Cognitive Dysfunction, Depression and Anxiety in a Cohort of Systemic Lupus Erythematosus Patients

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SLE is the prototype of connective tissue diseases that can present the complete spectrum of neurologic and psychiatric disorders, cognitive dysfunction, depression and anxiety being more prevalent compared to general population, with an input on patients' prognosis and quality of life. In this study we aimed to determine the presence of cognitive dysfunction, anxiety and depression in a cohort of SLE patients, and their relationship to disease activty and quality of life. We determined the presence of these neuropsychyatric manifestations in signfficant percentages, directly correlated to disease activity and with an impact of quality of life. Our results lead to its extension, with multicentric contribution, and underline the necessity and benefit of a careful and periodical neuropsychiatric examination, in order to recognize the clinical patterns in early stages, apply the proper therapeutic measures, quantify the future damage and improve the outcome of these patients.

Keywords: systemic lupus erythematosus, cognitive dysfunction, depression, anxiety, disease activity, life quality.

Systemic lupus erythematosus (SLE) is a complex connective tissue disease, characterized by multisystem involvement, and although any of the autoimmune, inflammatory disease can determine neuroinflammation, it represents their prototype, being the tipical pathology that can produce neurological and psychyatric disorders [1-11]. Compared to other clinical patterns, their primary etiologic diagnosis is not so very easily to be established despite the availablity of many imagistic techniques [2, 12-15]. The clinical spectrum of neuropsychyatric SLE is complex, includes 19 entities, focal or diffuse, with variable prevalences [16], and from those, cognitive dysfunction, depression and anxiety are relatively often observed, with an important input on patients prognosis and life quality. As noticed in any autoimmune disease, imaging methods, along with immunologic studies, enable an early diagnosis and individualized therapeutic measures [1, 17-25].

Experimental part

The aim of the study was to determine the presence of cognitive dysfunction, anxiety and depression in a cohort of SLE patients, and their relationship to disease activty and quality of life.

Matherial and methods

We performed a longitudinal, prospective study, which included a cohort of 22 patients, diagnosed with SLE, according to the ACR/SCLICC 2012 revised criteria [25], in the Department of Rheumatology, Emergency County Hospital of Craiova, Romania. The control group included 18 sex and age-matched subjects, without acute or chronic inflammatory diseases, history of connective tissue, other autoimmune diseases or neuropsychyatric pathology.

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova. All patients provided their written informed consent, after receiving a standard form which mentioned that the results would be used for research purposes.

Patients evaluation included anamnestic data, clinical examination, laboratory tests and imagistic methods. Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [26], that ranges from 0 to 105, and defines remission when is 0, low activity 1-5, moderate activity 6-11, high disease activity 11-19 and very high disease activity over 20; a persistent SLEDAI over 3 defines a chronic activity [27].

Cognitive dysfunction, depression and anxiety were evaluated by the same examiner, blinded by clinical and labortory date. In order to assess the presence of cognitive dysfunction we used scale Montreal Cognitive Assessment scale (MoCA), that is relatively easy to be performed and evaluates five cognitive domains (attention, executive function, memory, visuospatial function and language). The

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MoCA assesses several cognitive domains: visuospatial functions copy of cube (1 point), clock drawing (3 points); naming 3 pictures (3 points); memory learning of 5 words - delayed recall 5 words (5points); attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each); language repetition of 2 sentences (2 points); abstract thinking similarities (2 points); abstract thinking similarities (2 points); orientation 6 tasks (6 points). An MoCA score of less than 26 points was defined as cognitive dysfunction [28]. Depression was evaluated using HAM-D (Hamilton Depression Scale); a score under 7 points defines normal, 8-13 mild depresssion, 14-18 moderate, 19-22 severe and over 23 very severe depresion [29]. We assessed anxiety by using HAM-A (Hamiltopn Anxiety Rating Scale), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate and 25-30 moderate to severe [30].

Life quality was estimated using short form survey (SF-36) and Systemic lupus erythematosus-specific Quality of Life questionnaire (SLEQol). SF-36 form is an indicator of overall health status, has eight scaled scores (energy, physical functioning, general health, pain, role limitation due to emotional problems, role limitation due to physical problems, emotional well-being and social functioning), each of them ranging from 0 to 100; lower scores correspond to high disability, high scores to less disablity [31, 32]. SLEQol quantifies six domains, including physiscal functioning (6 items), activities (9 items), symptoms (8items), treatment (4 items), mood (4 items) and self-image (9 items), with a 7 points response scale. The scores range from 40 to 280, with higher values corresponding to worse quality of life [32].

Statistical analysis was performed using GraphPad Prism 5.5. Results are presented as mean±SD and data were analyzed using t-test and One-way ANOVA for comparing groups, and Pearson/Spearman's coefficient for evaluating correlations. We considered a level of $p<0.05$ statistically significant.

Results and disscusions

We included 22 consecutive patients, 19 women and 3 men, with a mean age of 43.41+11.04 years and a mean disease duration of 9.04+5.89 years. The main characteristics of the study group are presented in table 1.

Table 1
BASELINE CHARACTERISTICS OF SLE PATIENTS

Characteristics	
Age (years)	43.41±11.04
Sex (women)	19 (86.36)
Disease duration (years)	9.3±4.3
Education level (years)	11.01±4.12
Anti-dsDNA (UI/ml)	84.65±1116.7
Anti-Ro (UI/ml)	5.68±4.52
ACL IgG (GPL/ml)	21.77±17.42
ACL IgM (GPL/ml)	25.37±19.91
C3 (mg/dl)	83.93±21.98
C4 (mg/dl)	9.94.0±6.82
Immunosupressive treatment (n;%)	12 (54.54)
GC (n;%)	14 (63.63)
GC (mg)	3.88 ±4.81
SLEDAI	7.59±3.68
SLEQol	71.14±30.68

The results are presented as mean±standard deviation or percentages (n%).

Scoring disease activity, we recokned a mean SLEDAI of 7.59+3.68 (min 3, max 20) (table1); most of the patients (14; 66.63%) had a moderate disease activity, 36.36% (8 patients) had a low disease activity, 1 patient a SLEDAI corresponding to an intense activity and 1 patient had a severe disease activity.

Cognitive dysfunction was diagnosed in a percentage of 55.54 of SLE patients (12), statistically significant different ($p=0.001$) compared to control group (22.22%; 4 patients), and involved mostly orientation and attention (figure 1a). The mean score calculated using MoCA was 25.05+2.29 (min 20; max 28) (fig. 1b), for most of the patients registering a score corresponding to a mild cognitive dysfunction.

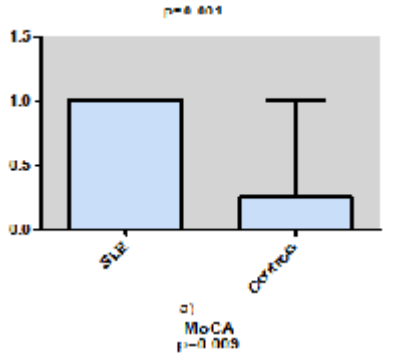

Fig. 1a. Cognitive dysfunction in patients/ controls; b. MoCA score for SLE/controls.

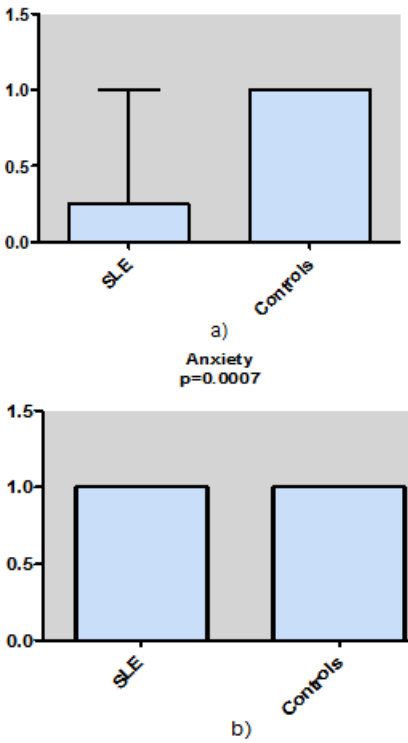

Fig. 2. The presence of a) depression and b) anxiety in SLE cohort/controls.

Evaluating the presence of anxiety, we found it present for 14 patients (63.63%) and for 5 of the controls (27.27%), $p<0.001$; depression was identified in 10 SLE patients (45.45%), significant different compared to controls

(p<0.001) (fig. 2 a, b). The mean HAM-D score was 8.13+3.35, most of the patients with a value associated to a mild depression; mean HAM-A score was 11.18+6.09, 8 patients with a mild level of anxiety and 5 with a moderate one (fig. 3 a, b).

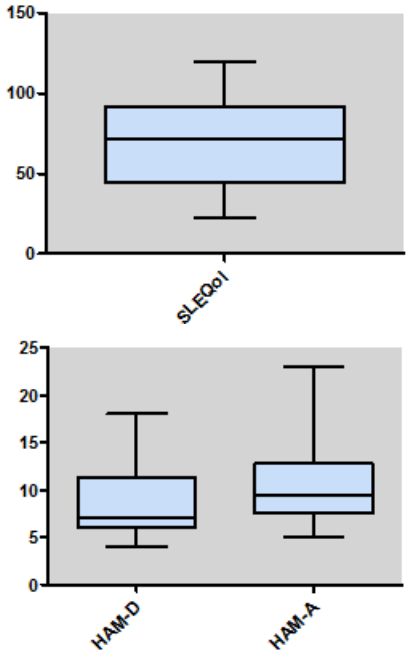

Fig. 3a. Mean HAM-A and HAM-D in SLE cohort; b) Mean SLEQol

Assessing quality of life, using SF 36 form, we obtained statistically significant differences between SLE patients and control group, mostly regarding physical functioning (60.21+12.31/ 77.21+13.02%; p=0.01), emotional well-being (67.41+26.71/83.80+12.21, p=0.002) and role limitations due to emotional problems (63.86+ 34.26/ 83.80+ 34.92%; p=0.002). The results are presented in table 2.

Using SLEQol, we obtained a mean score of 71.14+30.68, with limits between 50 and 200 (fig. 3b).

The presence of depression negatively correlated to SF-36 scores, regarding emotional well-being (r=-0.601, p=0.003), physical functioning (r=-0.497, p=0.018) and role limitation due to emotional problems (r=-0.412, p=0.015); similar observations were made for the presence of anxiety: r=-0.489, p=0.02 for physical functioning, r=-.0477, p=0.024 for emotional well-being and r=-0.644, p=0.001 for role limitation due to emotional problems. SLEQol scores moderately correlated both to the presence of anxiety and depression (r=-0.682; p<0.0001/r=-0.518; p=0.013).

We found a moderately positive correlation between SLEQol and HAM-D score (r=0.536; p=0.029), as for SLEQol and HAM-A (r=0.551, p=0.017); for cognitive dysfunction we established as well a moderately positive correlation (r=0.575, p=0.041) (table 3).

When evaluating the disease activity in relation to cognitive dysfunction, anxiety and depression, we found a positive correlation between SLEDAI, MocA, HAM-A and HAM-D (table 3).

SLE is the prototype of connective tissue diseases that can present the complete spectrum of neurologic and psychiatric alterations, cognitive dysfunction, depression and anxiety being more prevalent compared to general population, with an input on patients' prognosis and quality of life [1, 2, 16-19].

Our study found a prevalence of cognitive dysfunction of over 50%, most of the patients with a mild degree, frequently involving orientation and attention. The reported percentage varies between 15-80% in different studies, depends on the method of evaluation, heterogeneity of the patients and is more frequent compared to other autoimmune rheumatologic conditions. Several reports, that also used MoCA scale, reported increased percentages, as the report published by *Butt et al* [33] or *El-Shafei et al* [34]. Lower percentages, under 10, were published by other authors [35, 36]. A recent metanalysis, published in 2018, that included 78 reports and over 2400 patients, concluded that cognitive dysfunction prevalence was higher compared to healthy subjects or rheumatoid arthritis [37].

The observation of a positive correlation between disease activity and cognitive dysfunction found in our cohort, was also reported in the Lupus Outcomes Study [38], in the study published by *Conti et al* [39] or *Doman et al* [40], whereas other investigations didn't have similar results [41, 42].

Similar to *Calderon et al* in 2017 [18], our results showed an impact of cognitive dysfunction on our patients' quality of life; in a similar manner, a recent study that included 98 NPSLE patients concluded that quality of life is reduced both in physical and mental domains, especially due to emotional problems [17], as well as the results of *Hanly et al* [43].

Depression and anxiety are commonly diagnosed between SLE patients and the reported prevalence is variable between studies due to different methodology, screening tools and patient selection. Our cohort analysis showed the presence of depression and anxiety in a percentage significantly different compared to health individuals. Consistent to our data, a recent meta-analysis, concerning prevalence levels of depression and anxiety in adult SLE patients, published in 2017, that included 59 studies, reported a prevalence of depression between 2% and 91.7% and of anxiety between 4% and 84% [44], significantly higher compared to general population or other connective tissue diseases [45-51].

	SLE (mean SD	Controls	p
Physical functioning	60.21±12.31	77.21±13.02	0.01
General health	61.36± 16.77	56.94± 16.73	0.287
Energy/fatigue	83.18± 7.32	87.11±6.11	0.06
Pain	84.93± 7.95	87.44±8.07	0.342
Social functioning	84.93± 9.71	87.11±8.27	0.461
Role limitation due to physical health	76.26± 23.21	87.06±8.15	0.445
Role limitation due to emotional problems	63.86± 34.26	83.80± 34.92	0.002
Emotional well-being	67.41±26.71	83.80±12.21	0.002

Table 2
LIFE QUALITY ASSESSED BY SF-36 QUESTIONNAIRE IN SLE PATIENTS AND CONTROLS

	HAM-D		HAM-A		MoCA	
	r	p	r	p	r	p
SLEDAI	0.411	0.032	0.481	0.043	0.481	0.043
SLEQol	0.536	0.029	0.551	0.017	0.575	0.041

Table 3
CORRELATIONS BETWEEN DISEASE ACTIVITY, LIFE QUALITY AND DEPRESSION, ANXIETY AND COGNITIVE DYSFUNCTION SCALE

The relationship between disease activity, depression and anxiety constituted the aim of several studies, with inconsistent results; in our cohort, we noticed a moderately positive correlation between these variables, in consistency to those previously published by *Julian et al* [52], *Bachen et al.* [53] or by *Bai et al*, in 2016 [54].

Emotional disturbances are proven to negatively impact quality of life and are associated with long term progression of the disease and were extensively studied; a recent report that included a group of 113 SLE patients, concluded that patients with anxiety and/or depression reported lower SF-36 scores compared to that without psychological disorders [55]. In a similar manner, *Mok et al* concluded that depressive/anxiety symptoms were more common in SLE patents and associated with a low quality of life and work disability [56]. Lower scores on the SF-36 (for QOL) were found in both male and female SLE patients with depression and anxiety symptoms by *Macedo et al*, in a report published in 2016 [57]. It is noteworthy that, in agreement with these findings, we noticed that depression and anxiety are directly inter-related to life quality assessment scores.

Conclusions

These findings underline the necessity and benefit of a careful and periodical neuropsychiatric examination, in order to recognize the clinical patterns in early stages, apply the proper therapeutic measures, quantify the future damage and improve the outcome of these patients.

Despite the relatively low number of subjects included in the study, to the best of our knowledge is the first in our country that studies the prevalence of some of the most common neuropsychiatric manifestations in SLE patients and their possible inter-relation to disease activity and quality of life. Our results are in agreement with other recently published studies and suggest its extension, with multicenter contribution and larger SLE cohorts. Also, the future directions should establish a diagnostic algorithm, associated to immunologic and imagistic findings, in order to individualize each patient's monitoring and prevent future complications, along with improving their quality of life.

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