ABSTRACT

Fatigue and generalised pain are debilitating symptoms that negatively impact the quality of life in patients with systemic lupus erythematosus (SLE) and primary Sjögren’s syndrome (pSS). Chronic widespread musculoskeletal pain and fatigue are the clinical hallmarks of fibromyalgia (FM), a clinical entity which can be associated to connective tissue disease. The aim of the present study was to assess the prevalence of FM syndrome, fatigue and widespread pain in SLE and pSS patients and to evaluate the contribution of inflammatory disease and FM on those constitutional symptoms. Fifty SLE and 50 pSS patients were enrolled in the study. Patients rated fatigue, pain, and disease activity using a 100-mm visual analogue scale and completed the Health Assessment Questionnaire and the Fibromyalgia Impact Questionnaire. Zung depression and anxiety scales were used to quantify mood disorders. Tender points were evaluated using an algometer. Disease activity score was evaluated for each SLE and pSS patient. Fibromyalgia has been diagnosed in a significantly higher percentage of SLE patients than pSS patients (32% vs. 18%, p=0.022) even if the percentage of patients reporting fatigue and pain was higher among pSS patients. No correlation with disease activity was observed in either group of patients. FM seems to contribute to constitutional symptoms more in SLE than in pSS, suggesting a different underlying cause of fatigue and widespread pain in these two different connective tissue diseases.

Introduction

Fatigue and generalised pain are debilitating symptoms that negatively impact the quality of life in patients with connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE) and primary Sjögren’s syndrome (pSS). Fatigue is a state of awareness describing a range of afflictions, usually associated with physical and/or mental weakness; central fatigue is defined as a difficulty initiating and sustaining voluntary activities and represents a failure to complete physical and mental tasks (1, 2). Fatigue represents one of the most frequent symptoms in general population reported by more than a half of healthy subject (3).

Chronic widespread pain is very prevalent in general population (5–10%) and is characterised by pain in all four body quadrants, the neck and the back; chronic widespread musculoskeletal pain and fatigue are also the clinical hallmarks of fibromyalgia (FM), a disorder frequently associated to autoimmune diseases (4).

Fatigue is reported by 68-85% patients with pSS (5-9) and by up to 90% of SLE patients, 50% of whom consider it the most disabling of symptoms (10). In CTDs, physical and mental fatigue can be related to a multifactorial aetiology including comorbidities, such as mood and sleep disorders, behavioural factors (i.e. physical exercise) and disease- or drug-related factors (11). In a previous study on pSS patients, our group demonstrated no relationship between fatigue and disease activity (9). On the contrary, the contribution of SLE disease activity on fatigue has been widely investigated with conflicting results (12-19). As for widespread pain, it is reported by 72% of pSS patients (20) and 65% of SLE patients (21).

Among different possible factors, the association with FM must be considered, even if some physician consider that CTD and FM are mutually exclusive (22).
The pathogenesis of FM is complex and not completely understood; fibromyalgia syndrome is characterised by widespread pain, post-exertional fatigue not resolved by rest, sleep disturbances, and affective and neurocognitive disorders, which can coexist with a plethora of other symptoms, particularly of a neurovegetative origin such as highlighted in new ACR criteria (23, 24). The prevalence of FM is estimated at 2% of the general population, with the disorder being two times more prevalent among women than men (25). Less is known about the prevalence of FM in CTD.

The prevalence of FM in SLE ranges from 10 to 47% (22) and in pSS from 12 to 55% (6, 26, 27).

Taking into account that fatigue and widespread pain are common in SLE and pSS patients and that these symptoms often represent a matter for the differential diagnosis with concomitant FM, the aim of the present study was to assess the prevalence of fatigue and widespread pain reported by SLE and pSS patients referred to our Rheumatology outpatient clinic. Furthermore, we have correlated fatigue and widespread pain with age, disease duration, disease activity and damage indices, anxiety and depression to attribute the symptoms to the underlying CTD or to an overlapping FM.

Patients and methods

The study population included 50 patients with SLE diagnosed according to the 1997 American College of Rheumatology criteria (28) and 50 consecutive patients with pSS diagnosed according to the Euro-American criteria (29). SLE patients were excluded if they have concomitant SS. All the patients were female who attended the Rheumatology Unit of our Department.

After informed written consent was obtained, all patients underwent a complete clinical examination; a detailed medical history including present organ involvement and current medication was recorded.

Patients were asked if they had been feeling fatigued or unduly tired on most days for the last 3 months; they were also asked if they had been suffering with generalised body pain in the same period.

For SLE patients the Disease Activity Index (SLEDAI) (30) and Disease Damage Index (SLICC) (31) were calculated, for pSS patients Disease Damage Index (SSDDI) and Activity Index (SSDAI) (32).

Patients rated fatigue, pain, and disease activity using a 100-mm visual analogue scale (VAS) and completed the HAQ and the validated Italian version of the Fibromyalgia Impact Questionnaire (FIQ). Furthermore, the Zung depression and anxiety scales (ZSDS, ZSAS) were used to quantify aspects of mood disorders. Pressure pain threshold was determined at the 18 ACR (33) tender points (TP) using an algometer. A patient was deemed to have FM when fulfilling the 1990 ACR classification criteria for the disease.

Statistical analysis

Differences between groups were analysed using Fisher’s exact test and Mann-Whitney U-test. The Spearman test was used for correlation analysis. A p-value <0.05 was considered statistically significant.

Results

We enrolled 50 SLE and 50 pSS consecutive patients. Table I shows demographic and clinical data of both groups of patients.

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Fatigue was reported by 40/50 (80%) SLE and by 44/50 (88%) pSS patients (p=n.s.) while pain was reported by 40/50 (80%) and 45/50 (90%) of SLE and pSS respectively (p=n.s.). FM has been diagnosed in a significantly higher percentage of SLE patients (16/50, 33%) than pSS patients (9/50, 18%) (p=0.022). Mean number of positive TP was 7.5±6.1 in SLE and 5.7±4.7 in pSS patients (p=n.s.); a significant difference in TP number between SLE and pSS patients with FM was observed (15.1±2.27 vs. 12.88±1.96; p=0.02).

Table II shows the results of fatigue and pain VAS and questionnaire in SLE and pSS patients stratified for concomitant FM diagnosis.

In SLE patients, we observed a correlation between fatigue VAS and pain VAS (r=0.000, r=0.57) and both fatigue and pain VAS with number of TP (r=0.014, r=0.34 and p=0.013, r=0.35, respectively), FIQ (r=0.000, r=0.68 and p=0.000, r=0.62, respectively) and HAQ (r=0.000, r=0.55 and p=0.000, r=0.53, respectively).

A higher score in ZSDS and ZSAS correlated with fatigue VAS (r=0.000 for both with r=0.55 and r=0.53, respectively) and with pain VAS (r=0.003, r=0.41 and p=0.008, r=0.37). Moreover, the number of TPs correlated with ZSDS, ZSAS, HAQ and FIQ (r=0.000 for all, r=0.61, r=0.61, r=0.52 and 0.55, respectively). Finally, we observed a negative correlation between the number of TP and SLEDAI score (p=0.03, r=0.29) and no correlation with the SLICC score.

In the pSS group we observed a correlation between fatigue VAS and pain VAS (r=0.000, r=0.57) and both fatigue and pain VAS with number of TP (r=0.014, r=0.34 and p=0.013, r=0.35, respectively), FIQ (r=0.000, r=0.68 and p=0.000, r=0.62, respectively) and HAQ (r=0.000, r=0.55 and p=0.000, r=0.53, respectively).

A higher score in ZSDS and ZSAS correlated with fatigue VAS (r=0.000 for both with r=0.55 and r=0.53, respectively) and with pain VAS (r=0.003, r=0.41 and p=0.008, r=0.37). Moreover, the number of TPs correlated with ZSDS, ZSAS, HAQ and FIQ (r=0.000 for all, r=0.61, r=0.61, r=0.52 and 0.55, respectively). Finally, we observed a negative correlation between the number of TP and SLEDAI score (p=0.03, r=0.29) and no correlation with the SLICC score.

In the pSS group we observed a correlation between fatigue VAS and pain VAS (r=0.000, r=0.67 and r=0.59, respectively). Patients who reported fatigue (fatigue VAS >0) presented higher score in ZSDS and ZSAS (p=0.000 for both; r=0.55 and r=0.48, respectively); even patients who reported pain (pain VAS >0) presented higher score in both ZSDS and ZSAS (p=0.008, r=0.37 and p=0.001, r=0.46, respectively). Moreover, ZSDS and ZSAS correlated significantly with

### Table I. Demographic and clinical data of SLE and pSS patients.

<table>
<thead>
<tr>
<th></th>
<th>SLE (n=50)</th>
<th>pSS (n=50)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>44.16 ± 13.67</td>
<td>54.14 ± 14.06</td>
<td>0.0005</td>
</tr>
<tr>
<td>Disease duration (years, mean ± SD)</td>
<td>13.54 ± 9.56</td>
<td>8.74 ± 7.88</td>
<td>0.0046</td>
</tr>
<tr>
<td>Number of TP (mean ± SD)</td>
<td>7.59 ± 6.18</td>
<td>5.72 ± 4.71</td>
<td>ns</td>
</tr>
<tr>
<td>Fatigue VAS (mm, mean ± SD)</td>
<td>46.45 ± 34.82</td>
<td>57.20 ± 37.67</td>
<td>ns</td>
</tr>
<tr>
<td>Pain VAS (mm, mean ± SD)</td>
<td>38.37 ± 31.97</td>
<td>46.10 ± 33.44</td>
<td>ns</td>
</tr>
<tr>
<td>FQI (mean ± SD)</td>
<td>43.61 ± 25.28</td>
<td>49.28 ± 24.57</td>
<td>0.0386</td>
</tr>
<tr>
<td>HAQ (mean ± SD)</td>
<td>0.54 ± 0.59</td>
<td>0.48 ± 0.57</td>
<td>ns</td>
</tr>
<tr>
<td>ZSAS (mean ± SD)</td>
<td>48.24 ± 17.20</td>
<td>49.46 ± 13.63</td>
<td>ns</td>
</tr>
<tr>
<td>ZSAS (mean ± SD)</td>
<td>50.04 ± 13.48</td>
<td>48.86 ± 11.16</td>
<td>ns</td>
</tr>
</tbody>
</table>

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incidence of FM in their SLE and pSS patients (34).

The results of our observation suggest that fatigue reported by pSS patients is mostly related to the disease itself, even if no significant correlation between fatigue and disease activity has been observed; in fact, in pSS patients, FM has been diagnosed in only 18% of subjects. As reported in previous studies evaluating the impact of SS on fatigue, in our pSS patients a strong association with depression (35, 36) and a lack of correlation with disease activity has emerged (9).

In the last 20 years, many studies have investigated the extent of fatigue in SLE patients trying to attribute the symptom to disease itself, comorbidities or mood disorders. Among our SLE patients we observed the higher prevalence of FM described to date; in fact, while fatigue is reported by up to 90% of SLE patients the association with FM ranges between 5.0 and 22.1% of patients (21, 37-42). Up to one third of our SLE patients were diagnosed as having a concomitant FM, which was related to a significantly higher score in fatigue and pain VAS. Thus, in this group of subjects, we suppose that fibromyalgia features account for fatigue more than inflammatory disease.

In our study, most other authors failed to demonstrate a correlation between fatigue and disease activity even in SLE patients; only few studies have observed a higher disease activity among patients reporting fatigue (11, 17, 18). Actually, in our SLE patients the number of positive tender points and disease activity score were inversely correlated. Diffuse musculoskeletal pain occurs in a significant number of rheumatic patients and it is described in high percentage of SLE and pSS patients (21, 43). As for pain VAS, we have observed a significant correlation with fatigue, depression and anxiety in both groups of patients; moreover, in SLE a correlation with FIQ and number of tender points was observed, while in pSS patients with FIQ only. However, it should be considered that besides FM symptoms, some items of the FM questionnaire could be influenced by additional CTD features, mainly musculoskeletal, and it seems to be unable to discriminate between widespread pain and inflammatory pain.

On the other hand, pain might affect the report of other symptoms and signs and the self-reported outcome measure (44). As a matter of fact, we have observed a correlation between HAQ and fatigue and pain VAS but not with disease activity indices in either SLE or pSS patients.

Studies involving the completion of validated questionnaires and VAS consistently showed a high prevalence of fatigue in patients with rheumatic diseases (45). A limit of our study could be represented by the use of a single method to determine the degree of fatigue in the two patient’s cohorts. In fact, we used only a 100-mm VAS for fatigue and pain detection, where the patient feels range across a continuum from 0, which means absence of symptom, to 100 which represents extreme amount of that symptom; on the contrary, many previous studies on this topic utilised specific questionnaire (11, 15, 17, 19, 34-36, 46). One of the main issues with fatigue is its measurement. In fact, some instruments only measure physical fatigue (i.e. limitation on daily living activities), while others also consider mental fatigue and its associated distress. The VAS is one of the simplest

| Table II. Comparison between SLE and pSS patients with and without FM. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | SLE (n=34)      | SLE+FM (n=16)   | p               | SS (n=41)       | SS+FM (n=9)     | p               |
| TP number (mean ± SD) | 3.93 ± 3.57    | 15.12 ± 2.27   | 0.0001          | 4.14 ± 3.51    | 12.88 ± 1.96   | <0.0001         |
| Fatigue VAS (mean ± SD) | 38.67 ± 32.97  | 62.5 ± 33.96   | 0.01            | 54.76 ± 38.4  | 68.33 ± 33.91  | ns              |
| Pain VAS (mean ± SD)   | 32.52 ± 31.04  | 52.5 ± 30.0    | 0.02            | 44.15 ± 33.87  | 55 ± 31.72     | ns              |
| FIQ (mean ± SD)       | 33.41 ± 19.75  | 64.66 ± 22.61  | <0.0001         | 41.02 ± 24.12  | 51.93 ± 26.05  | ns              |
| HAQ (mean ± SD)       | 0.38 ± 0.43    | 0.89 ± 0.75    | 0.0092          | 0.44 ± 0.52    | 0.63 ± 0.76    | ns              |
| ZSDS (mean ± SD)      | 41.93 ± 13.47  | 61.25 ± 17.08  | 0.0002          | 48.8 ± 13.16   | 52.4 ± 16.11   | ns              |
| ZSAS (mean ± SD)      | 44.84 ± 9.66   | 60.75 ± 14.18  | 0.0001          | 47.63 ± 10.54  | 54.44 ± 12.85  | ns              |

Discussion
In chronic systemic disease, as in the general population, fatigue is widely recognised as a symptom of multifactorial origin. In our study we have detected a significantly higher prevalence of FM among SLE patients than among pSS patients; this result seems to suggest diverse underlying causes of fatigue and widespread pain in the two systemic inflammatory diseases. Unexpectedly, regardless of FM diagnosis, number of TP did not significantly differ among SLE and pSS patients but the number of TP was significantly higher in SLE patients with secondary FM than in pSS with FM; however, only in SLE patients we have observed a correlation between tender points and all the clinimetric parameters and questionnaires administered.

In 2000, Giles and Isenberg firstly compared the prevalence of fatigue in primary SS and SS associated to SLE and observed a significantly higher percentage of patients both reporting fatigue and with a diagnosis of FM among pSS; in our study, we have excluded a priori patients with SLE and concomitant SS. Similarly to Giles and Isenberg, Ostuni et al. found a higher prevalence of FM among pSS patients (22%) compared to SLE and scleroderma patients (1% and 2%, respectively).

More recently, Bowman et al. compared different instruments for measuring fatigue in CTD and detected similar disease duration (p=0.03, r=0.3 and p=0.015, r=0.34, respectively) and with HAQ (p=0.001, r=0.4 for both). Fatigue and pain VAS were significantly correlated with FIQ score (p=0.037 r=0.29 and p=0.043, r=0.28, respectively). Finally, no correlation with activity and chronicity indices were observed.

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and most popular methods for measuring fatigue severity, even if it does not describe in detail the dimension of experienced fatigue (e.g. physical, mental, motivational and affective) (47). However, VAS has been largely used in other inflammatory autoimmune disorders and it seems to perform better for the assessment of physical rather than mental fatigue. Thus, extent of fatigue and its impact on quality of life mostly depends on the instrument used to evaluate the symptom. None of the available clinical assessment methods can produce a clear picture of fatigue (45).

In conclusion, among the studies designed to compare fibromyalgia symptoms in CTD, the present one is the first to demonstrate a higher prevalence of FM in SLE than in pSS. FM seems to contribute to constitutional symptoms more in SLE than in pSS suggesting a different underlying cause of fatigue and widespread pain in these two different connective tissue diseases.

Acknowledgement
We thank Jessica Brandt for revising the manuscript.

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