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Dry eyes and mouth syndrome—a subgroup of patients presenting with sicca symptoms

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Abstract

Objective. To evaluate the characteristics of patients presenting with symptoms suggestive of Sjögren's syndrome (SS) but failing to satisfy diagnostic criteria.

Methods. Clinical, serological and histological data were collected on 34 patients presenting with dry eyes and/or mouth who did not satisfy the Vitali criteria for the diagnosis of SS. They were compared with 136 patients with primary SS, 38 patients with secondary SS, and 13 patients without SS. Questionnaires on symptoms from each group were compared with 43 healthy controls.

Results. The 34 patients who did not satisfy the diagnostic criteria for SS or any other connective tissue disease were designated dry eyes and mouth syndrome (DEMS). Their demography including age was similar to that of a primary SS group and there was no more atrophy seen on their biopsies compared with SS and non-SS controls. They scored highly on visual analogue scales of symptoms but had few objective signs. All were negative for anti-Ro and anti-La although the prevalence of antinuclear antibodies (19%) was increased compared with a normal population. There was no excess of SS-associated tissue types.

Conclusion. There was no evidence that age, salivary gland atrophy or subclinical SS accounted for the symptoms in DEMS. Most of the patients fitted into a spectrum of disease which tended more towards fibromyalgia and/or chronic fatigue syndrome.

KEY WORDS: Sicca, Dry eyes and mouth syndrome (DEMS), Sjögren's syndrome.

A proportion of patients presenting with symptoms of dry eyes and mouth suggestive of primary Sjögren's syndrome (SS) do not satisfy diagnostic criteria. Such patients represent an increasing clinical load for rheumatologists or other specialists with an interest in SS, and are often referred to as 'sicca', 'non-systemic SS' [1] or diagnosed as not having SS, in spite of being quite symptomatic. An association has been described between dry eyes and the presence of nodal osteoarthritis [2] and such patients have been termed 'SOX', although it is possible that referral bias, attributable to an accumulation of rheumatic symptoms such as joint pains and sicca symptoms, may explain this apparent association. It is also widely assumed, although not systematically studied, that these patients are suffering from exocrine atrophy as part of the ageing process. In our study, among 221 patients presenting with symptoms of dry eyes and mouth in whom salivary gland biopsies were performed, 34 patients were identified who did not fulfil sufficient criteria for a diagnosis of SS or any other connective tissue disease. These patients have been designated dry eyes and mouth syndrome (DEMS). This study represents an attempt to explain their symptoms in terms of ageing, subclinical SS or other conditions which could lead to their referral.

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Patients and methods

Labial salivary gland biopsies were performed in 221 patients presenting to the Rheumatology Clinic at Charing Cross Hospital with symptoms suggestive of dry eyes and mouth. Diagnostic features of SS and other connective tissue diseases were sought. Patients with other causes of dry eyes and mouth, including viral infection (HIV, HTLV-I, hepatitis C) drugs and sarcoidosis, were excluded. Labial salivary gland biopsies were assessed histologically using criteria initially described by Chisholm and Mason [3] and subsequently modified by Greenspan *et al.* [4] to provide a quantitative scoring method. Grade scores ranged from 0 to 4, where 0 = absent infiltrate, 1 = slight infiltrate, 2 = moderate infiltrate, 3 = 1 focus of at least 50 lymphocytes/4 mm^2 of gland, 4 = > 1 focus of at least 50 lymphocytes/4 mm^2 of gland. The focus score was the actual number of foci/4 mm^2 ($F = 0, 1, 2, 3, 4, 6, 8, 12$). The atrophy stage was an arbitrary score derived by us and was

determined using a $\times 10$ objective to view haematoxylin and eosin-stained sections. Assessment was only made within lobules, not between, by looking for replacement of acini (atrophy), and fibrosis within the interstitial tissue between the acini. A sample was graded as stage 1 if there was no fibrosis, atrophy or replacement of acini; stage 2 if there were minimal, patchy areas of fibrosis affecting $<10\%$ of the glandular tissue and with normal intervening tissue; stage 3 when there were diffuse fibrotic areas with acinar atrophy affecting between 10 and 70% of the glandular tissue, but with some surviving normal tissue with reasonable preservation of acini; stage 4 if there was diffuse fibrotic change with widespread replacement of acini affecting $>70\%$ of the glandular tissue.

All patients were asked to complete a questionnaire, which included the six standardized questions which form part of the Vitali criteria [5]. In addition, the questionnaire included five questions based on symptoms, as measured by visual analogue scales. The scales were from 0 to 100, where 0 = no trouble at all and 100 = the worst problems they could imagine. The five questions assessed oral dryness, eye symptoms, joint pain and stiffness, and level of tiredness. Questionnaires were also completed by 43 healthy volunteers, none of whom responded positively to the six standardized questions specified in the Vitali criteria [5]. There were 38 female and five male subjects with a mean age of 58.1 yr (S.D. 16.8 yr) in the healthy control group.

Oral dryness was measured objectively by the collection of unstimulated, total salivary flow over 5 min. A total $\leqslant 0.5$ ml/5 min was regarded as positive for diagnostic purposes [5]. Schirmer's tests were performed using 'Sno strips' (Smith & Nephew Pharmaceuticals, Romford, UK) and tear flow measured by the distance of wetting of the strips over 5 min. Less than 5 mm of wetting in 5 min was regarded as positive for diagnostic purposes [5]. The measurement of immunoglobulins (IgG, IgA and IgM), thyroid function tests, including thyroxine and thyroid stimulating hormone, and Westergren erythrocyte sedimentation rates (ESR) were performed in the routine laboratories at Charing Cross Hospital using standard techniques.

Serum samples were assayed for the presence of antinuclear antibodies (ANA) by indirect immunofluorescence on Hep-2 cells using a screening dilution of 1 in 40. Rheumatoid factor (RF) was measured by latex fixation agglutination and anti-Ro and anti-La antibodies were measured by both counter-immunoelectrophoresis (CIE) and enzyme-linked immunosorbent assay (ELISA; Shield Diagnostics, Dundee, UK). Class I and II typing was performed by Terasaki's microlymphocytotoxicity technique [6] using well-characterized antisera for all common HLA-A, -B, -Cw, -DR and -DQ specifications and most splits.

This study, including labial salivary gland biopsy following informed consent, was approved by the Riverside Research Ethics Committee, London, UK (no. RREC 102).

Means (S.D.) were calculated with the aid of minitab statistical software. Comparisons between groups were analysed using the χ^2 test with the application of Yates' correction and Fisher's test where appropriate. The Mann–Whitney *U*-test was used for comparison of groups where a normal distribution could not be assumed and significance was assessed by referral to a *z* table.

Results

Thirty-four patients who did not satisfy the diagnostic criteria for SS or any other connective tissue disease, were identified among 221 patients undergoing labial salivary gland biopsy for investigation of symptoms and signs suggestive of SS (Table 1). Among the remaining 187 patients undergoing biopsies, primary SS was diagnosed in 136, of whom 65 had antibodies to Ro and/or La (48%) and another connective tissue disease in 51.

The clinical and serological features of the DEMS group are summarized in Table 2. All 34 DEMS patients gave positive answers to at least one of the questions for dry eyes and mouth forming part of the Vitali criteria [5]. Twenty-five of the 34 who returned questionnaires scored highly on visual analogue scales of oral and ocular symptoms, fatigue, joint pain and stiffness (Fig. 1a–d) and were as symptomatic as patients with confirmed connective tissue diseases. In spite of the positive responses to both the Vitali questionnaire and visual analogue scale questions, only 14 had abnormal Schirmer's tests (<5 mm/5 min in each eye) and four had reduced salivary flow (<0.5 ml/5 min) (Table 2, Fig. 2a, b).

The DEMS patients were of a similar age (mean 53.9 yr, range 29–72 yr) to patients with primary SS

TABLE 1. Diagnosis, age and sex of the study population

Diagnosis	Number biopsied	Male : female	Mean age	Returned questionnaires
Primary SS (Ro/La^+)	65	1 : 12	55.6	46
Primary SS (Ro/La^-)	71	1 : 8	59.3	49
SS/CTD	19	0 : 19	51.3	10
SS/RA	19	1 : 18	59.9	12
DEMS	34	1 : 8	53.9	25
RA alone	3	0 : 3	67.3	2
CTD alone	10	0 : 10	58.1	8
Total	221			152
Questionnaire-only controls	43	1 : 8	58.1	43

TABLE 2. Summary of clinical and serological findings among the 34 patients with DEMS

Sex	Age	Sch (R/L)	Saliva	Grade	Focus	Atrophy	Ro/La	ANA (H/S)	RF	ESR
F	52	2/20	2.5	2	0	2	–	–	*	8
F	57	10/5	*	3	1	1	–	–	–	19
F	49	8/5	2.0	0	0	1	–	+ (S)	–	3
M	65	6/4	1.5	1	0	2	–	–	–	16
M	73	1/2	0.5	2	0	2	–	+ (H)	–	60
F	67	0/0	2.5	2	0	1	–	+ (H)	–	25
F	48	3/2	3.0	2	0	1	–	–	*	11
F	51	7/15	*	1	0	1	–	–	*	6
F	76	8/3	*	1	0	2	–	+ (H)	–	13
F	40	3/3	3.0	1	0	2	–	–	–	3
F	71	16/10	0.5	1	0	2	–	–	*	28
F	41	1/0	2.5	3	1	2	–	+ (H)	*	7
F	42	30/30	1.5	2	0	2	–	–	–	9
F	55	1/3	1.0	1	0	1	–	–	–	8
F	77	15/15	1.0	1	0	1	–	–	–	8
F	54	2/1	2.5	2	0	2	–	–	–	8
F	65	N	N	1	0	2	–	–	–	*
F	74	5/3	2.0	2	0	3	–	+ (H)	–	14
F	41	35/35	*	2	0	1	–	–	–	7
F	57	5/3	5.0	2	0	2	–	–	–	4
F	37	8/2	*	2	0	2	–	–	–	12
F	72	1/0	2.0	2	0	2	–	–	–	9
F	67	N	N	2	0	2	–	+ (H)	–	7
F	44	10/8	4.0	1	0	1	–	–	–	3
F	59	1/5	1.0	1	0	2	–	–	–	17
M	29	8/12	1.0	1	0	1	–	–	–	2
F	29	12/10	1.0	1	0	1	–	–	–	31
M	38	5/2	2.5	3	1	1	–	–	–	2
F	46	14/14	1.0	1	0	1	–	+ (S)	–	4
F	57	2/2	1.0	1	0	1	–	–	+	27
F	55	10/20	2.0	1	0	1	–	–	+	14
F	62	3/9	0.5	2	0	3	–	+ (S)	–	24
F	37	4/5	0.7	1	0	2	–	+ (S)	–	8
F	54	14/14	0.5	1	0	2	–	–	–	8
F	34	15/15	1.0	1	0	1	–	+ (H)	–	6

Sch (R/L), Schirmer's test, right and left eye; ANA (H/S), antinuclear antibody (homogeneous or speckled pattern); N, normal (i.e. tear secretion >5 mm in each eye over 5 min; unstimulated saliva flow >0.5 ml in 5 min).
*Data not available.

(mean 57.5 yr, range 15–83 yr) and thus the presence of dryness cannot be wholly attributed to involutional changes associated with age. Atrophy scores were also comparable to those in patients with primary SS as well as the groups without SS (Table 3). It is noteworthy that none of the patients had severe atrophy, i.e. stage 4, and those patients with stage 3 changes tended to be older but with well-preserved salivary flow. With regard to the histological score, three patients had grade 3 changes (i.e. one focus of at least 50 lymphocytes/4 mm^2 of gland). It is of interest that two of the three with 'positive' biopsies had normal salivary flow rates, suggesting that the inflammation observed was not associated with functional impairment. Thirteen patients had grade 2 changes (i.e. moderate infiltrate) on salivary gland biopsy, but the remainder had no significant changes (grade 0 or 1). All patients were negative for antibodies to Ro and La both by CIE and ELISA. Ten patients were ANA positive (29%), significantly ($P = 0.002$) above that expected for a normal population [7]. Two (6%) patients were RF positive—this is equivalent to the population prevalence of a positive RF of 5% [8]. The mean ESR was 11 mm/h, but there was a broad range, with nine patients having ESRs above the normal range (>15 mm/h). Four of 23 tested were hypothyroid (17%). Among 12 patients tissue typed there was no excess of DR3, DRw52 and DQw2 compared with the control population (Table 4). There was an increase in DR4 (50% compared with 27% in the normal controls), but this did not reach statistical significance.

Discussion

We studied a group of patients, designated DEMS, with symptoms of dry eyes and/or mouth who did not satisfy the criteria for the diagnosis of primary SS or any other connective tissue disease. We undertook this analysis because these patients tended to be polysymptomatic, to have sought multiple opinions and to be demanding of medical time. The term 'sicca' has been avoided because it implies a similar pathogenesis to the keratoconjunctivitis sicca described by Sjögren [9]. We used the term syndrome in preference to disease because the latter implies a single aetiology whereas these patients formed a diverse group.

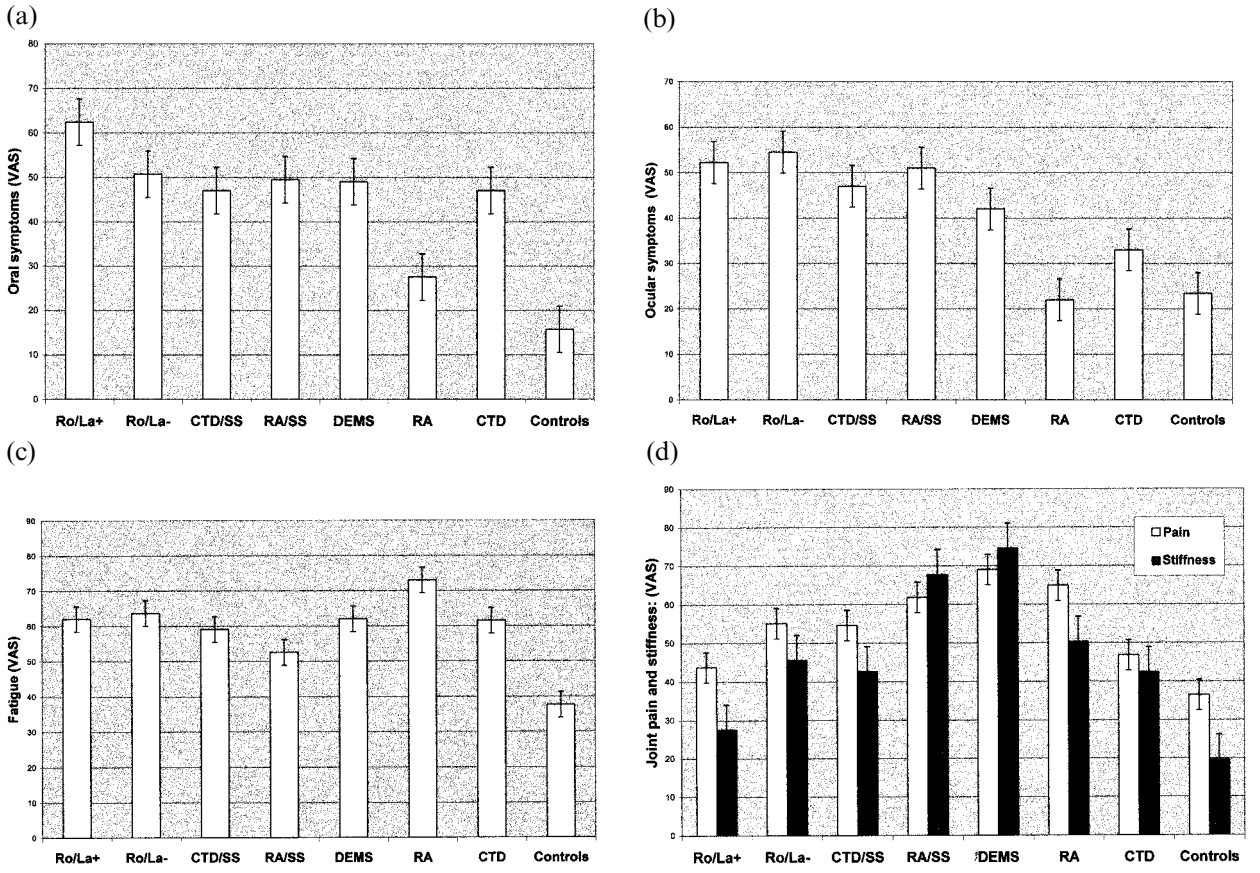

FIG. 1. Visual analogue scale (0–100) measures of symptoms in patients with DEMS, SS, rheumatoid arthritis (RA) and connective tissue disease (CTD). (a) Oral symptoms. Oral symptom scores were significantly higher in the following patient groups when compared with the control group: Ro/La$^+$ ($z = 5.79$, $P = 0.002$), Ro/La$^-$ ($z = 5.67$, $P = 0.002$), CTD/SS ($z = 2.38$, $P = 0.05$), RA/SS ($z = 4.8$, $P = 0.002$) and DEMS ($z = 4.3$, $P = 0.002$). (b) Ocular symptoms. Ocular symptom scores were significantly higher in the following patient groups when compared with the control group: Ro/La$^+$ SS ($z = 3.76$, $P = 0.002$), Ro/La$^-$ SS ($z = 4.76$, $P = 0.002$), CTD/SS ($z = 2.21$, $P = 0.05$), RA/SS ($z = 2.66$, $P = 0.01$) and DEMS ($z = 2.64$, $P = 0.01$). (c) Fatigue symptoms. Levels of fatigue were significantly higher in the following patient groups compared with the controls Ro/La$^+$ SS ($z = 3.12$, $P = 0.002$), Ro/La$^-$ SS ($z = 4.28$, $P = 0.002$), SS/CTD ($z = 1.96$, $P = 0.05$) and DEMS ($z = 2.86$, $P = 0.01$), but failed to reach statistical significance in the RA/SS group ($z = 1.65$, $P = 0.1$). (d) Mean joint pain and stiffness scores. Scores for joint pain and stiffness were significantly higher than those recorded by the control group for patients with Ro/La$^-$ SS (joint pain $z = 5.77$, $P = 0.002$; joint stiffness $z = 0.46$, $P = 0.002$), SS/RA (joint pain $z = 2.49$, $P = 0.05$; joint stiffness $z = 4.167$, $P = 0.002$) and DEMS (joint pain $z = 3.16$, $P = 0.002$; joint stiffness $z = 5.15$, $P = 0.002$). There was no significant difference between the joint symptom score recorded by controls and the Ro/La$^+$ primary SS patients (joint pain $z = 1.42$, $P > 0.1$; joint stiffness $z = 0.79$, $P > 0.1$) suggesting that joint symptoms are not a frequent feature of true antibody-positive primary SS. The SS/CTD patients showed a significant increase in joint stiffness scores ($z = 2.78$, $P = 0.01$) compared with controls, but not in joint pain scores ($z = 1.76$, $P = 0.1$). The bars represent standard error of the mean.

Patients with DEMS scored highly on subjective symptoms but with a low prevalence of positive objective tests. None of them satisfied criteria for a diagnosis of SS or any other connective tissue disease. One purpose of our study was to see if there was a proportion of patients in whom a specific diagnosis could be made or whether they were a group who were over-reporting their symptoms. Of 211 patients undergoing labial salivary gland biopsy, 34 (17%) fell into the DEMS group. All patients had been referred, by their general practitioner or another hospital, to a rheumatology clinic with a special interest in SS, thereby creating a selection bias. However, it is likely that these patients formed a higher proportion of actual referrals as we only included in our analysis those in whom salivary gland biopsy was performed.

Possible underlying diagnoses in the DEMS group include atrophy with age, drug side-effects, subclinical primary SS, hypothyroidism, viral infection, or fibromyalgia. Our study has directly challenged widely held assumptions that ageing, atrophy or use of antidepressants are the underlying causes of dry eyes and mouth in patients who do not have SS. The patients with DEMS had the same age range as those with SS. Atrophy tended to rise with age, but in none of the 34 samples examined could the changes have accounted for the degree of symptoms reported. Indeed, it was striking that objective measures of salivary and lachrymal flow

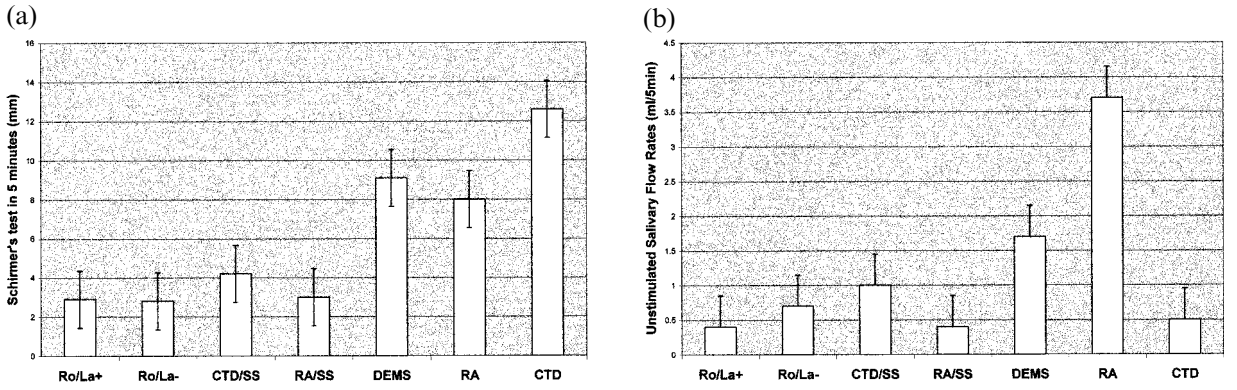

FIG. 2. Signs of oral and ocular disease in patients with DEMS compared with patients with SS, rheumatoid arthritis (RA) and connective tissue disease (CTD). (a) Mean tear production measured over 5 min using Schirmer's test strips. Tear flow was significantly higher in the patients with DEMS compared with both of the primary SS groups ($P = 0.0002$), CTD/SS ($P = 0.0014$) and RA/SS ($P = 0.0014$) patient groups. (b) Mean unstimulated salivary flow over 5 min for each patient group. Salivary flow rates were significantly lower in primary SS patients (both Ro/La$^+$ and Ro/La$^-$, $P = 0.0001$), RA/SS ($P = 0.002$) and CTD/SS ($P = 0.05$) patients compared with those with DEMS. The bars represent standard error of the mean.

TABLE 3. Mean (S.D.) histological grade, focus and atrophy score for patients with SS, DEMS and other groups

Diagnosis	Number studied	Grade	Focus	Atrophy
Primary SS (Ro/La$^+$)	65	3.7 (0.7)	3.8 (3.08)	2.4 (0.4)
Primary SS (Ro/La$^-$)	71	3.2 (0.9)	2.0 (2.33)	2.3 (0.7)
SS/CTD	19	3.2 (1.0)	1.9 (1.8)	1.9 (0.7)
SS/RA	19	2.8 (1.0)	1.4 (1.9)	2.0 (0.7)
DEMS	34	1.6 (0.7)	0.1 (0.3)	1.5 (0.7)
RA alone	3	2.6 (1.0)	1.3 (1.3)	1.3 (0.5)
CTD alone	10	1.7 (0.5)	0 (0)	1.6 (0.5)

TABLE 4. Tissue type (%) of patient groups (analysis confined to European Caucasians for all groups)

Diagnosis (*n*)	A1	B8	DR3	DR2	DR4	DRw52	DQw1	DQw2	DQw1 + w2
Normal[a] (100)	33	18	23	25	27	57	54	33	11
Ro/La$^+$ (45)	52	**73**	**80**	23	18	**93**	55	**68**	**36**
Ro/La$^-$ (33)	30	33	33	6	45	39	39	**55**	24
SS/CTD (9)	44	**55**	55	22	33	77	77	66	**44**
SS/RA (17)	29	18	12	6	**71**	24	24	29	6
DEMS (12)	33	17	25	17	50	50	25	17	0

[a]Normal control population of 100 healthy British Caucasian blood donors.
Figures in bold type are statistically significant compared with the control population corrected for the number of variables examined.

were normal in the majority of the patients, in spite of sicca symptoms which matched those of patients with confirmed SS. None of the patients studied was taking anti-depressants. Most patients with DEMS specifically avoid these drugs because it worsens their symptoms.

We also considered a diagnosis of 'subclinical' primary SS in our patients with DEMS. In favour of this possibility was the high female:male ratio, the findings of positive Schirmer's tests in 13 patients and abnormal salivary flow in four. The high frequency of ANA (29%) suggests that an underlying autoimmune process may be present in at least a proportion of patients. However, it is difficult to assign a diagnosis of 'subclinical' SS to any individual in our group, as there was no single subject in whom a high frequency of these abnormalities appeared to occur together. The frequency of a positive RF (6%) is equivalent to the population prevalence of 5% [8]. Against the diagnosis of SS is the absence of any association with HLA-DR3, the absence of antibodies to Ro and La and the low grade and focus scores on labial salivary gland biopsy.

Four of 24 tested were hypothyroid (17%). This compares with a prevalence of approximately 11% in a female population of similar age with non-inflammatory joint disease [10] and 10% in a random British female population over 60 yr [11]. The finding of hypothyroidism with an elevated thyroid stimulating hormone may be of relevance in light of animal data which suggest that

hypothyroidism can lead to a reduction in salivary flow [12]. Stiffness, cramp and muscle pain increasing with exercise are common in hypothyroidism [13] and joint effusions and synovial thickening occur in the small and large joints [14]. As with 'subclinical' SS it is difficult to identify a single individual in whom hypothyroidism could account for the DEMS symptoms. Moreover, only 24 of the 34 patients were tested for thyroid dysfunction and there may have been bias in favour of testing those in whom a diagnosis of hypothyroidism was suspected on clinical grounds. If this was the case, four of 34 would be hypothyroid (11.8%) virtually the same as the general population [10, 11]. Nevertheless, these findings emphasize the importance of thyroid function testing in all patients with sicca symptoms, whether or not they have SS.

The high levels of fatigue and occurrence of a positive ANA in DEMS would also be concordant with an underlying viral infection. As a group, our patients fell into low-risk categories for infection with HIV, HTLV-1 or hepatitis. Where this was considered a possibility, serological testing was consistently negative for all three. It is possible that an as yet undiscovered virus is the cause, but as a group these patients are at low risk of infection by conventional retroviruses or hepatitis viruses. It is more likely to be an uncommon reaction to a common infection than vice versa and newly discovered viruses such as human retrovirus-5 (HRV-5) [15] may merit further study, particularly as proviral DNA from HRV-5 was isolated from one patient with DEMS [16]. However, in more recent (unpublished) work we have not detected HRV-5 DNA in any further patients with DEMS.

The high frequency of musculoskeletal symptoms and fatigue raised the possibility of chronic fatigue syndrome and/or fibromyalgia in some of the patients. The patients in this study were not formally assessed for chronic fatigue syndrome or fibromyalgia, but in no case was this the clinical diagnosis. If the patients had been specifically examined for diagnostic criteria of widespread body pain plus 11 out of 18 tender points [17], it is possible that this unexpected diagnosis might have been made in a proportion of the cases. The very high pain score on the visual analogue scale would be in support of this. However, some patients did not report any pain at all and it is clear that fibromyalgia cannot be a unifying diagnosis for all patients with DEMS. Therefore, it can only be argued that DEMS patients are part of the spectrum of diseases related to fibromyalgia or chronic fatigue syndrome.

Other studies have highlighted overlaps between symptoms of SS and chronic fatigue syndrome/fibromyalgia. Raynaud's phenomenon and dry eyes and mouth have been reported in 20–35% of patients with fibromyalgia and a positive ANA in 10–20% [18]. Calabrese *et al.* [19] studied a cohort of 172 patients with chronic fatigue syndrome and found features of SS in 27. Results of Schirmer's test were abnormal for 16 of the 27 and labial salivary gland biopsy was abnormal in 20 of the 25. Over half of them were ANA positive but only one was anti-Ro positive. About two-thirds satisfied diagnostic criteria for SS and thus represent either the co-existence of two conditions or misclassification of patients with true SS as chronic fatigue syndrome. The remaining patients resembled those described in this paper. Nishikai *et al.* [20] studied 75 patients with chronic fatigue syndrome defined by standard criteria. Sicca symptoms were reported by 73%, but only eight patients satisfied the Vitali criteria [5]. Again, it is likely that this group was similar to the patients with DEMS described here. A recent study [21] found that the prevalence of fibromyalgia in patients with well-defined SS was not increased above that found in lupus, suggesting that SS-like symptomatology was more of a feature of fibromyalgia than vice versa. In a recent review, Fox *et al.* [22] argued that many patients with fibromyalgia will be misdiagnosed as having SS with softer symptom-based criteria, particularly if histological grading is not rigorously performed on biopsies. Our study, in which every patient with DEMS did have a biopsy, would be in support of this view, as a proportion did have low-grade inflammation, but only three of them fulfilled the histological criteria for a diagnosis of SS.

Although our study has failed to define a single pathological process which characterizes DEMS, we have shown that some of the previously held assumptions regarding this difficult group are incorrect. Our study has strongly suggested that management of DEMS should include careful diagnostic tests (including biopsy in many cases), thyroid function testing, consideration of a chronic viral infection and specific examination for fibromyalgia and/or chronic fatigue syndrome.

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