Association between fibromyalgia and psychiatric disorders in systemic lupus erythematosus

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ABSTRACT

Objectives. *Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect many organs, with musculoskeletal symptoms being the most common. Fibromyalgia (FM) is frequent in SLE patients. Psychiatric disorders such as anxiety and depression are also present in many SLE patients. The aim of our study is to determine the relationship between FM and psychiatric symptoms (PS), both anxious (AS) and depressive (DS), and its impact on health status in SLE patients.*

Methods. *In a total of 84 SLE patients we studied the presence of both FM and PS using specific questionnaires (Hamilton). We also evaluated health status and SLE disease activity by both the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and serological markers. Patients performed the Short Form 12 (SF-12) questionnaire as a quality of life measure. Qualitative variables were compared using Pearson's chi-square test and Fisher's exact test, and Student's t-test was used for quantitative variables. The Mann-Whitney U-test was applied if a normal distribution was not observed.*

Results. *Thirty patients were diagnosed with FM (35.7%), 16 had clinical signs DS (19%) and 30 had clinical signs AS (35.7%). We found a statistically significant association between FM and AS ($p<0.001$), and between FM and DS ($p<0.001$). Higher SF-12 physical component and mental component scores were observed in FM group compared to non-FM group ($p<0.001$). We have not found any associations between SLE activity and FM and PS.*

Conclusion. *There is a high prevalence of FM in SLE patients, and a strong association with DS and AS. FM contributes to worsening health status in SLE patients. SLE activity has little or no impact either on psychiatric symptoms or FM.*

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect many body tissues and organs, most commonly the skin, kidney and locomotor apparatus. It is characterised by flares that affect different parts of the body to varying degrees. Most patients present fatigue and musculoskeletal symptoms (1). It is often difficult to establish a direct relationship between symptoms and disease activity (2). SLE patients show a high prevalence of fibromyalgia (FM) though rates vary considerably from one study to another (13% (3), 22–45% (4), 8.2% (5)). The main clinical features of FM are generalised pain and pain hypersensitivity (American College of Rheumatology criteria). No significant differences have been reported between SLE patients with FM and those without this condition in terms of sociodemographic characteristics, previous or concomitant SLE treatment, or severity of SLE, although FM appears to be more common in Caucasian patients and in the lower social strata. In addition, prevalence of FM increases with the duration of SLE (3). Patients with SLE are more likely to develop psychiatric disorders than the general population, with reports showing an incidence of up to a quarter of patients (6, 7). Psychiatric disorders can also be observed in patients with isolated FM, and an incidence of depression of more than 70% has been described (8, 9). The prevalence of psychiatric disorders in SLE patients is remarkable, like in other chronic diseases such as rheumatoid arthritis and inflammatory bowel disease, which may have increased psychiatric disorders prevalence. Some studies have found depression in up to 44% of such SLE patients (10-12).

Our hypothesis is that psychiatric symptoms (PS) might predispose to FM in patients with SLE. We also con-

sider that the presence of PS and/or FM in patients with SLE could have a direct influence on quality of life, independently of the activity of the underlying disease. The study aimed to: 1) determine the prevalence of FM, anxiety symptoms (AS) and depression symptoms (DS) in a cohort of patients with SLE; 2) establish an association between these conditions; 3) establish their relationship with the activity of the disease; 4) determine the extent to which the presence of these disorders can affect quality of life.

Patients and methods

Study sample

The sample in this study consisted of 84 consecutive SLE patients (n=84) treated between May 2005 and May 2007 at the outpatient clinic of the Rheumatology Service at the Hospital Universitari del Mar-IMAS, Barcelona, Spain. This centre is a specialised tertiary care hospital with a catchment area of 250,000 inhabitants. The inclusion criteria were age over 18 and diagnosis of SLE according to the criteria established by the American College of Rheumatology (ACR) (13). Patients were excluded from the study if they had cognitive deterioration and/or neuropsychiatric symptoms of SLE that could affect the interpretation of the self-questionnaires, or if they could not complete the questionnaires due to visual impairment.

Evaluation of the presence of fibromyalgia (FM)

FM was evaluated (according to the ACR 1990 criteria (ACR'90)) in all patients by the same researcher (VT) by means of digital palpation at each of the tender point sites defined by ACR'90, using the thumb of the dominant hand and applying a pressure of 4~kg/cm^2, with the patient being asked to indicate whether any pain was felt (14). Patients were also required to have a six-month history of widespread musculoskeletal pain, with or without concurrent fatigue and sleep disorder (15).

Patients completed the Fibromyalgia Impact Questionnaire (FIQ) during the visit to determine the degree of severity of FM, obtaining a final score between 0 and 100 following adjustment by the required mathematical operations (16). According to Bennet, the condition is considered to be severe for scores over 70 (17).

Evaluation of psychiatric symptoms (PS)

Features of AS and DS were evaluated using the Spanish versions of the Hamilton Anxiety Scale and Hamilton Depression Scale, respectively (18, 19). The two scales consist of a series of questions designed to measure the severity of symptoms (Anxiety: 14 items (score: 0 to 4); Depression: 17 items (score: 0 to 2 or 4)). A patient's condition is considered pathological or indicative of pathological features for total scores of >14. The anxiety and depression tests were performed by the same researcher at each visit (VT).

Evaluation of the clinical activity of SLE

SLE activity was measured according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (20), which identifies 24 potentially reversible organ dysfunctions divided into 9 groups (central nervous system, vascular system, renal system, musculoskeletal system, serosa, skin, immune system, haematological system, and constitutional symptoms) over the last ten days. The final score ranges from 0 to a maximum of 105, and disease activity is considered to be relevant for all final scores equal to or greater than 5 (SLEDAI ≥5: clinical activity; SLEDAI <5: no clinical activity). The SLEDAI was performed by same researcher (VT) at each visit. The alteration of several biological parameters considered to be indicators of SLE activity according to values established by the reference laboratory at the study hospital was also evaluated: erythrocyte sedimentation rate (ESR) (>20mm/h), C-reactive protein (CRP) (>0.8mg/dL), anti-dsDNA antibodies positivity (anti-dsDNA-Abs) (>40UI/ml), complement C3 (C3) (<90mg/dl), complement C4 (C4) (<10 mg/dL), complement CH50 (CH50) (<35UI/ml), anticardiolipin antibodies (aCL) positivity (-IgG >15GPL, IgM >11MPL), lupus anticoagulant (LA) positivity (positive/negative) (21).

Evaluation of health status/quality of life and functional disability

Health status was determined from the Short Form-12 (SF-12) quality-of-life questionnaire, a shortened version of the Short Form-36, which is a widely accepted diagnostic tool for evaluating the state of health in patients with SLE (22, 23). SF-12 is a self-evaluation test with 12 questions designed to evaluate a patient's physical and mental well-being. Statistical analysis in this case required a Spanish control population and the statistical method used had been validated for the Spanish population (24, 25).

Health status was also determined by completing the Stanford Health Assessment Questionnaire (HAQ) (26), a self-report that measures the difficulty faced by patients in carrying out everyday tasks in 8 different areas (dressing, rising, eating, walking, hygiene, reach, grip, and common activities). The final score ranged from 0 to 3. The HAQ was originally created to evaluate patients with rheumatoid arthritis, but it has also been used in studies of patients with SLE showing good reproducibility and validity and a good correlation with psychosocial factors (27). For the purpose of the present study the Spanish modified version was used (mHAQ).

Statistical analysis

Results for the qualitative variables are expressed as percentages and absolute frequencies and results for the quantitative variables as means and standard deviations or as medians and quartiles 1-3 if a normal distribution was not observed. Comparison of qualitative variables was performed using Pearson's chi-square test and Fisher's exact test when appropriate. The Student's *t*-test was used for quantitative variables and the Mann-Whitney U-test was applied if a normal distribution was not observed. The significance level was $\alpha \leq 0.05$. Data were analysed using the SPSS package for Windows (version 12.0).

Results

The 84 patients evaluated (81/95.2%

women; 85.7% Caucasian, 8.3% South-American, 3.6% East Asian, 1.2% West Asian) had an average age of 43.2 (16.6 SD) years and average disease duration of 6.9 years (2-11). A total of 30 patients showed clinical features of FM (35.7%), 16 patients showed signs of DS (19%), and 30 patients showed signs of AS (35.7%). No association was found between the presence of these three conditions and disease duration. No differences were observed between groups with respect to gender, age or race or with respect to the presence of FM, AS or DS.

In the assessment of clinical activity coinciding with the evaluation of FM and PS, 2 patients had a SLEDAI score of >5(2.4%). A total of 27 patients had raised ESR (32.1%); 10 had raised CRP (11.9%); 48 had anti-dsDNA-Abs (57.1%); 13 had decreased C3 (15.5%); 12 had decreased C4 (14.3%); and 8 had decreased CH50 (9.5%). A total of 10 patients showed positive ACA (13.3%) and 12 had a positive ACL (18.05%). No significant association was found between these variables and the presence of FM, AS and/or DS.

A total of 30/84 patients presented clinical symptoms of FM at some point during follow-up, and 33.3% of these patients showed a high FIQ score. An association analysis was conducted between SLE patients with FM and those without FM. Results showed a statistically significant association between FM and AS ($p<0.001$), and between FM and DS ($p<0.001$). Higher scores were observed for the SF-12 physical component and mental component in the FM group than in the non-FM group ($p<0.001$, in both) (Table I). We did not find any differences in mHAQ impairment between the groups.

Table I. Variation in SF-12 scores in the presence/absence of FM (n=84).

	Presence (n=30)	Absence (n=54)	*p*-value
Age*	44.86 (18.35)	42.42 (15.81)	NS
Mental SF-12*	37.06 (11.93)	46.22 (12.61)	<0.001
Physical SF-12*	32.87 (9.66)	44.68 (10.7)	<0.001

*Mean (SD) values are shown.

Discussion

The prevalence of FM in the SLE patients included in this study was equal to or slightly higher than that found in other studies. FM presence was not associated with higher SLE activity. Several authors have shown that FM is not directly linked to increased lupus activity (3, 4, 5, 11). We can therefore deduce that these entities are clearly differentiated in each case (2). Nevertheless, since there is a higher prevalence of FM in SLE patients than in the general population, some doubt is cast on this hypothesis. The results of this study would appear to confirm the lack of correlation between FM and lupus activity. The high prevalence of FM in some autoimmune inflammatory diseases may be due to the existence of a common genetic substrate, although this has yet to be demonstrated. Psychological stress caused by chronic disease could also be an influential factor in the generalisation of pain and the development of FM. SLE clinical approach is difficult in those patients with widespread pain, since its presence may induce medication changes. The knowledge of the coexistence of both FM and SLE, and the strong need to know where symptoms come from should help with its specific treatment. The last allows a correct assignation of symptoms to each entity in order to treat them with a proper counseling and treatment.

We found a significant association between SLE patients with FM and PS. However, PS was not associated with increased lupus activity, suggesting that such symptoms are not the result of neuropsychiatric damage caused by SLE. It has been reported that a high proportion of African Americans with severe or highly active SLE present a lower prevalence of FM than other ethnic groups, corroborating the assertion that FM is not associated with lupus activity (3). As our results show an association between FM and PS even when SLE activity is not increased, it cannot be concluded that SLE directly leads to these symptoms. Nevertheless, the fact that SLE patients have a higher prevalence of psychiatric disorders than the general population suggests they are more susceptible to such disorders (6). We consider that FM is perhaps promoted by PS and should therefore be treated independently from SLE. The psychiatric disorder should perhaps also be approached as a separate entity. Without these considerations, the SLEDAI performance may contribute to a medication modification with catastrophic consequences for the patient. In presence of PS, widespread pain and low SLEDAI scores we should assess the presence of joint hypersensibility. We also should assess the presence of anxiety and depressive symptoms.

Different theories suggest that FM and psychiatric disorders in SLE have an autoimmune pathophysiology mediated by antibodies. In the case of FM, some studies have reported the presence of anti-GAD (Glutamic Acid Decarboxylase) antibodies in patients with SLE. This enzyme is involved in the production of neurotransmitters that inhibit gamma-aminobutyric acid (GABA) present in the dorsal and ventral horns of the spinal cord. Such inhibition contributes to the appearance of neuropathic pain (28).

Similarly, following inoculation of anti-ribosomal P antibody in a murine lupus model has been shown to have a strong correlation with psychosis and depression due to SLE (29), which recede upon administration of antidepressants such as fluoxetine (30). The presence of this antibody has been linked to SLE hepatitis and nephritis (31, 32) supporting the theory that anti-ribosomal P antibody is associated with systemic lupus activity. Similarly, the neuropsychiatric manifestations of SLE, which include anxiety and depression, have been associated with the coexistence of several antibodies: anti-dsDNA-Abs, anti-NMDA (N-Methyl-D-Aspartate), anti-endothelial cell antibodies (AECA), and even the presence of aCL (7, 33). In the present study, no association was observed with either anti-dsDNA-Abs

or ACA, indicating that the presence of PS is not directly related to the presence or activity of SLE. This suggests that SLE was not the cause of PS in the sample population considered and that patients should not be treated exclusively for SLE. FM presence should be treated, according to EULAR recommendations, through the use of drugs, psycotherapy, exercise, and proper patient information. The use of drugs such as noradrenaline and serotonine inhibitors may have a positive effect either in psychiatric symptoms and widespread pain symptoms.

A significant association has been reported between FM and unemployment, use of social services, low work performance, low educational level, self-reported depression, traumatic experiences and situations causing increased psychological stress such as divorce or hysterectomy (34, 35). The incidence in Caucasian subjects is also reportedly higher than in other ethnic groups (4). Taking the results of our study into account, we believe that the level of anxiety and/or depression should also be considered a contributory or predisposing factor in the appearance of FM in SLE patients. This association has previously been suggested by other research groups, but in these cases no specific psychiatric assessment was reported (3). The presence of FM has a significant negative impact on the perceived state of physical and mental health of SLE patients, dramatically reducing their quality of life despite the absence of SLE activity. It is therefore essential to consider the presence or absence of FM, to adopt the correct strategies for its evaluation, and to use the appropriate tools to improve the situation of affected patients and enhance other areas of their lives such as work performance, social relations and sleep quality (36). The SF-12 questionnaire is a vital tool for evaluating patients with inactive SLE, determining their quality of life, and identifying a subgroup of patients susceptible to FM, AS and DS. Abu-Shakra *et al*. showedthat SLE might reduce quality of life *per se* (37). If this is considered alongside the loss of quality of life associated with the presence of FM, as identified in the present study, perceived quality of life is significantly reduced and measures are needed to improve wellbeing.

The results described provide a general overview of a broad sample of SLE patients and identify a high prevalence of FM, its strong association with the presence of PS, and the absence of a correlation with the clinical activity of the underlying disease. The limitations of our cross-sectional study cannot establish a direct causation between the presence of PS and FM in SLE patients. We consider that specific psychiatric evaluation is mandatory in SLE patients. Knowledge of these conditions, both FM and PS, facilitates better understanding of important clinical features of SLE patients with impaired health status and quality of life.

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