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Lupus patients with fatigue—is there a link with fibromyalgia syndrome?

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Abstract

Objective. To determine whether fibromyalgia syndrome (FMS) was more common in patients with lupus who were complaining of fatigue.

Methods. We interviewed 216 patients attending two lupus clinics, all of whom fulfilled the revised American College of Rheumatology (ACR) criteria for lupus. The patients completed a questionnaire and were examined to determine the presence of fatigue and whether they fulfilled the ACR criteria for FMS. Disease activity was measured using the British Isles Lupus Assessment Group (BILAG) index and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage score. Measurements of erythrocyte sedimentation rate, complement C3, lymphocyte count and DNA titre were also performed.

Results. Fifty per cent of our patients complained of fatigue, but only 10% of these patients fulfilled criteria for FMS. FMS did not correlate with any measure of disease activity although patients with FMS had lower mean DNA antibody titres and mean SLICC/ACR damage scores.

Conclusion. A minority of lupus patients with fatigue fulfil the ACR criteria for FMS. Other possible factors leading to fatigue should be considered.

KEY WORDS: Systemic lupus erythematosus, Fatigue, Fibromyalgia syndrome.

Non-specific pain syndromes, under a variety of names, have been recognized as a source of considerable musculoskeletal morbidity for well over a century [1]. It is only since the more recent work of Smythe and Moldofsky in 1977 [2] that fibromyalgia syndrome (FMS) has become a more clinically distinct entity. FMS is defined as primary when there are no other coexisting diseases and secondary-concomitant when it coexists with another disorder, e.g. systemic lupus erythematosus (SLE). The main features of FMS are fatigue, non-restorative sleep, generalized pain and the presence of multiple tender points on examination. Only the last two requirements are necessary to make a diagnosis of FMS using the American College of Rheumatology (ACR) diagnostic criteria for FMS [3].

Fatigue is not a specific feature of FMS, but is present in a variety of rheumatic syndromes [4] including 40–50% of patients with SLE among whom it is often unresponsive to drug therapy. The prevalence of FMS in patients with SLE has been reported at 20–30% [5–8]. These figures, based on our clinical impression, seem rather high.

We therefore set out to determine whether FMS was more common in patients with SLE who were complaining of fatigue and to ascertain whether there were any links to SLE disease activity or damage.

Patients and methods

We interviewed 216 consecutively attending patients at two SLE clinics in the UK, one in London (Bloomsbury Rheumatology Unit) and one in Birmingham (University of Birmingham). All the patients fulfilled four or more of the revised ACR criteria for the classification of SLE. At the Bloomsbury Rheumatology Unit, 117 patients were interviewed. The median age was 39 yr (interquartile range 32–49), 112 were female and 84 (71%) were Caucasian, 13 (11%) Afro-Caribbean, 13 (11%) Asian, two (2%) Oriental and five (5%) from other racial groups. At the University of Birmingham, 99 patients were interviewed. The median age was 38 yr (interquartile range 30–50.5), 95 were female and 71 (72%) were Caucasian, 11 (11%) Afro-Caribbean, 16 (16%) Asian and one (1%) from other racial groups. Data for each patient were collected prospectively using a pro-forma questionnaire. The patients completed a

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questionnaire to determine the presence of fatigue ('Have you experienced excessive fatigue daily for the last 3 months?' Yes/No) and persistent pain ('Have you experienced pain in any body part(s) daily for the last 3 months?' Yes/No). The areas of pain were defined by the patients on a body chart. The definition of generalized pain was in accordance with the ACR diagnostic criteria for FMS. Patients were subsequently examined to determine the number of tender points and to exclude alternative diagnoses for the cause of pain. All personnel involved in patient examinations were experienced rheumatology practitioners. A point was considered tender if there was a spontaneous verbal affirmation of pain, or a physical wince/evasion manoeuvre, from the patient, in response to firm pressure. The ACR-defined trigger point sites were used for our assessment. Our patients were then divided into those complaining of fatigue and those who were not. From the information obtained we determined the number of patients in each group who fulfilled the ACR criteria for FMS.

We also determined disease activity using the British Isles Lupus Assessment Group (BILAG) index [9]. The index assesses disease activity in patients with SLE on the basis of the physician intention to treat principle, in each of eight organ or system domains. The score for each of the eight domains can vary from an 'A' grade implying severe activity requiring major immunosuppressive therapy to an 'E' grade meaning there has never been any evidence of activity for that domain. The BILAG index, although not designed to be a global score, can be converted into one by ascribing A = 9, B = 3, C = 1, D/E = 0 for each of the eight domains and then totalling the score [10]. In addition we assessed the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage score [11] for each patient. Both the BILAG and SLICC/ACR instruments are used routinely in our specialist SLE clinics and all personnel involved in the care of our patients receive full training in their use. Measurements of erythrocyte sedimentation rate (ESR; Westergen method), complement C3 (by laser nephelometer; normal 0.75–1.75 g/l), lymphocyte count and DNA antibody titre (Shield Diagnostics, Dundee, UK; normal <50 units, used in the Bloomsbury Rheumatology Unit; and The Binding Site, Birmingham, UK; normal <75 units, used in the University of Birmingham) were also performed.

Statistics

Non-parametric testing by Mann–Whitney's *U*-test for independent samples was used to compare differences between groups (Tables 1–3). Fisher's exact test (Table 4a) and χ^2-test (Table 4b) were used for discrete variables. A χ^2-test for trend was also performed on the data in Table 4b. *P* values (two-tailed) <0.05 were considered significant.

Results

There was no significant difference in age or racial composition in the populations studied at each centre.

TABLE 1. Disease-related measures (shown as median with interquartile range) and reported fatigue and fibromyalgia from each centre

	Bloomsbury	Birmingham
n	117	99
Global BILAG	4.0 (2–6)	4.0 (2.5–6)
DNA titre units/l	32 (10–76)	24 (0–81)
C3 g/l	0.90 (0.71–1.07)	0.89 (0.77–0.99)
ESR mm/h	25 (15–49)	25 (15–51)
Lymphocytes $\times 10^6$	1.30 (0.90–1.80)	1.00 (0.70–1.40)
SLICC/ACR	1.0 (0–2.0)	1.0 (0–2.0)
No. with fatigue (%)	54 (46)	54 (55)
No. with FMS (%)	8 (7)	3 (3)

As shown in Table 1 there was no difference in clinical parameters, reported fatigue and fibromyalgia between the groups of patients studied in London and Birmingham. Therefore subsequent analysis refers to pooled data from both groups.

Fifty per cent of patients had fatigue, but only 11 of 216 patients, 5% in total, met the criteria for FMS (Table 2). There was a trend for FMS patients to be female (11 of 11 patients) and Caucasian (10 of 11 patients), which was not significant due to the small overall number of patients with FMS.

Fatigue was associated with disease activity, as measured by the global BILAG score, but was associated with higher levels of complement C3 (Table 3). There was no association demonstrated between fatigue and ESR, DNA antibody titre, lymphocyte count or SLICC/ACR damage index. The clinical diagnosis of FMS was not associated with any of the above measures, although there was a trend for lower mean DNA levels (93.0 *vs* 43.0 IU/ml in Bloomsbury and 78.9 *vs* 31.0 IU/ml in Birmingham) and a lower mean SLICC/ACR damage index (1.39 *vs* 0.67) in patients with FMS.

Fatigue was associated with current disease activity in the domains for mucocutaneous ($P = 0.02$) and haematological ($P = 0.02$) manifestations of SLE as measured by the BILAG disease activity index. The presence of FMS was not associated with disease activity in any of the eight domains measured by the BILAG index.

Only 11 of 108 patients with fatigue met criteria for FMS (Table 4). Patients with fatigue were found to have more tender points than those patients without fatigue and all patients with more than 11 tender points had FMS. In the absence of fatigue no patients had FMS.

Discussion

Previous reports of FMS in lupus suggest a prevalence rate of up to 30% when the ACR criteria for FMS are used [5–8]. The prevalence of FMS in our patients was 5% (Bloomsbury 7% and Birmingham 3%) which is considerably lower than the figures reported from North America and no different from reported estimates of prevalence of FMS for patients attending general rheumatology clinics [12–15]. As the rates of FMS are similar in the general population of the UK and the

TABLE 2. Demographic data by age [median (interquartile range) in yr], sex and ethnic group (number and percentage in parentheses) for each clinical group

	All	No fatigue	Fatigue	No FMS	FMS
n	216	108	108	205	11
Age	38 (30–50)	37 (30–44)	42 (32–52.3)	38 (30.8–50)	40 (29.5–51)
Sex	9M:207F	5M:103F	4M:104F	9M:196F	0M:11F
Caucasian	153 (71%)	67 (64%)	86 (78%)	143 (70%)	10 (91%)
Afro-Caribbean	24 (11%)	15 (14%)	9 (9%)	24 (12%)	0
Asian	31 (14%)	21 (17%)	10 (10%)	30 (14%)	1 (9%)
Oriental	2 (1%)	2 (2%)	0	2 (1%)	0
Mixed race	4 (2%)	1 (1%)	3 (3%)	4 (2%)	0
Others	2 (1%)	2 (2%)	0	2 (1%)	0

TABLE 3. Measures of disease activity and accumulated damage scores for each group, median and interquartile range (*$P < 0.05$)

	All	No fatigue	Fatigue	No FMS	FMS
Global BILAG score	4.0 (2–6)	4.0 (1–5)	4.0* (3–6)	4.0 (2–6)	5.0 (2–8)
ESR (mm/h)	25.0 (15–50)	27.0 (15–50)	22.5 (14–49)	24.5 (14–49)	28.0 (19–54)
DNA (Bloomsbury) (units/l)	32 (10–76)	36 (10–91)	21 (10–69)	32 (10–86)	28 (13.5–52)
DNA (Birmingham) (units/l)	24 (0–81)	29 (0–103)	22 (0–51)	24 (0–80.5)	0 (0–46.5)
C3	0.90 (0.71–1.07)	0.84 (0.70–1.03)	0.93* (0.78–1.05)	0.90 (0.74–1.03)	0.84 (0.78–1.23)
Lymphocytes ($\times 10^6$)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.2 (0.7–1.7)	1.1 (0.7–1.6)	1.7 (1.2–2.3)
SLICC/ACR	1.0 (0–2)	1.0 (0–2)	1.0 (0–2)	1.0 (0–2)	1.0 (0–1)

USA [16, 17], this may well reflect a difference between our population of patients and those SLE patients reported from the USA. Our survey of out-patients with SLE may introduce bias by selecting those patients at the milder end of the SLE disease spectrum. However, 62 of 216 (29%) of our patients had a BILAG global disease activity score greater than or equal to 6, indicating notable disease activity and 26 of 216 patients (12%) had activity scores greater than 9. More importantly, it is precisely in the out-patient setting and in those patients with milder disease where FMS might lead to confusion in assessing disease activity in patients with SLE. However, one cannot rule out the possibility that differing medical practice may account for some of the discrepancy.

In common with previous reported groups of patients with FMS, our patients were predominantly Caucasian and female [3]. Fatigue, in this study, was associated with the global BILAG score and in particular with active mucocutaneous and haematological manifestations of SLE. Conversely, fatigue was associated with higher complement C3 levels. Fatigue was not associated with any other serological markers of disease activity. Similarly, there was no association between cumulative damage, measured by the SLICC/ACR index, and fatigue. There was a significant trend for fatigue to be associated with higher numbers of tender points (χ^2 for trend 22.4, $P < 0.001$), but FMS was present in only 11% of these patients. Thus, most patients with SLE may have multiple tender points because they are fatigued. Interestingly patients with FMS had lower mean DNA antibody levels and lower mean cumulative damage scores, suggesting that in this subgroup the disease may have run a more benign disease course.

The concurrence of SLE and FMS can cause considerable confusion both in the initial diagnosis of SLE and in subsequent evaluations of disease activity [7, 8, 18–20]. Patients with FMS tend to over-report symptoms and cope less well [21, 22] as measured by psychological profiles. Furthermore, they are less likely to be able to perform activities of daily living or be employed. Active intervention, in the form of psychotherapy and a graded exercise programme, may improve their general health perception [22].

Conversely, if fatigue itself is a manifestation of SLE, that can also lead to the presence of higher numbers of tender points, it can result in an erroneous diagnosis of FMS when an alternative diagnosis should be considered.

Our definitions of fatigue, generalized pain and therefore FMS were very strict, reflecting the criteria used by the ACR. Thus, we must bear in mind that most practitioners use a more liberal definition of FMS than the ACR criteria which after all are designed as a

TABLE 4. Patients with and without fatigue classified by (a) diagnosis of FMS and (b) according to number of tender points (TP)

(a)

	FMS no	FMS yes
Fatigue no	108	0
Fatigue yes	97	11*

*$P < 0.01$.

(b)

	< 4 TPs	4–10 TPs	11+ TPs
Fatigue no	98	10	0
Fatigue yes	71	26	11**

**$P < 0.001$.

research tool to identify a homogeneous population of patients that could be labelled as having FMS. Nevertheless it is difficult to see that such difference in practice would account for the disparate nature of our findings, especially as most of the studies from the USA incorporate many of the features of the ACR criteria as a basis for defining FMS.

The role of FMS should be considered in SLE patients who complain of fatigue as they may benefit from psychological evaluation as part of their treatment. It is evident that most of the fatigue in patients with SLE is due to the disease itself or failing that to other associated medical conditions that cause fatigue (e.g. hypothyroidism, anaemia).

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