

Fatigue in primary Sjögren's syndrome: Is there a link with the fibromyalgia syndrome?

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Abstract

Objective—To determine whether fibromyalgia (FM) is more common in patients with primary Sjögren's syndrome (pSS) who complain of fatigue. The association and prevalence of fatigue and FM was recorded in a group of patients with pSS and a control group of lupus patients, a subset of whom had secondary Sjögren's syndrome (sSS).

Methods—74 patients with pSS and 216 patients with lupus were assessed with a questionnaire to identify the presence of fatigue and generalised pain. From the lupus group, in a subset of 117 lupus patients (from the Bloomsbury unit) those with sSS were identified. All patients were studied for the presence of FM.

Results—50 of 74 patients with pSS (68%) reported fatigue—a prevalence significantly higher than in the lupus group (108/216 (50%); $p < 0.0087$). Fatigue was present in 7/13 (54%) patients with SLE/sSS. FM was present in 9/74 patients with pSS (12%), compared with 11/216 lupus patients (5%), and in none of the patients with SLE/sSS. None of these values corresponds with previously reported figures of the incidence of FM in pSS.

Conclusion—The results show that fatigue in patients with pSS and sSS is not due to the coexistence of FM in most cases. A lower incidence in the United Kingdom of FM in patients with pSS was found than has been previously reported.

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Sjögren's syndrome (SS) is a chronic autoimmune rheumatic disease of unknown cause, characterised by lymphocytic infiltration of exocrine glands resulting in xerostomia and keratoconjunctivitis sicca, as well as extraglandular (systemic) disease. The latter can affect the lungs, kidneys, blood vessels, and muscles. The syndrome may occur alone—primary Sjögren's syndrome (pSS), or in association with other autoimmune disease—secondary Sjögren's syndrome (sSS).¹

The major presenting symptom of pSS is dryness of the mucous membranes, but severe fatigue is also one of the most often reported symptoms.² The incidence of fatigue in pSS is reported to be as high as 57% and possibly linked with subclinical dysfunction of the autonomic nervous system.³ Sleep disturbances, particularly in initiating and maintaining sleep, in patients with pSS have also been suggested as a contributing factor to fatigue, which

sometimes is the most disabling symptom of the disease.⁴

Previous studies examining fatigue in rheumatic diseases have found that disease activity, especially joint pain, sleep disturbance, depression, and increased physical effort, most strongly contribute to patient complaints of fatigue.⁵ Other possible mechanisms of fatigue, apart from a process fundamental to the condition itself, may be comorbidities such as hypothyroidism, anaemia, lifestyle, or fibromyalgia, which is why we chose to study the last of these.

The precise cause of fatigue in pSS remains unclear and is particularly worthy of study as previous work from this centre has shown that patients with pSS have considerable disability in all aspects of health, particularly pain and fatigue, which is comparable with that of lupus patients.⁶

There are few studies of the prevalence of fibromyalgia (FM) in pSS but to our knowledge this is the first time that primary and secondary SS have been compared to assess any variation in the prevalence of fatigue and FM in these conditions.

Fatigue, as well as dryness of the mucous membranes, is often reported in FM, a form of non-articular rheumatism characterised by chronic pain and stiffness in multiple areas of the musculoskeletal system,⁷ accompanied by trigger points at specific anatomical sites.⁸ Fibromyalgia may present alone (primary FM) or in combination with other diseases (secondary FM), such as pSS, where an incidence of 44–55% for FM has been found.^{9–11} Fatigue, though a major feature of FM, was not found to be a sensitive discriminator and hence does not form part of the classification criteria, which rely upon the presence of widespread pain and mild or greater tenderness in at least 11 of 18 specific trigger points. This has been shown to yield the greatest sensitivity and specificity in identifying both primary and secondary FM equally,⁸ thus a coexistent autoimmune rheumatic disease should not be considered an exclusion to the diagnosis of FM.

The cause of FM is poorly understood and there is a concern that it may be an early manifestation of an autoimmune rheumatic disease. Previous studies have found either no association between FM and autoimmune rheumatic disease features, with the exception of subjective dry mouth¹² or a subgroup of patients with FM who on further testing have features consistent with pSS.¹³ The question raised by this latter group was whether the patients they described already had SS, which in some way predisposes to the later development of FM.

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The purpose of this study was to look at the incidence of fatigue and fibromyalgia in patients with pSS and sSS compared with a control group of lupus patients to assess the contribution of FM to fatigue in pSS.

Method

Seventy four consecutive patients with pSS attending a Sjögren's clinic at the Centre for Rheumatology, Middlesex Hospital were investigated. All patients were diagnosed as having SS according to the proposed European Community criteria,¹⁴ which included a positive salivary gland biopsy in all of our patients. A simple questionnaire was completed by the patients to answer the following questions: (a) Have you felt fatigued or unduly tired on most days for the last three months? Yes/No; (b) Have you suffered with pain in more than one area of the body on most days for the last three months? Yes/No. The final question asked the patient to mark on two line drawings of the human body (front and back) any areas or points that had been painful for the past three months. The patients were then subsequently examined, predominantly by the two authors, one of whom was also involved in the overlapping study of the lupus patients, to assess the number of tender points (TP), from the total of 18 specified by the American College of Rheumatology (ACR) criteria for FM.⁸

The TP were evaluated by palpation using the pulp of the thumb or first two fingers at a pressure of approximately 50 mmHg. This level of pressure was determined by the examiner's palpation of a semi-inflated sphygmomanometer cuff and observing the effort required to reach the 50 mmHg mark.

A patient was deemed to have FM by the presence of widespread pain of at least three months' duration, which was axial and present in two contralateral quadrants, thus satisfying the ACR criteria.⁸

The same questionnaire and examination method has been used in a group of 216 lupus patients, at the Department of Rheumatology, University of Birmingham and the Bloomsbury

Centre for Rheumatology in an overlapping study which was taken as the control for this study¹⁵ and is now in press. Further analysis of the case notes of lupus patients from the Bloomsbury Centre identified those with sSS for comparison.

The results of testing for antinuclear antibodies ((ANA) on Hep-2 cells) and anti-Ro and anti-La antibodies (by enzyme linked immunosorbent assay (ELISA) using the Shield Diagnostic kit, Dundee) were also recorded.

Statistical analysis was performed with the χ^2 test.

Results

Of the 74 patients with pSS studied, 70 were female. Their mean (SD) age was 57.7 (13.2) years (range 21–86). These patients were compared with 216 patients with SLE (207 female), from whom a subset of 117 patients from the Bloomsbury unit were further analysed; the remainder were studied by Dr C Gordon in the Department of Rheumatology, The University of Birmingham. The Bloomsbury subset comprised 104 patients with SLE (99 female) and 13 patients with SLE/sSS (13 female). Patients with SLE each had four or more of the revised American Rheumatism Association criteria for the disease.¹⁶ In the total SLE group, mean age was 40.5 years, in the Bloomsbury patients with SLE mean (SD) age was 39.7 (11.8), and in the group with SLE/sSS 45.5 (10.7) (table 1).

Of the patients with pSS, 58/74 (78%) were ANA positive, 30/74 (41%) Ro positive, and 16/74 (22%) La positive. In the patients with FM identified from this group only 7/74 (9%) were ANA positive, 2/74 (3%) had anti-Ro antibodies while none displayed anti-La antibodies. The presence of these antibodies was not sufficient to identify the fatigue or FM subgroups amongst the patients with pSS (table 2).

The results of this study showed that 50 of the 74 patients (68%) with pSS had fatigue in contrast with 108/216 (50%) lupus patients ($p < 0.0087$), whereas FM was present in 9/74 (12%) of the patients with pSS compared with 11/216 (5%) lupus patients ($p < 0.038$), and in no patients with SLE/sSS (NS) (table 1).

The patients with pSS were mainly women in all groups and those in the FM and fatigue subsets were older (table 2). In the groups with pSS, and SLE with or without sSS, all the patients with FM had fatigue as well, though its presence alone was not sufficient to identify those with FM (table 3). The subset of lupus patients from the Bloomsbury unit with sSS, had a similar incidence of fatigue (7/13 (54%)) to that of the overall SLE group (50%). None

Table 1 Demographic variables and reported fibromyalgia (FM) and fatigue from each study

	Sjögren's patients (n=74)	SLE** All patients (n=216)	SLE (no sSS**) Bloomsbury (n=104)	SLE (and sSS) Bloomsbury (n=13)
Age (years) mean	57.7	40.5	39.7	45.5
Sex	4M:70F	9M:207F	5M:99F	13F
No (%) with fatigue	50 (68)	108 (50)*	47 (45)†	7 (54)¶
No (%) with FM	9 (12)	11 (5)‡	8 (8)¶	0¶

* $p < 0.0087$; † $p < 0.0031$; ‡ $p < 0.038$; ¶NS.

**SLE = systemic lupus erythematosus; sSS = secondary Sjögren's syndrome.

Table 2 Age (mean) and sex distribution of the fatigue and fibromyalgia (FM) groups in primary Sjögren's syndrome

	All	No fatigue	Fatigue	No FM	FM
No (%)	74	24 (32)	50 (68)	65 (88)	9 (12)
Age (years)	57.7	53.5	59.7	57.3	60.6
Sex	4M:70F	2M:22F	2M:48F	3M:62F	1M:8F
ANA* (No (%))	58 (78)	19 (26)	39 (53)*	51 (69)	7 (9)*
Ro* (No (%))	30 (41)	13 (18)	17 (23)*	28 (38)	2 (3)*
La* (No (%))	16 (22)	5 (7)	11 (15)*	15 (20)	0*

ANA* $\geq 1/80$ on Hep, Ro*/La* = by ELISA (Shield Diagnostics, Dundee).

*NS.

Table 3 Patients with primary Sjögren's syndrome classified by presence/absence of fibromyalgia (FM) and fatigue, and according to the number of tender points (TP)

	FM no	FM yes	<4 TP	4–10 TP	>11 TP
Fatigue no	24	0	21	2	1
Fatigue yes	41	9*	26	14	10

* $p < 0.027$.

of the patients with SLE/sSS had FM, which did not achieve a level of statistical significance because of the small number in the sSS group.

Discussion

A previous study has clearly shown fatigue to contribute towards a reduced quality of life in all aspects of functional status and wellbeing in patients with pSS and SLE (with or without SS), with no difference between all three groups.⁶ There was, however, a marked difference in end organ damage as assessed by the SLICC/ACR¹⁷ damage index. The patients with SLE and SS had the greatest renal, peripheral vascular, and musculoskeletal damage, followed by the SLE group, whereas patients with pSS had the greatest damage in the oral section. Hence end organ damage is uncommon in pSS (with the exception of oral damage), but the degree of functional disability is as great as in patients with SLE, and fatigue is a prominent component of this.

Thus it is important to recognise the presence of fatigue, and how this may affect functional ability in patients with pSS. Treating this problem of fatigue is, however, not easy, therefore the recognition of coexistent conditions, such as FM which we chose to study, that may be contributing to the fatigue is vital. In the case of FM active intervention with psychotherapy may improve patients' general health perception.¹⁸ Graded exercise regimens and drugs, such as low dose tricyclic antidepressants, may also help.⁷

This study shows that the high prevalence of fatigue in patients with pSS was significantly greater than that of the control lupus group and could not be attributed to coexistent FM in most cases, in either patients with pSS or with lupus. The fact that no patients with FM were identified in the SLE/sSS group, despite the fact that 54% of them had fatigue, further testifies to the lack of correlation between FM and fatigue in all three study groups.

A possible confounding factor for this is the age difference of 18.5 years between the patients with pSS and those with SLE as chronic widespread pain and fatigue may be expected to increase with age. The peak age of onset of FM, however, is in the fifth and sixth decade,⁸ and both groups of patients were within this time span, but, nevertheless, the age gap within this period cannot be excluded as a source of bias.

Previous studies of the incidence of FM in pSS differ somewhat from ours with values from 44% to 55%.⁹⁻¹¹ A possible explanation may be the use of different criteria for the diagnosis of FM between studies. A prevalence of 47% was found by Vitali *et al.*⁹ In this study they used the criteria of Yunnus *et al.*⁹ for the recognition of FM. The guidelines produced by Yunnus *et al.* identify major criteria—namely, the presence of generalised aches and pains or prominent stiffness in at least three anatomical sites for at least three months; the absence of secondary causes; and only five typical tender points. Minor criteria, at least three, are also required, which include modulation of symptoms by physical activity and the

weather, aggravation of symptoms by weather factors and anxiety; poor sleep and fatigue are also cited. The subsequent development of ACR criteria for FM demonstrated from a large multicentre study with matched controls that FM can be distinguished with good sensitivity (88.4%) and specificity (81.1%) from other rheumatic conditions by the presence of widespread pain and 11 of 18 tender points only.⁸ Fatigue and sleep disturbance are not part of the ACR classification criteria because, although they are prominent symptoms in FM, they are not as powerful in discriminating FM from controls.

Other groups, however, who used the ACR criteria to identify FM in patients with pSS found incidences of 55%¹¹ and 44%.¹⁰ Thus there may be methodological differences between those studies and ours, especially as the incidence of FM among our patients with SLE is also lower than has been reported elsewhere.¹⁵ The groups that found a 44–55%^{10, 11} incidence of FM in patients with pSS do not clearly state if dolorimeters, to identify tender points, were used. If this were the case, as opposed to using the pressure of the examiner's hand at approximately 50 mmHg as we did, then this may explain an underestimation on our part. The latter seems unlikely as the tendency of uncalibrated testing of TP would intuitively be to overestimate 50 mmHg, hence a higher prevalence of FM would then be expected.

Patient selection bias should not account for the difference either as both the groups of patients with pSS and SLE were referred from local general practitioners and hospital doctors with a low threshold for referral, though it is conceivable that the referral practices differ between Birmingham and London. For the patient groups seen in Birmingham and Bloomsbury, however, it is reassuring that the prevalence of FM in each group was not statistically different.¹⁵ Thus both groups of patients should be representative of other groups of patients with pSS and SLE.

A possible explanation for the difference between our prevalence of fatigue and that of other studies may be accounted for by international differences as the aforementioned studies^{10, 11} were carried out in different countries. Population studies from the north of England¹⁹ have shown a point prevalence of chronic widespread pain, satisfying the ACR definition,⁸ of 11.2% that corresponds well with the figure we report for FM.

Further studies have shown that the presence of chronic widespread pain does not absolutely correlate with the presence of FM as most patients with chronic widespread pain have fewer than 11 of 18 TP.²⁰ Thus patients who fulfil ACR FM criteria do not form a discrete clinical disease but are at one end of a spectrum of pain status and TP count. This has been taken one step further and the ACR definition of chronic widespread pain compared with a more stringent definition using line drawings in which each limb is divided into four segments. The new definition of chronic widespread pain requires axial skeleton pain

and contralateral limb pain in at least two segments of the latter, hence being more truly widespread. Of the patients with FM according to the ACR definition, only a quarter met the more stringent definition of chronic widespread pain as well as having 11 of 18 TP, and this group scored worse on general health questionnaires and sleep.²¹ If this latter definition of FM were used in our study then the prevalence of FM in our patients would be five (7%) of the original nine who fulfilled ACR criteria.

Our figure of 9/74 (12%) with FM in patients with pSS indicates that the high incidence of fatigue (68%) in pSS is due to other factors, such as mental fatigue, reduced motivation, disease activity, subclinical autonomic dysfunction, and sleep disturbances, which should not be overlooked.

Future studies should thus look to identify other possible factors responsible for fatigue in patients with pSS above and beyond those already mentioned above. A direct case-control study with normal, age matched controls would help to record the background prevalence of FM and assess its relation to fatigue in the normal population.

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