

## 'SERONEGATIVE' SJÖGREN'S SYNDROME MANIFESTED AS A SUBSET OF CHRONIC FATIGUE SYNDROME

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### SUMMARY

We determined the extent to which chronic fatigue syndrome (CFS) patients with sicca symptoms fulfil the diagnostic criteria for Sjögren's syndrome (SS). Three sets of diagnostic criteria for SS, formulated by the Japanese, Europeans and Fox, were used. One-third of the CFS patients with sicca symptoms fulfilled the diagnostic criteria for SS. However, they were 'seronegative', differing from the ordinary primary SS.

**KEY WORDS:** Chronic fatigue syndrome, Sjögren's syndrome, Anti-La (SSB) antibodies, Anti-Ro (SSA) antibodies.

CHRONIC fatigue syndrome (CFS) is a clinical syndrome consisting of debilitating chronic fatigue, generalized myalgias and/or arthralgias, insomnia, depression, chronic headache and flu-like symptoms of unknown aetiology [1, 2]. Dry eyes and/or dry mouth are found in up to 30-87% of CFS patients, according to previous reports [3-5]. Conversely, severe fatigue and neurocognitive dysfunction are the main subjective symptoms of Sjögren's syndrome (SS) [6, 7]. In our experience and that of others [8], SS or suspected SS, instead of CFS, is a common diagnosis made 'erroneously' by doctors.

The purpose of this study was to determine the extent to which CFS patients with sicca symptoms meet the diagnostic criteria for SS and, further, to determine the characteristics of such SS patients.

### MATERIALS AND METHODS

#### Patients

Seventy-five patients were diagnosed as having CFS using the working case definition advocated by the Centers for Disease Control and Prevention, Atlanta, Georgia, USA [1]. For the diagnosis of SS, the Japanese criteria [10], the European criteria [11] and Fox's criteria [12] were used (Table I). The Japanese criteria were modified by substituting sialoscintigraphy for the sialogram.

Thirty-seven sicca symptoms listed in Table II, consisting of 13 ocular, 11 oral and 13 other sicca symptoms, were selected from several classic reports on SS [12-15]. Sicca symptoms were scored as present or absent in all of the 75 CFS patients by questionnaire. In order to define the grade of the sicca symptoms, the number of sicca symptoms present was compared between the 'typical' SS patients and age- and sex-matched control subjects. In the present study

group, 22 'typical' SS, 10 primary and 12 secondary SS, strictly fulfilled the Japanese criteria and had positive anti-Ro (SSA) and/or anti-La (SSB) antibodies, and positive results on lip biopsies as well. The lip biopsy histology was defined as positive when it was found to be of grade 3 or 4 by the histological criteria of Chisholm and Mason [16]. Of the 22 SS patients, 15 showed grade 4 and seven showed grade 3. The control subjects consisted of 20 osteoarthritis patients who had typical roentgenographic changes on their knee and/or distal interphalangeal joints, and 24 patients who had mild arthralgia and/or morning stiffness, but were not given definite diagnoses in spite of standard physical and laboratory examinations.

As possible causes for 'dry mouth', the prevalence of anticholinergic and/or antidepressant medication was compared between the CFS patients with and without 'the sicca symptoms characteristic for SS'.

#### Examinations

Ocular examinations included Schirmer's test and the Rose Bengal test. The results of the Rose Bengal test were divided into three categories: negative, mildly positive and strongly positive [9]. Tests for oral involvement included the stimulated salivary flow test (gum test), salivary scintigraphy using <sup>99m</sup>Tc pertechnetate and lip biopsy.

The gum test was defined as 'positive' and 'strongly positive' when the estimated volumes of saliva were <10 and <5 ml/10 min, respectively.

Anti-La (SSB) and the anti-Ro (SSA) antibodies were examined using the double immunodiffusion method with calf thymus extract as source of antigens. Antinuclear antibodies were estimated by indirect immunofluorescence using HEp-2 cells as substrate. Rheumatoid factor was quantitated by latex nephelometry.

### RESULTS

The numbers of sicca symptoms in the typical SS patients and in the control subjects are shown in Fig. 1. 'The sicca symptoms characteristic of SS' were defined

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TABLE I  
Three diagnostic criteria for 'definite' Sjögren's syndrome

|                                           | Japanese criteria [9]                                                                        | European criteria [10]                                                  | Fox's criteria [11]                                |
|-------------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------|
| 1. 'Dry eyes'                             | +                                                                                            | +                                                                       | +                                                  |
| 2. 'Dry mouth'                            | +                                                                                            | +                                                                       | +                                                  |
| 3. Ocular signs                           |                                                                                              |                                                                         |                                                    |
| (a) Schirmer test                         | -                                                                                            | +                                                                       | +                                                  |
| (b) Rose Bengal test                      | +                                                                                            | +                                                                       | +                                                  |
| 4. Minor salivary gland biopsy            | +*                                                                                           | +*                                                                      | +†                                                 |
| 5. Salivary gland involvement             |                                                                                              |                                                                         |                                                    |
| (a) Salivary scintigraphy                 | +                                                                                            | +                                                                       | +                                                  |
| (b) Parotid sialography                   | +                                                                                            | +                                                                       | -                                                  |
| (c) Salivary flow rate                    | -                                                                                            | +                                                                       | +                                                  |
| 6. Autoantibodies                         |                                                                                              |                                                                         |                                                    |
| (a) Anti-Ro/SSA or anti-La/SSB antibodies | -                                                                                            | +                                                                       | +                                                  |
| (b) Antinuclear antibodies                | -                                                                                            | +                                                                       | +                                                  |
| (c) Rheumatoid factor                     | -                                                                                            | +                                                                       | +                                                  |
| Diagnostic criteria                       | 1 and/or 2 are needed as obligatory criteria. In addition, 3b, or 4, or 5a (or 5b) is needed | Any four of six items are needed. 1 and/or 2 are not necessarily needed | 3a + 3b, 2 + 5c, 4 and 6a (or 6b or 6c) are needed |

+, included as an item for diagnostic criteria; -, not included as an item for diagnostic criteria.

\*Focus score  $\geq 1$ ; †focus score  $\geq 2$  (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci/4 mm<sup>2</sup> of glandular tissue).

tentatively as positive when eight or more sicca symptoms were seen in a single patient. The background and number of sicca symptoms in the CFS patients with and without the sicca symptoms, SS, and controls are shown in Table III.

'The sicca symptoms characteristic of SS' were found in 55 (73%) of the 75 CFS patients. The prevalence of anticholinergic and/or antidepressant medication was not statistically different between group 1 and group 2 (Table III). Of the 55 CFS patients, 32 (58.2%) underwent at least ophthalmological examination(s) and the gum test, and these were further studied. Among 20 CFS patients without 'the sicca symptoms characteristic of SS', five (25%) had undergone these tests. Of the five patients, one fulfilled the Japanese criteria and another one fulfilled the European criteria. In the respective patients, five and six sicca symptoms were found, and anti-Ro and anti-La antibodies were negative in both patients.

TABLE II  
Thirty-seven sicca symptoms reported in Sjögren's syndrome

(A) Sicca symptoms of eyes

1. Foreign body (or sandy) sensation; 2. burning sensation; 3. eye discharge; 4. decreased tearing; 5. redness; 6. photophobia; 7. eye fatigue; 8. itching; 9. blurring; 10. eye discomfort; 11. ocular pain; 12. smarting sensation; 13. difficulty in moving the eyelids

(B) Sicca symptoms of the mouth

1. Inability to eat dry food; 2. difficulty in swallowing food; 3. adherence of food to buccal surfaces; 4. abnormality of taste; 5. fissures of the tongue; 6. fissures of the lips; 7. frequent ingestion of liquids, especially at meal times; 8. a marked increase in dental caries; 9. carrying bottles of water; 10. oral dryness; 11. loss of tooth filling

(C) Other sicca symptoms

1. Abnormality of smell; 2. nasal dryness; 3. epistaxis; 4. hoarseness; 5. parotid gland enlargement; 6. oral pain; 7. skin dryness; 8. decrease or absence of sweating; 9. vaginal dryness; 10. abnormal sensation at sexual intercourse; 11. dry earwax; 12. dry cough; 13. sputum

The details of the 32 CFS patients for each diagnostic test for SS are shown in Table IV. Of the 32 CFS patients examined, 10 (31.3%) had a positive Rose Bengal test. Among these, three (9.4%) were strongly positive. Of the 32 CFS patients examined, the gum test was positive in 24 (75.0%), among which seven (21.9%) were strongly positive. Of the 20 CFS patients examined, seven (35.0%) had clearly decreased accumulation and/or secretion of <sup>99m</sup>Tc pertechnetate. The histology of lip biopsies in 20 CFS patients was scored as grade 0 in 11, grade 1 in five, grade 2 in one, grade 3 in two and grade 4 in one. None of the 32 CFS patients were positive for anti-La (SSB) antibody and only one was positive for anti-Ro (SSA) antibody. Six (18.8%) of 32 CFS patients showed positive

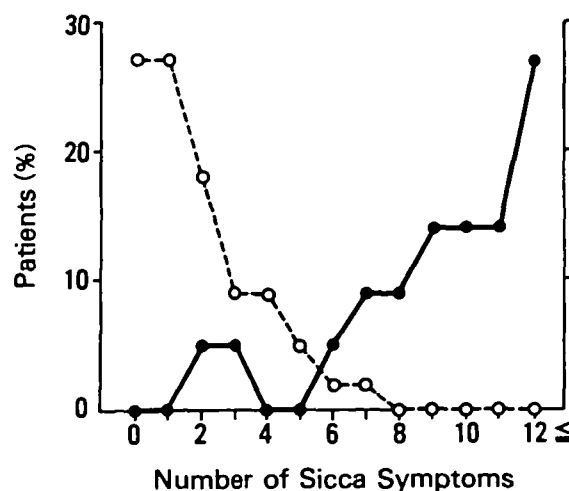


FIG. 1.—Number of sicca symptoms in patients with Sjögren's syndrome (solid line) and control subjects (broken line). The presence of eight or more sicca symptoms was considered to be 'sicca symptom characteristic of Sjögren's syndrome'.

TABLE III  
Background and number of sicca symptoms in the patients with CFS, SS and controls

|                                                                       | No. of patients | Male/female | Mean age (yr) | Mean no. of sicca symptoms |
|-----------------------------------------------------------------------|-----------------|-------------|---------------|----------------------------|
| Group 1<br>CFS patients with 'sicca symptoms characteristic of SS'    | 55              | 3/52        | 50.5          | 11.8                       |
| Group 2<br>CFS patients without 'sicca symptoms characteristic of SS' | 20              | 2/20        | 41.3          | 3.8                        |
| Group 3<br>SS                                                         | 22              | 0/22        | 57.7          | 11.0                       |
| Group 4<br>Controls                                                   | 44              | 0/44        | 53.9          | 1.8                        |

CFS, chronic fatigue syndrome; SS, Sjögren's syndrome.

antinuclear antibodies. Eight (25.8%) of the 31 CFS patients tested were positive for rheumatoid factor.

Five of the 32 CFS patients fulfilled both the Japanese and European diagnostic criteria for SS (Table IV). Two fulfilled the Japanese criteria only and three fulfilled the European criteria only (Table IV).

None of the 10 CFS patients who met the Japanese and/or European criteria fulfilled Fox's criteria, although four were diagnosed as having possible SS (Table IV).

Anti-La (SSB) antibody and anti-Ro (SSA) antibody were negative in almost every CFS patient who fulfilled the diagnostic criteria of SS (Table IV).

## DISCUSSION

Our study on the similarity of SS and CFS is the first in which the new diagnostic criteria for both SS and CFS were used.

The prevalence of sicca symptoms in CFS (40/46; 83%) was higher in our previous series [5] compared to that of Komaroff *et al.* [3] (204/510; 40%) or Kuratsune *et al.* [4] (28/59; 48%) ( $P = 0.0001$ , respectively). This difference may be present because we are rheumatologists and they are not: rheumatologists may have a higher index of suspicion and rate of recognition [8] and the introduction of a larger number of patients with sicca symptoms by other doctors.

The sicca symptoms, with the exception of photophobia, are not included as items of diagnostic

TABLE IV  
Details of 32 CFS patients with 'sicca symptoms characteristic of Sjögren's syndrome'

| Patient | Age | Sex | Schirmer test | Rose Bengal test | Gum test* | Sialoscintigraphy | Lip biopsy (grade†) | Anti-Ro | Anti-La | ANA | RF |
|---------|-----|-----|---------------|------------------|-----------|-------------------|---------------------|---------|---------|-----|----|
| 1†§     | 21  | F   | +             | -                | 10.0      | +                 | 0                   | -       | -       | -   | +  |
| 2†§¶    | 48  | F   | +             | +                | 9.0       | +                 | 1                   | -       | -       | +   | +  |
| 3†§     | 58  | F   | +             | +                | 5.1       | -                 | 0                   | -       | -       | +   | -  |
| 4†§     | 32  | F   | +             | -                | 0.0       | +                 | 0                   | -       | -       | -   | +  |
| 5†§     | 57  | F   | +             | +                | 6.8       | -                 | 3                   | -       | -       | -   | -  |
| 6†§¶    | 43  | F   | +             | +                | 9.0       | nd                | nd                  | -       | -       | +   | +  |
| 7†§     | 58  | F   | +             | +                | 8.0       | -                 | 3                   | -       | -       | -   | -  |
| 8†§     | 66  | F   | +             | +                | 5.0       | +                 | 0                   | -       | -       | -   | -  |
| 9†§¶    | 60  | F   | +             | +                | 2.4       | +                 | 2                   | -       | -       | +   | -  |
| 10†     | 55  | F   | +             | +                | 18.0      | nd                | nd                  | -       | -       | -   | +  |
| 11†     | 58  | F   | +             | -                | 6.5       | -                 | 4                   | -       | -       | -   | -  |
| 12§¶    | 48  | F   | -             | -                | 0.0       | nd                | nd                  | +       | -       | +   | nd |
| 13§     | 71  | F   | +             | -                | 1.6       | -                 | 0                   | -       | -       | -   | -  |
| 14§     | 64  | F   | +             | +                | 0.0       | nd                | 1                   | -       | -       | -   | -  |
| 15      | 47  | F   | nd            | -                | 7.1       | -                 | 0                   | -       | -       | -   | -  |
| 16      | 37  | F   | +             | -                | 6.5       | nd                | nd                  | -       | -       | -   | -  |
| 17      | 47  | M   | +             | -                | 16.0      | -                 | nd                  | -       | -       | -   | -  |
| 18      | 54  | F   | -             | -                | 6.1       | nd                | nd                  | -       | -       | -   | -  |
| 19      | 54  | F   | +             | -                | 22.0      | -                 | 0                   | -       | -       | -   | +  |
| 20      | 69  | F   | +             | -                | 10.0      | nd                | 1                   | -       | -       | -   | -  |
| 21      | 69  | F   | +             | -                | 5.2       | -                 | 0                   | -       | -       | +   | -  |
| 22      | 41  | F   | +             | -                | 7.6       | -                 | 1                   | -       | -       | -   | -  |
| 23      | 45  | F   | +             | -                | 10.0      | nd                | nd                  | -       | -       | -   | -  |
| 24      | 46  | F   | +             | -                | 7.0       | nd                | nd                  | -       | -       | -   | +  |
| 25      | 53  | F   | -             | -                | 10.3      | nd                | nd                  | -       | -       | -   | +  |
| 26      | 52  | F   | +             | +                | 9.5       | -                 | 0                   | -       | -       | -   | -  |
| 27      | 48  | M   | +             | nd               | 12.0      | nd                | nd                  | -       | -       | -   | -  |
| 28      | 26  | F   | -             | -                | 4.0       | +                 | 1                   | -       | -       | -   | -  |
| 29      | 46  | F   | +             | -                | 3.8       | -                 | 0                   | -       | -       | -   | -  |
| 30      | 43  | F   | -             | -                | 7.0       | nd                | nd                  | -       | -       | -   | -  |
| 31      | 55  | F   | +             | -                | 6.5       | -                 | 0                   | -       | -       | -   | -  |
| 32      | 50  | F   | +             | -                | 6.4       | nd                | nd                  | -       | -       | -   | -  |

nd, not done; ANA, antinuclear antibodies; RF, rheumatoid factor.

\*ml/10 min.

†See the text.

‡ and §Patients who fulfil the Japanese and European criteria for SS, respectively.

¶Patients diagnosed as 'possible SS' by Fox's criteria.

criteria for CFS [1]. Photophobia, which is one of the sicca symptoms in SS [12–15], was included as a 'neuropsychiatric' complaint in the CFS criteria [1]. Later, however, sicca symptoms were described as one of the common clinical manifestations of CFS [3–5, 8].

In the present study, it was determined that 'the sicca symptoms characteristic of SS' are common in CFS patients and were irrelevant to the drugs used. In addition, CFS patients frequently had positive results on the Schirmer, Rose Bengal and gum tests. Therefore, these tests may not be helpful for differentiating CFS from SS. On the other hand, sialoscintigraphy and lip biopsy examination are not frequently positive in CFS. It was especially interesting that anti-La (SSB) and anti-Ro (SSA) antibodies were not positive in almost every CFS patient with 'seronegative' SS. The presence of immunological abnormalities has been established as a cardinal factor in SS [17]. Accordingly, whether 'seronegative' SS differs from 'seropositive' SS as a separate disease entity needs to be examined.

In contrast to the Japanese and European criteria, none of the present cases with CFS fulfilled Fox's diagnostic criteria for SS. Accordingly, Fox's criteria may be useful for the differential diagnosis of SS and CFS.

Of the 20 patients without 'the sicca symptoms characteristic of SS', two fulfilled the Japanese and European criteria. These results may suggest the presence of 'subclinical' seronegative SS in CFS.

There is controversy as to whether CFS is the same disease entity as fibromyalgia [18, 19]. It is impressive that the 'sicca symptoms' are listed as additional main clinical features in fibromyalgia [20, 21]. Actually, 36 of our 75 CFS patients (48%) met the classification criteria [20] for fibromyalgia.

In conclusion, when CFS patients complain of sicca symptoms, some of them may be diagnosed as having 'seronegative' SS.

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