and quality of life was also studied. Eighty-five patients, with an average age of 34.12 ± 11.5 years were included, of which 94% were females. 71% of participants (60 patients) had at least one mental disorder evaluated in this study. The most frequent was cognitive impairment ($n=43$, 51%) followed by anxiety disorders ($n=35$, 41%), mood disorders ($n=34$, 40%) and psychosis ($n=1$; 1%). 38% presented mild cognitive impairment and 13% had moderate cognitive impairment. Memory and visuospatial/executive function were the most affected domains in the cognitive assessment. 38% of participants were previously diagnosed with antiphospholipid syndrome, of which 78% had a mental disorder (OR = 1.83, $p=0.2$). Most patients ($n=84$; 99%) were treated with corticosteroids, of these, 59 patients presented a mental disorder (OR = 0.9, $p=0.8$). Associations with APS or corticosteroid use were not statistically significant. However, the multivariate regression suggests an association between presence of mental disease and quality of life. There were statistically significant alterations in anxiety/depression and pain. There is a high prevalence of neuropsychiatric syndromes in this cohort of patients. Almost ¾ of our cohort had at least one mental disorder, the most common was cognitive impairment.

Keywords Systemic lupus erythematosus · Mental disorders · Psychiatric syndromes · Cognitive disorders · Quality of life

Introduction

The definition and prevalence of mental disorders in patients with SLE have always constituted a challenge for investigators. Indeed, although the American College of Rheumatology (ACR) formed a multidisciplinary committee in 1999, to develop criteria for the classification of 19 neuropsychiatric syndromes in SLE, the prevalence of neuropsychiatric syndromes still varies considerably between studies [1]. Systematic reviews report a prevalence between 17 and 71%, owing to various factors such as population, study design, different concepts and instruments used [2].

The ACR defined neuropsychiatric systemic lupus erythematosus (NPSLE) as neurological syndromes of the central, peripheral and autonomic nervous system or the psychiatric syndromes present in patients with SLE and in whom other causes are excluded. However, in clinical practice, identifying if the cause of a mental disorder is secondary to a diagnosis of a chronic, incurable, unpredictable disease or, if it is exclusively due to direct physiopathological mechanisms of SLE in the central nervous system is more complicated, especially with milder manifestations of these disorders.

✉ Ruth Jimbo Sotomayor
rejimbo@puce.edu.ec

[1] Department of Internal Medicine, Eugenio Espejo Hospital, Gran Colombia Street, Quito, Pichincha, Ecuador

[2] Postgrado de Medicina Interna, Pontificia Universidad Católica del Ecuador, 12 de Octubre Ave, 1076 Quito, Pichincha, Ecuador

Apparently, some risk factors for developing NPSLE are a high level of disease activity at diagnosis and the presence of antiphospholipid antibodies [3–5].

In spite of this, since the survival of patients with SLE has crucially improved with the development of better diagnostic and therapeutic tools, screening and identifying mental disorders such as anxiety, mood disorders or cognitive impairment is essential to offer the possibility of a better quality of life in these patients and make a difference in their prognosis. Many studies show that the quality of life in patients with SLE is lower than in the general population [6]. In Ecuador, there is little evidence and few data related to any of these topics.

Materials and methods

Study design

This cross-sectional study included patients 15 years and older diagnosed with SLE in a tertiary referral hospital in Quito, Ecuador. 85 patients diagnosed with SLE attending the internal medicine outpatient clinic during October 2017–May 2018 were included. Participants in this study were previously diagnosed with SLE according to the 2012 SLICC criteria [7]. Patients with antiphospholipid syndrome met the 2006 revised Sydney criteria [8]. This study describes the prevalence of psychiatric syndromes and cognitive dysfunction in patients with SLE and their association with risk factors such as corticosteroids use, active SLE and APS syndrome. Quality of life was also evaluated in this group of patients.

Data collection and measurement

Medical records were reviewed in search of sociodemographic and relevant clinical information such as comorbidities and medical treatment.

Psychiatric syndromes (psychosis, anxiety and mood disorders) were evaluated through the use of the MINI International Neuropsychiatric Interview. Cognitive disorders were studied with the Montreal scale (MoCA) and quality of life was assessed with EuroQol-5D.

The MINI International Neuropsychiatric Interview is a structured interview instrument which comprises modules for 17 psychiatric diagnoses with high accuracy for depression and acceptable accuracy for panic disorder and generalized anxiety disorder. In our study, the assessment needed took about 10–15 min depending on the patient. It may be administered by clinicians after short training.

On the other hand, the MoCA test evaluates cognitive impairment (attention, concentration, executive functions, memory, language, visuospatial cognitive capacity, abstraction, calculation, and orientation). In a study carried out in Mexico, MoCA was able to identify the largest number of patients with cognitive impairment, followed by the MMSE and CSI. The MoCA test proved to be useful for the detection of cognitive impairment in patients with SLE. It is a brief test that does not require special training which would facilitate its use in the outpatient setting [9].

EuroQol-5D is also a brief test. It has been previously used to evaluate quality of life in patients with lupus which would facilitate future comparisons.

Data were stored in a Microsoft Excel version 15.24 database. Afterwards, a descriptive and quantitative statistical analysis was performed. A bivariate analysis was used to study the association with other variables such as corticosteroid use, antiphospholipid syndrome (APS), active SLE and quality of life.

Statistical analysis

We first developed a univariate description of the sociodemographic, psychiatric syndromes, cognitive disorders and an assessment of quality of life of the patients included in our study. This was followed by a bivariate analysis of the presence of mental disorders and presence of antiphospholipid syndrome, corticosteroids dose, disease activity and diverse parameters that measure quality of life. All the associations with a $p < 0.25$ were considered for inclusion in our saturated multivariate regression model. We then developed a final model by backward variable reduction. The final model was compared to the saturated model through the likelihood ratio test and then assessed the ability of discrimination of our final model by the AUC of the ROC curve.

Ethics

The study was approved by hospital authorities and the Human Research Ethics Committee. Written informed consent or assent was obtained from all patients.

Results

Eighty-five patients with an average age of 34.12 ± 11.5 years were included in this study. There were 80 female patients (94%) and 5 male patients (6%). Forty-five patients (53%) completed high school; 34 patients (40%) were single and 31 patients (36%) were married. Mean disease duration was 73.4 months (6.1 years).

The main affected organ system manifestation was lupus nephritis (38%) and only 9% of participants had active SLE when assessed. In addition, 32 patients (38%) met APS criteria. Regarding medication, 84 participants (99%) were treated with corticosteroids and 47% of these patients took

intermediate doses (between 7.5 and 30 mg per day); 73 patients (86%) used immunomodulators and 3 patients (4%) received biologics. Table 1 describes the sociodemographic and clinical characteristics of the population.

The mental disorders (psychosis, anxiety, mood disorders and cognitive disfunction) were evaluated through the use of the MINI International Neuropsychiatric Interview and the Montreal cognitive assessment. Out of the 85 participants, 60 had at least one mental disorder (71%) (Fig. 1). Out of the 43 patients diagnosed with cognitive impairment, 38% were defined as mild and 13% as moderate. No severe cognitive disorders were reported in this study.

Table 1 Sociodemographic and clinical characteristics of the population

Variable	*N* (%)
Average age (Range–years)	34.12 (17–66)
Age groups	
15–18 years	3 (4%)
19–30 years	33 (39%)
31–65 years	48 (56%)
> 65 years	1 (1%)
Gender	
Female	80 (94%)
Male	5 (6%)
Education	
None	3 (4%)
Primary	21 (25%)
Secondary	45 (53%)
Higher education	16 (19%)
Marital status	
Single	34 (40%)
Civil Union	14 (16%)
Married	31 (36%)
Divorced	4 (5%)
Widowed	2 (2%)
Mean disease duration	73.4 months
Organ system manifestations	
Renal	32 (38%)
Cardiovascular	1 (1%)
Neurologic	5 (6%)
Hematologic	2 (2%)
None	41 (48%)
Multiple	4 (5%)
Active SLE	
Yes	8 (9%)
No	77 (91%)
Corticosteroid use	
Yes	84 (99%)
No	1 (1%)
Corticosteroid dose	
< 7.5 mg	37 (44%)
7.5–30 mg	40 (47%)
> 30 mg	8 (9%)
Antiphospholipid syndrome	
Yes	32 (38%)
No	53 (62%)

The Montreal cognitive assessment test (MoCA) was used to evaluate different types of cognitive abilities such as visuospatial/executive, naming, attention, language, abstraction, memory/delayed recall and orientation. The most frequent cognitive impairment found was memory/delayed recall followed by visuospatial/executive, and attention (Table 2).

We then performed a bivariate analysis of the association between several variables included in our study and mental disorders in patients with SLE (Table 3).

The prevalence of mental disorders was higher in patients without APS ($n = 35$) than in patients with APS ($n = 25$), though the association was not statistically significant (OR = 1.83; $p = 0.23$). A risk analysis was also carried out between mental disorders and the use of corticosteroids at low versus medium/high doses in patients with SLE. The majority of patients ($n = 84$; 99%) were treated with corticosteroids during the study, of these, 59 patients presented mental disorders. There was a higher prevalence of mental disorders in patients with medium/high doses. The association was not statistically significant (OR = 0.9, $p = 0.8$). We did not find a statistically significant association between disease activity in patients with SLE, assessed with SLEDAI, and presence of mental disorders. According to our study, patients with mental disorders present statistically significant alterations in mobility, pain and anxiety/depression. The most affected dimension was pain with 48 patients followed by anxiety/depression with 40 patients. The results are presented in Table 3.

Taking into consideration the results of the bivariate analysis, the variables included in the regression model were presence of antiphospholipid syndrome, quality of life measured by mobility, quality of life measured by self-care, quality of life measured by pain and quality of life measured by anxiety/depression. By backward elimination and testing the ability of discrimination of several models, we obtained our final model (Table 4) that contains APS, quality of life measured by mobility, quality of life measured by pain and quality of life measured by anxiety/depression.

We assessed the ability of discrimination of our model by the AUC of the ROC curve where we obtained a 0.74, considered a good ability to differentiate.

We assessed the ability of quality of life to predict the presence of mental disorders when adjusting for presence of antiphospholipid syndrome. We found a statistically significant relationship between quality of life measured by level of anxiety/depression and by level of pain with the presence of mental disorders in patients with SLE.

Fig. 1 Mental disorders

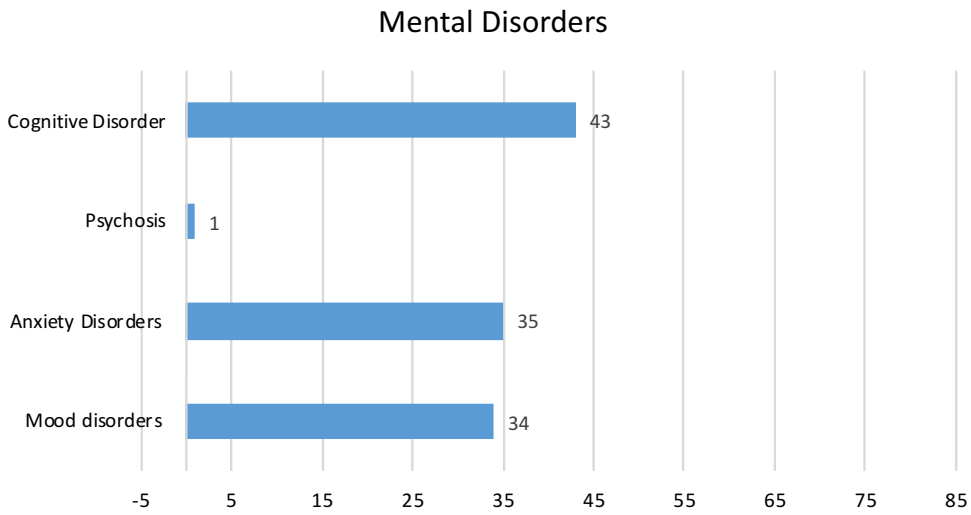

Table 2 Cognitive Assessment

Cognitive disorder	Patients ($N=85$)
Visuospatial/executive	
Yes	51 (60%)
No	34 (40%)
Naming	
Yes	32 (38%)
No	53 (62%)
Attention	
Yes	48 (56%)
No	37 (44%)
Language	
Yes	27 (32%)
No	58 (68%)
Abstraction	
Yes	19 (22%)
No	66 (78%)
Memory/delayed recall	
Yes	55 (65%)
No	30 (35%)
Orientation	
Yes	2 (2%)
No	83 (98%)

Discussion

The main diffuse central nervous system psychiatric syndromes in SLE (psychosis, anxiety and mood disorders) and cognitive dysfunction were evaluated. The prevalence of these mental disorders in our cohort was high, 71% (60 patients). This figure fits in the wide range of rates reported worldwide, as some suggest it may affect between 12 and 95% of SLE patients [10–14]. In spite of the ACR publication in 1999, which attempted to homogenize criteria and the wide variety of data on the prevalence of neuropsychiatric disorders in SLE, many studies continue to obtain data that vary enormously. A review of 21 articles carried out between 1969 and 1991, before the ACR criteria, estimated a prevalence between 17 and 71% [15]. However after the ACR criteria, a Chilean group reported the results of 6 studies from different centers worldwide carried out between 2001 and 2011. The lowest prevalence, 37%, was described by a Canadian group; and the highest, that reached 91%, was reported in a study of 46 Finnish patients [2]. The vast difference in prevalence between studies may be due to various factors such as the types of disorders included, population characteristics, patient selection, study design, different concepts and instruments used. We also found that we have a higher prevalence when compared with other Latin American studies such as one published in 2011 in Chile, which obtained a prevalence of 44.6% of neuropsychiatric disorders [16].

Cognitive impairment was assessed with the MoCA test which proved to be highly useful for the detection of cognitive deterioration in patients with SLE [9]. According to our results, the most prevalent mental disorder was cognitive impairment (51%); much higher than that reported by Jarpa et al. (7.3%), in which only severe cognitive impairment was assessed, although other studies report a prevalence between 6.6 and 80% across a broad range of domains [1, 11, 16–19]. According to a meta-analysis of 11 studies, the prevalence of cognitive impairment may vary between 23 and 60% when proper neuropsychological testing is conducted [11]. Mild cognitive dysfunction is common in patients with SLE, in which case the MoCA test is a valuable tool for assessment. Attention, visual and verbal memory, executive function and psycho-motor speed are the most affected domains [19]. Most of our patients with a cognitive disorder had mild

Table 3 Association of Mental Disorders and Characteristics of patients with SLE

	With mental disorders	Without mental disorders	OR (95% CI)	*p* value
Antiphospholipid syndrome			1.83 (0.6–5.0)	0.23
With APS	25	35		
Without APS	7	18		
Corticosteroid dose			0.9 (0.3-2.4)	0.8
< 7.5 mg	25	34		
> 7.5 mg	11	14		
Disease activity			1.2 (0.2–6.8)	0.7
Disease activity	6	54		
No disease activity	2	23		
Quality of life—mobility			3.74 (1.2–11.2)	0.01
Without problems	20	31		
With problems	5	29		
Quality of life—self care			4.80 (0.5–39)	0.14
Without problems	24	50		
With problems	1	10		
Quality of life—usual activities			1.60 (0.6–4.13)	0.32
Without problems	15	29		
With problems	10	31		
Quality of life—pain			7.11 (2.5–19.9)	0.0002
Without pain	16	12		
With pain	9	48		
Quality of life—anxiety/depression			3.55 (1.3–9.44)	0.01
Without problems	16	20		
With problems	9	40		

Table 4 Association of mental disorders and characteristics of patients with SLE

	Odds ratio	Standard error	*p* > *z*	[95% Conf. Interval]	
APS					
Absence	1				
Presence	1.407165	0.8561737	0.575	0.4270131	4.637127
QoL mobility					
1	1				
2	1.275202	0.9277588	0.738	0.306406	5.307146
3	1	(empty)			
QoL Pain					
1	1				
2	6.250937	3.85207	0.003	1.868107	20.91648
3	1.955727	2.90094	0.651	0.1068357	35.80141
QoL anxiety/depression					
1	1				
2	2.04607	1.199018	0.222	0.6487957	6.452576
3	1	(empty)			
_cons.	0.4110018	0.205563	0.075	0.1542107	1.095401

impairment, and no severe cases were reported, similar to a Texas cohort where mild cognitive impairment was predominant with few severe cases [20].

Forty-one percent of our patients had anxiety disorder, which is higher than others reported in the literature. For example, in the aforementioned Texas cohort, the prevalence reported was 24% [20]. Likewise, a meta-analysis published in 2017 revealed the prevalence of anxiety in patients with SLE to be 37% using clinical interviews and 40% with other screening tools [21]. It would be necessary to evaluate the possible causes of this difference, such as socio-economic characteristics, as well as screening tools used.

The third most frequent mental disorder in this study was mood disorder (40%). According to a systematic review conducted by a Brazilian group that included 13 articles, the prevalence reported was between 4.8 and 75% [22]. It is difficult to compare mood disorder because there are different categories and assessment tools used in different studies. Some may determine the presence of depression, dysthymia and bipolar disorders individually; while others report these, and other syndromes together. A metanalysis identified a prevalence of depression of 30–39% in SLE patients using screening tools [21]. Others such as Palagini et al. published a systematic review of 17 articles with a

prevalence of depressive disorders between 17 and 75% [23]. Risk factors related to mood disorders have been described, such as the existence of another CNS manifestation, concomitant neuropsychiatric disorders, use of corticosteroids at high doses or the patients' perception of their disease [24].

Only 1 of 85 patients in our study was classified as having a psychotic disorder which represents 0.85% of our population. This is consistent with the literature worldwide which describes this disorder as infrequent (prevalence between 0 and 11%) but of great severity [25]. The fact that our study was performed in the outpatient setting may justify this finding.

One purpose of this study was to determine if mental disorders impacted our patient's quality of life. According to our results, patients with mental disorders had a greater and statistically significant limitation in pain/discomfort and anxiety/depression. The association between depressive/anxiety disorders and low quality of life in patients with SLE has been previously seen in some studies [26, 27]. One publication included other types of neuropsychiatric manifestations other than depression and anxiety. It confirmed the correlation between the presence of at least one neuropsychiatric manifestation (headache, convulsions, delirium, cognitive deterioration, psychosis, depression and peripheral nervous system disorders) with a lower level of quality of life in 101 patients with SLE [28].

Attributing these mental disorders specifically to SLE may be difficult as they can also be found in the general population. The burden of having the disease itself may predispose the patient to many of these syndromes [10, 29]. It is important to take into account that in the context of a patient with SLE, neuropsychiatric manifestations can also be due to infectious diseases, metabolic alterations or side effects of drugs used [30]. For now, no laboratory or imaging test is sensitive or specific enough to confirm the diagnosis of NPSLE. There is a possible association of mental disorders with factors such as disease activity or APS, specifically with their antibodies [31]. However, in our study, neither disease activity nor antiphospholipid syndrome was statistically significant.

Study limitations

- The study was based on 4 central nervous system neuropsychiatric manifestations. Most studies include focal manifestations which made comparisons difficult.
- The study was conducted in an outpatient setting of a public hospital. There may be differences in the characteristics of the population private centers.
- SLE is a fluctuating disease and these manifestations may appear at any time during the evolution of the disease. Our study was cross-sectional, so it may have limited itself to assessing the prevalence during the study period.
- There are many screening tools available for neuropsychiatric evaluation. Many studies use different tools, making comparisons more complicated.

Conclusions

There is a high prevalence of neuropsychiatric syndromes in this cohort of patients. Almost ¾ of our cohort had at least one mental disorder, the most common was cognitive impairment. However, we cannot attribute these manifestations exclusively to mechanisms of brain tissue injury due to lupus. Nevertheless, we found a relationship between the quality of life and the presence of mental disorders in these patients. Additional studies are needed to describe other diagnostic tools required to establish this particular cause and also continue studying certain risk factors for the development of these disorders in our population. The results of this study denote the need to create multidisciplinary units that include rheumatologists, internists, psychiatrists and psychologists for the timely detection and treatment of these manifestations. Disease control and fewer flares along with an integral treatment that also involves studying socioeconomic problems, solving sleep problems, comorbidity and pain management, should positively influence patients with SLE to have a better quality of life.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest HF declares no conflict of interest; AC declares no conflict of interest; RJS declares no conflict of interest; FN-S declares no conflict of interest; DM declares no conflict of interest; EB declares no conflict of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Eugenio Espejo Hospital-Ministry of Public Health) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by hospital authorities and the Human Research Ethics Committee.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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