Clinicopathological Findings Consistent with Primary Sjögren's Syndrome in a Subset of Patients Diagnosed with Chronic Fatigue Syndrome: Preliminary Observations

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ABSTRACT. ***Objective.*** Some patients diagnosed with chronic fatigue syndrome (CFS) have symptoms commonly observed in Sjögren's syndrome (SS), particularly xerophthalmia and xerostomia, leading to speculation that some patients with CFS might have primary SS or that the 2 disorders share common pathophysiological features. We investigated the prevalence of symptoms of mucosal dryness, salivary gland pathology, lacrimal hyposecretion, and autoantibodies (antinuclear antibody, SSA/SSB) among patients diagnosed with CFS.

Methods. Twenty-five subjects with CFS and 18 healthy control subjects were interviewed and examined, had a Schirmer test and fluorescein tear dilution, and underwent minor salivary gland (MSG) biopsy. Antibody to nuclear antigen as well as anti-La (SSA) and anti-Ro (SSB) antibody were available for subjects with CFS. Pathologists unaware of the subject group assignment examined labial salivary gland biopsy specimens and calculated a standard MSG score for each specimen.

Results. Mucosal dryness was reported by 13/25 (52%) subjects with CFS, of which 8 (32%) also had MSG score, low Schirmer test value, and symptoms consistent with primary SS ($p = 0.05$). No control subject met diagnostic criteria for primary SS. MSG focus scores ≤ 1 were common among both groups (CFS 14/25; controls 15/18). MSG results without pathological alteration were rare, seen in only one control and no CFS patients. Low Schirmer values were found in 10/25 (40%) CFS patients and 1/18 (6%) control ($p = 0.01$).

Conclusion. A subset of patients with CFS may have primary SS. (J Rheumatol 2001;28:126–31)

Key Indexing Terms:
SJÖGREN'S SYNDROME CHRONIC FATIGUE SYNDROME DIAGNOSIS

Chronic fatigue syndrome (CFS) is an illness characterized by fatigue lasting at least 6 months not explained by any other known medical cause and reducing activity by at least 50%, with associated polyarthralgia and/or myalgia, insomnia, headache, neurocognitive impairment, and flu-like symptoms of unknown etiology[1,2]. Prior to the Center for Disease Control (CDC) working case definition[1] several other terms were used to describe the condition, including chronic active Epstein-Barr virus infection, chronic infectious mononucleosis, neuromyasthenia, myalgic encephalomyelitis, and low natural killer syndrome[3-7]. Although CFS is characterized by chronic, debilitating fatigue, it is an uncommon cause of fatigue[8,9].

The etiology of CFS is unknown. Some believe CFS is a primary psychiatric disorder characterized by anxiety and depression with somatization[10,11]. Others propose a poorly understood postviral syndrome, supported by the occurrence of over 12 CFS "epidemics" involving more than 2000 patients during the last 60 years[12], as well as the common report of an acute flu-like illness that antedates the onset of CFS symptoms. Most speculation and investigation for an infectious etiology has focused on viruses such as human herpesvirus-6[13,14], enteroviruses[15,16], Epstein-Barr virus[17,18], and retroviruses (HTLV I, II)[19,20]. Although primary infection by many of these viruses occurs during childhood, subsequent reactivation and persistent viral replication is hypothesized to exist in CFS. Infections such as human immunodeficiency virus and Lyme disease can also cause CFS-like symptoms. Thus, it is likely that patients with non-epidemic CFS represent a group with etiologically diverse disorders.

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Many systemic connective tissue disorders have symptoms similar to CFS, such as myalgia, arthralgia, weakness, and neurocognitive impairment. Patients with Sjögren's syndrome (SS), an autoimmune exocrinopathy characterized chiefly by mucosal dryness, also experience CFS-like musculoskeletal[21,22] and neurocognitive[22,23] symptoms, and the 2 disorders share some similar immunologic defects such as activated T lymphocytes, hyperactive B lymphocytes, impaired natural killer cell activity, and impaired delayed-type hypersensitivity[24-28]. Many patients with CFS also complain of mucosal dryness[29-31]. These clinicopathologic similarities have led to speculation that a subset of patients with CFS may have undiagnosed SS or that the 2 disorders share some common pathophysiological features[29-31]. We investigated the prevalence of SS-like mucosal symptoms, salivary gland histopathological changes, and lacrimal gland hyposecretion among patients with CFS and a group of healthy control subjects.

MATERIALS AND METHODS

Consecutive patients diagnosed with CFS using the CDC working case definition[1,2,32] were recruited from the Chronic Fatigue Syndrome Center at the New Jersey Medical School during a 6 month study period. Control subjects were recruited from the university community and were paid for their participation in this study. Exclusion criteria for the control group included complaints of fatigue, chronic headache, myalgia, or arthralgia; medical illness; the use of any medications; or pregnancy. All research was approved by the Institutional Review Board and all subjects gave signed informed consent.

All subjects completed a medical history and a study questionnaire (Figure 1). For all subjects in both groups a Schirmer test was performed without anesthesia for 5 minutes; a value ≤ 10 mm/5 min was considered abnormal[33,34]. A labial minor salivary gland (MSG) biopsy consisting of 4 or 5 glands was performed on all patients and controls. Biopsy specimens were fixed in 10% formalin and sections were cut at 3 levels. Hematoxylin and eosin stained sections were coded to conceal their subject group source and slides from each level were jointly examined by 3 experienced oral pathologists. The total tissue area of intact gland lobules was calculated as the mean area of the 3 sections. For each specimen the number of lymphocytic foci (> 50 cells) was recorded according to Daniels[35] as well as other histopathological features such as plasma cell infiltration, fibrosis, ductal ectasia, fatty replacement, and necrosis. Scores were determined by consensus among the pathologists. The MSG scores and Schirmer test values in the 2 groups were compared by chi-square analysis (Fisher's exact test).

Figure 1. Study questionnaire.

1. Do you experience difficulty swallowing or chewing food?
2. Do you feel your mouth is excessively dry?
3. Do you have difficulty speaking?
4. Does food frequently stick to your teeth?
5. Do you have abnormal taste sensations?
6. Are you frequently thirsty?
7. Do you develop dental decay frequently?
8. Do you have difficulty wearing dentures?
9. Do you have burning or aching sensations in your mouth?
10. Does your face ever swell?
11. Are your teeth sensitive to temperatures?
12. Do you experience a sandy or gritty feeling in your eyes?
13. Do you feel like there is a foreign object in your eye?
14. Do you experience blurry vision?
15. Do you experience excessive secretions or mucus in your eyes?
16. Are your eyes unusually sensitive to bright light?
17. Do your eyes fatigue easily?
18. Do you get sores, lumps, or rashes on your skin?
19. Do you experience frequent joint pain?
20. Do you experience frequent muscle aches?
21. Do you experience stomach aches or constipation?
22. Do you experience frequent colds or infections?
23. Is your skin excessively dry?

RESULTS

A total of 25 subjects with CFS (age 38 ± 10 yrs, range 22–55; 23 female, 2 male) and 18 control subjects (age 37 ± 8, range 25–52; 16 female, 2 male) were enrolled in and completed the study. There was no significant age or sex difference between the 2 groups. The racial distribution in the CFS group was 23 Caucasian and 2 Hispanic; racial distribution in the control group was 14 Caucasian, 3 Hispanic, and one Asian.

Table 1 summarizes the clinicopathologic findings in all subjects. Thirteen of 25 (52%) of the CFS subjects complained of mucosal dryness; no control complained of mucosal dryness. MSG scores consistent with SS according to Daniels[35] (> 1 focus) were observed in 11 (44%) CFS subjects, 8 of whom (32%) had other signs and symptoms that fulfilled primary SS diagnostic criteria[36,37] ($p = 0.05$) (Table 2); 3 controls had a MSG focus score > 1 but did not meet other criteria for primary SS. One CFS subject had ANA titer of 1:160, all others were seronegative for ANA, SSA, and SSB.

The Schirmer test was abnormal in 10/25 CFS (40%) and 1/18 (6%) controls (Table 3) ($p = 0.01$). Eight of 11 CFS patients with MSG focus score > 1 also had a low Schirmer test and complained of mucosal dryness. Three of 6 CFS subjects with symptomatic dryness and a low Schirmer test had MSG focus score < 1. Interestingly, only one healthy control had "normal" MSG histology, with most biopsy results revealing grade 1 or 2 MSG scores, according to Chisholm and Mason[38], characterized by scant mononuclear infiltrates or lymphocytic foci with < 50 cells.

Fourteen of 25 CFS subjects were taking anticholinergic medications during the 3 month period before this study (amitriptyline, nortriptyline, sinequan, welbutren, clonazepam). Of the 14 CFS subjects taking these medications, 8 (57%) belonged to the group with symptomatic dryness and MSG score > 1 and one exhibited lacrimal hyposecretion. Of the remaining 6 (43%) CFS subjects taking these medications none had MSG scores > 1, none exhibited mucosal dryness, and 2 exhibited lacrimal hyposecretion. There was no relationship between medication use and any combination of SS diagnostic criteria.

Table 1. Clinicopathologic findings in all subjects.

Subject	Sex, Age, yrs	MSG Score (0–2,3,4)	Schirmer, < 10 mm/5 min, n	Symptomatic Dryness	ANA ≥ 1:160	SSA/SSB > 1:50
CSF cases						
1	F 31	2	–	+	–	–
2	F 22	4	+	+	+	–
3	F 31	1	–	–	–	–
4	F 40	3	+	+	–	–
5	F 34	2	–	+	–	–
6	F 30	2	–	–	–	–
7	F 43	2	–	–	–	–
8	F 44	3	–	+	–	–
9	F 48	4	+	+	–	–
10	M 55	2	–	–	–	–
11	F 51	3	+	+	–	–
12	F 26	3	+	+	–	–
13	F 23	2	–	–	–	–
14	F 31	4	+	+	–	–
15	M 36	3	–	+	–	–
16	F 39	2	–	–	–	–
17	F 28	3	–	+	–	–
18	F 52	1	–	–	–	–
19	F 46	2	–	–	–	–
20	F 40	2	–	–	–	–
21	F 38	4	+	+	–	–
22	F 46	2	–	–	–	–
23	F 35	4	+	+	–	–
24	F 36	1	–	–	–	–
25	F 34	2	–	–	–	–
Controls						
26	F 30	1	–	–	NA	NA
27	F 43	1	–	–	NA	NA
28	F 44	2	–	–	NA	NA
29	F 48	1	–	–	NA	NA
30	M 26	1	–	–	NA	NA
31	F 25	0	–	–	NA	NA
32	F 31	3	–	–	NA	NA
33	F 36	2	–	–	NA	NA
34	F 39	1	+	–	NA	NA
35	M 28	2	–	–	NA	NA
36	F 52	3	–	–	NA	NA
37	F 46	1	–	–	NA	NA
38	F 40	1	–	–	NA	NA
39	F 38	2	–	–	NA	NA
40	F 49	2	–	–	NA	NA
41	F 35	3	–	–	NA	NA
42	F 36	2	–	–	NA	NA
43	F 34	1	–	–	NA	NA

Table 2. Number of subjects in control and CFS groups and MSG scores (Daniels[35]).

	Score < 1	Score ≥ 1
CFS	14	11*
Control	15	3*

*p = 0.05.

DISCUSSION

We examined 25 patients diagnosed with CFS and found that 32% met diagnostic criteria for primary SS according to the European criteria (4 out of 6 major category signs or symptoms)[36,37], namely: (1) complaint of oral dryness; (2) complaint of ocular dryness; (3) MSG biopsy with > 1 lymphocytic foci/4 mm^2; (4) lacrimal hyposecretion; and (5) no serological evidence for another connective tissue disorder. The questions shown in Figure 1 are not identical

Table 3. Schirmer test scores in control and CFS subjects according to mucosal symptoms and MSG score.

	25 CFS Subjects				18 Controls	
	(+) Symptom of Mucosal Dryness		(–) Symptom of Mucosal Dryness		None with Symptom of Mucosal Dryness	
MSG Score	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer
Normal	0	0	0	0	0	1
< 1	2	3	0	12	1	16
≥ 1	8*	0	0	0	0*	0*

*p = 0.01.

with those used in the European Cooperative Study[36,37] because this study was conducted before publication of the Cooperative Study results. However, the key questions that address symptoms of mucosal dryness are essentially the same in both studies.

Recently, Nishikai, *et al*[29] examined a group of 75 seronegative patients diagnosed with CFS and found that 22 (29%) fulfilled the criteria for primary SS[36,37,39]. A recent retrospective study also described results similar to ours: 15% of a CFS population met diagnostic criteria for primary SS[31]. This is considerably higher than the prevalence of primary SS in the general population, which may be as high as 1–2%[40,41]. Our finding that 100% of patients with MSG focus scores > 1 also had a low Schirmer value is similar to that recently reported for patients with primary SS[42].

Two CFS patients who complained of mucosal dryness also with a low Schirmer test value had a MSG focus score < 1 (equivalent to Chisholm and Mason grade 3 MSG score[35]); this group may represent a potentially larger primary SS cohort who require only time to progress to more prominent MSG inflammation and to develop other signs and symptoms of mucosal dryness, thereby meeting primary SS diagnostic criteria. Supporting this possibility is the finding that a single MSG biopsy has low sensitivity and reproducibility compared to subsequent re-biopsy[43]. Additionally, another study recently reported that quantitative immunohistological examination of MSG tissue for IgA and IgG-containing plasma cells confirmed the diagnosis of primary SS in patients without multifocal MSG infiltration[44]. Although the overall prevalence of MSG scores < 1 was similar in both groups (CFS 6/25, 24%; controls 3/18, 17%), the CFS group may comprise 2 distinct subgroups with different relative risks for primary SS: those with symptoms and low Schirmer test values (n = 3; higher risk) versus those with symptoms but normal Schirmer test values (n = 3; lower risk). This speculation must be confirmed by subsequent MSG re-biopsy.

Any potential relationship between CFS and primary SS is complicated by the lack of a sensitive test or agreement regarding the diagnostic criteria for primary SS[36,37,39,41,43-47]. To complicate matters, a category of "probable" primary SS has also been introduced based on a combination of clinical and/or laboratory abnormalities[36,37]. Nonetheless, when properly performed and interpreted, multifocal lymphocytic infiltration of the MSG is a widely accepted diagnostic criterion for SS[35-37,39,41,48] and, based on autopsy and necropsy material, has not been reported to occur in healthy adults[49–51]. Daniels and Whitcher[42] compared MSG histopathologic findings to ocular findings in 618 patients with SS and concluded that MSG multifocal lymphocytic infiltration is essential for a diagnosis of SS in cases where keratoconjunctivitis sicca is missing. Our MSG findings from 18 living, healthy controls failed to reveal multifocal MSG lymphocytic infiltration, although low grade inflammation (Chisholm and Mason Grade 1–2) was very common (78%) and grade 3 was occasionally observed (17%); others have found similar degrees of nonspecific sialadenitis in post-mortem[49-51] and clinical[42] MSG. Although MSG pathology has been reported in a variety of other connective tissue disorders[50,52,53], no patient with CFS in this study had evidence of any such disorder based on the absence of serologic markers.

One explanation for the high prevalence of symptomatic mucosal dryness in the CFS group is the use of psychotropic medications with anticholinergic side effects. Fourteen of 25 CFS patients had taken such medications during the 3 month period before this study (amitriptyline, nortriptyline, sinequan, welbutren, clonazepam); there was no association between medication use and SS criteria: of the 14/25 CFS patients taking medications, 8 also belonged to the group with both symptomatic dryness and MSG score > 1, whereas 6 did not meet these other criteria. Lacrimal hyposecretion was also nearly equal among those taking medication and those not taking medication (one vs 2, respectively). Thus, while some (8/14) patients taking anticholinergic medications did complain of dryness, there was no association between drug use, MSG inflammation, and mucosal dryness. Drugs with anticholinergic actions decrease salivary gland secretion by neurochemical blockade and would not be expected to induce lymphocytic infiltration. The xerostomia side effect is usually dose related and reversible when medication is discontinued[54]. However, since no studies of drug induced MSG lymphocytic infiltration have been performed, this possibility

cannot be excluded. Further investigation of MSG changes in a group of patients taking psychotropic medications with anticholinergic activity would provide additional insight.

Xerostomia of nonrheumatologic origin (i.e., medication induced) could lead to mucous plug inspissation resulting in salivary ductal injury and inflammation. However, it would not be expected that the resulting infiltrate would be of the multifocal nature characteristic of SS. Indeed, the salivary lymphocytic infiltration observed following irradiation for head and neck cancer has been posited to be due in part to salivary obstruction[55-59]. However, the pattern is very different, characterized by fibrosis, acinar atrophy, parenchymal loss, intercalated duct proliferation and dilatation, and a diffuse lymphocytic infiltration with occasional plasma cells and rare eosinophils[55,58,59]. Adherence to the multifocal infiltrate criterion will minimize the possibility of confusion between SS and nonspecific inflammation.

In summary, we discovered that a subset of patients with CFS may have undiagnosed primary SS based on the finding of MSG focus score > 1, lacrimal hyposecretion, symptomatic oral or ocular mucosal dryness, and no underlying connective tissue disorder. This cohort may be even larger if those symptomatic patients with a MSG focus score < 1 and low Schirmer test values represent "probable SS" patients, requiring only time to progress to more marked MSG inflammation and other signs and symptoms of SS. The potential subset of patients with CFS who may require investigation for Sjögren's syndrome include those who complain of mucosal dryness when appropriately questioned and have a low Schirmer test score. Investigation of clinical features and/or laboratory abnormalities that reliably identify the primary SS subset is desirable, as well as investigations that explore common pathophysiological processes.

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