Hemostatic Factors and Cardiovascular Disease in Active RA: An 8 Year Followup Study
S. Wåhlberg-Granman, M. Cederfelt
http://scad.bireme.br/cgi-bin/wil.exe/scad

Dr Antonio Filpi Coimbra da Costa
Rua Antônio Basílio 415 Ap 504
20511-190 - Rio de Janeiro - RJ
BRASIL

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Anxiety and Depression in Patients with Primary Sjögren’s Syndrome

SIGRÍDUR T. VALTYSÓDÓTTIR, BJÖRN GUDBJÖRNSSON, ULLA LINDBVIST, ROGER HÄLLGREN, and JERKER HETTA

ABSTRACT. Objective. To examine the degree of anxiety and depression and to assess well being and general symptoms in patients with primary Sjögren’s syndrome (SS).

Methods. A standardized questionnaire, the Hospital Anxiety and Depression Scale, was used to examine the degree of anxiety and depression in patients with primary SS (n = 62) and in age matched healthy female controls. The Gothenburg quality of life instrument (GQOL) was used to assess well being and general symptoms. Patients with rheumatoid arthritis (RA; n = 38) were used as patient controls.

Results. The patients with primary SS had significantly higher scoring rate for “possible” clinical anxiety (48%) and for “possible” clinical depression (32%) compared with reference groups (p < 0.05). The physical and mental well being of the patients with primary SS were significantly reduced compared with controls. Furthermore, patients with primary SS complained more commonly of low mood, irritability, headache, gastrointestinal symptoms, and impaired concentration and memory than the patients with RA.

Conclusion. The results indicate that patients with primary SS often have psychiatric symptoms and worse well being, which may affect their quality of life. (J Rheumatol 2000;27:165–9)

Key Indexing Terms:
PRIMARY SJOGREN’S SYNDROME
DEPRESSION

From the Rheumatology Unit, Department of Medical Sciences; and the Sleep Disorder Unit, Department of Neuroscience, University Hospital, Uppsala, Sweden, and the Department of Medicine, Akureyri Hospital, Akureyri, Iceland.

S.T. Valtýsdóttir, MD; B. Gudbjörnsson, MD, PhD, Rheumatologist; U. Lindqvist, MD, PhD, Rheumatologist; R. Häggren, MD, PhD, Professor, Department of Rheumatology; J. Hetta, MD, PhD, Professor, Department of Neuroscience, University Hospital.

Address reprint requests to Dr. S. Valtýsdóttir, Department of Medical Science, Rheumatology, University Hospital, S-751 85 Uppsala, Sweden. E-mail: sigridur.valtysdottir@medicin.uu.se


Primary Sjögren’s syndrome (SS) is a chronic inflammatory connective tissue disease of unknown etiology. The disease primarily involves salivary and lachrymal glands infiltrated by lymphocyte and plasma cells, resulting in oral and ocular dryness, i.e., sicca symptoms. However, secretory glands of all mucous membranes may be involved. The most frequent symptom triad is muscular and joint pain, sicca symptoms, and fatigue. In addition, a wide spectrum of extraglandular features from various organs may be seen. In recent years interest has been focused on symptoms emanating from the central nervous system, and some investigators have reported frequent psychiatric symptoms in patients with primary SS, including high frequency of sleep disturbances.

Psychiatric illness may be difficult to diagnose in the presence of physical disorder, especially if the disorder is chronic. Symptoms of anxiety and depression often accompany physical disease. Nevertheless, measurements of psychiatric symptom profiles may give important aspects of how individuals are affected by a chronic disorder. Our aim was to evaluate anxiety and depression in patients with primary SS and assess how psychiatric symptoms might influence their well being.

The first study to investigate the spectrum of neuropsychiatric manifestations associated with primary SS by Malinov et al. found hypochondriasis and hysteria to be the most common disturbances. In our study depression and anxiety were the most frequent symptoms. Such symptoms may significantly influence the quality of life in patients with primary SS.

MATERIALS AND METHODS

Patients. Sixty-six female patients and one male patient (mean age 58, range 28–85 years) with primary SS according to the preliminary EEC criteria were included in the study. Patients also fulfilled the Copenhagen criteria. Thus, each patient had keratoconjunctivitis sicca by pathological Schirmer test (< 10 mm/5 min) and/or short breakup time (< 10 s) and/or positive rose bengal staining (2 of 3 tests abnormal); keratoconjunctivitis sicca was confirmed by a total salivary gland secretion rate of < 0.7 ml/min and/or abnormal lower lip glandular biopsy and/or pathological salivary gland scintigraphy (2 of 3 tests abnormal). Patients were investigated at the outpatient clinic of the Department of Rheumatology, University Hospital of Uppsala.

The onset of disease occurred 1–18 years (mean 6.5 years) prior to the study. Twenty-three patients had only glandular symptoms, whereas 41 patients also had extraglandular manifestations — Raynaud’s phenomenon (n = 22), arthralgias (n = 5), vasculitis (n = 2), insufficiency of the pancreas.
(n = 2), and pleuritis (n = 3). Eighteen patients were treated with disease modifying drugs: hydroxychloroquine (n = 14), cyclophosphamide (n = 2), methotrexate (n = 1), or azathioprine (n = 1). Eight patients were taking glucocorticoids (mean dosage of prednisolone 5 mg/day) at the time of evaluation.

**Patient controls.** Thirty-eight consecutive outpatients (mean age 60 years, range 29–84) who fulfilled the American Rheumatism Association criteria for classical rheumatoid arthritis (RA) served as patient controls. All were matched for age and sex.

**Healthy controls.** We also used 63 healthy controls (mean age 57 years, range 54–60) living in Uppsala and selected from a random population sample.

**Questionnaire.** Two sets of questionnaires were used. Sixty-seven patients received the Hospital Anxiety and Depression (HAD) Scale and also the Gothenburg quality of life (GQOL) questionnaire by mail 3 weeks later. The response rate for the HAD was 93% and for GQOL 61%. The questionnaires were handed out to the patients with RA, who responded anonymously. The controls received the questionnaires by mail.

The HAD scale is a brief, self-administered rating scale designed to measure anxiety and depression in somatically ill individuals. It has been validated for screening for psychiatric morbidity in cancer patients, in patients with cerebral stroke, and in several other patient groups. The questionnaire contains 14 items for self-assessment on a 0–3 scale. Seven questions are related to anxiety and 7 to depression. The whole scale range is 0–21 for depression and anxiety measurements. Scores of 8 or more on each subscale represent “possible” psychiatric morbidity and a score of 11 or more represents “definite” clinical anxiety or depression. The depression subscale has been constructed so that somatic items are largely excluded.

**The Gothenburg quality of life instrument (GQOL).** All participants answered a standardized self-administered questionnaire. The first part, assessing social, physiological, and psychological well being, uses a scale constructed with 7 steps (score 1–7) with extreme points denoted “excellent” (score = 7) and “very bad” (score = 1). The second part includes 30 questions about different symptoms. The participants were asked: “Have you been troubled by any of the following symptoms during the last three months? Answer with yes or no.” The GQOL instrument has been validated to assess well being and symptoms and is useful both as a descriptive tool and as a help in evaluating treatment.

**RESULTS**

**The Hospital Anxiety and Depression Scale. Anxiety subscale.** The HAD scale contains 7 questions concerning anxiety. The patients with primary SS responded significantly differently in 4 of these 7 items compared to the RA group. The patients with primary SS felt more restless and tense and reported having problems relaxing. Furthermore they more frequently reported a sudden feeling of panic than the patients with RA.

The mean score on the HAD scale for anxiety was 7.45 in patients with primary SS (Table 1) and 48% of them were in the range for possible clinical anxiety, i.e., a score ≥ 8. The score for patients with RA was 5.05 (p < 0.05), and 22% of them were in the range of possible anxiety (Figure 1). Nineteen percent of patients with primary SS and 7% of patients with RA had a score ≥ 11, reflecting definite anxiety.

**Depression subscale.** The patients with primary SS responded with a significantly higher score than healthy controls and patient controls (Table 1) to questions measuring the degree of depression. Patients with primary SS reported that they had lost interest in their own appearance and in enjoying a good book or TV program. As well, they reported cheerfulness less frequently.

The mean score on the HAD depression scale was 6.1 for patients with primary SS (Table 1) and 32% were in the range for possible clinical depression, i.e., a score ≥ 8, while only 10% of the patients with RA had scored ≥ 8 (p < 0.05). Thus, the patients with primary SS showed a significantly higher score for depression than the RA group, 3.95 (p < 0.05) (Figure 1). Eight percent of patients with primary SS and 2.5% of patients with RA had a score ≥ 11, reflecting definite depression.

**The Gothenburg quality of life instrument.** The prevalence of various symptoms was studied in patients with primary SS and RA. Comparison between patients with primary SS and RA revealed differences with regard to various aspects of well being (Table 2). With regard to physical well being the patients with primary SS were significantly more affected with impaired memory, vision, and appetite. The mental well being regarding mood, energy, and the quality of sleeping was significantly reduced in patients with primary SS. Furthermore, they experienced their family situation to be significantly worse than patients with RA.

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Table 1. Comparison of the mean scores (± SD) of the Hospital Anxiety and Depression Scale concerning the 2 patient groups (primary SS and RA) and healthy female controls (HC).

<table>
<thead>
<tr>
<th></th>
<th>Primary SS</th>
<th>RA</th>
<th>HC</th>
<th>p</th>
<th>pSS/RA</th>
<th>pSS/HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>7.48 (± 3.66)</td>
<td>5.0 (± 2.85)</td>
<td>6.2 (± 3.3)</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>6.1 (± 3.7)</td>
<td>3.9 (± 2.77)</td>
<td>4.0 (± 2.8)</td>
<td>0.05</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation.
Patients with primary SS had more depression symptoms than those with RA, and the most prominent complaints were low mood, general fatigue, and sleep disturbances (Table 3). Tension symptoms including difficulty relaxing and restlessness were also reported significantly more often in primary SS patients.

Abdominal pain, nausea, and constipation were common in primary SS and occurred significantly more often than in RA. Both groups had high scores for musculoskeletal symptoms, but patients with primary SS had backache more often than RA patients. Headache and eye problems were significantly more often reported in the primary SS group (Table 3).

Disease activity and psychiatric symptoms. No correlation was seen between age and the scores of depression and anxiety in the patient groups. Patients with primary SS who were subgrouped with regard to extraglandular symptoms and treatment with disease-modifying drugs had similar profiles in the questionnaires. Sicca symptoms in the patients with RA had no influence on their psychiatric symptoms.

**DISCUSSION**

Primary Sjögren's syndrome is a chronic and slowly progressive disorder, characterized by constant discomfort from dryness in almost every mucus membrane, arthralgia, and myalgia. However, severe fatigue is often the main complaint among patients with primary SS. Reports have also documented frequent sleeping disturbances in primary SS. Patients with RA have a crippling disease with severe joint inflammation and prominent deterioration of functional capacity. It is reasonable to assume that the symptoms in primary SS and in RA may affect the psychiatric symptomatology of patients. However, our clinical impression has been that effects on psychiatric health are more common in primary SS than in RA. The present study confirms this suspicion by revealing that almost half the patients with primary SS suffered various degrees of anxiety. Probable and definite depression were also frequent findings and were present in one-third of the patients. In contrast, patients with RA had these symptoms to the same extent as healthy controls. The symptoms of anxiety and depression in patients with primary SS were also reflected in their social, physical, and mental well-being. The response rates for the 2 questionnaires used in this study were adequate for the HAD scale (93%), but the lower response rate for the Gothenburg quality of life instrument (61%) may have some effect on the results.

The first study of neuropsychiatric manifestations associated with primary SS was reported by Malinow, et al, who found that 25 of 40 unselected patients with primary SS had psychiatric abnormalities; most common was depression, while persistent hypomania followed by depression occurred less frequently. A psychiatrist performed the psychiatric evaluation in that study. By using the Minnesota Multiphasic Personality Inventory (MMPI) they also found that 10 out of 25 patients with primary SS were on the Schizophrenia scale of the test. Applying the MMPI,
Hietaharju, et al. found that 33 of 44 patients with primary SS had psychiatric symptoms, and the most frequent were depressive symptoms, hypochondriasis, and hysteria. Drosos, et al. investigating 33 patients with primary SS, found high levels of introverted hostility, but a relatively low incidence of depression (15%) and anxiety (12%). Our instrument for evaluating depression and anxiety, the HAD Scale, is specially designed for patients with physical disorders, since it avoids symptoms like insomnia, pain, or anorexia that might result from physical illness as well as from a mood disorder. In our test, anxiety was the dominating symptom, in contrast to the findings of Malinow, et al, Hietaharju, et al, and Drosos, et al, who reported a low incidence of this psychiatric manifestation. Vitali, et al., in 30 patients with primary SS, found a high frequency of fibromyalgia features that correlated with the depression state. In their study 47% of the patients had moderate to severe depression. They suggest that the fibromyalgic pain might be consequent to these psychological changes, rather than related to other disease-specific mechanisms. The differences in results might reflect differences in the sensitivity and specificity of the various tests. Previous reports have showed, as in our study, that depression and anxiety are relatively uncommon in RA patients, with an estimated prevalence ranging from 15 to 23%. Thus, a chronic, painful, and disfiguring disease like RA, affecting functions and social life, seems to have very little psychiatric impact. Since the somatic symptoms in primary SS in most situations are less prominent, mechanisms other than musculoskeletal pains must underlie the psychiatric abnormalities in primary SS.

Several studies show that clinical involvement of the central nervous system (CNS) occurs in about 25% of patients with primary SS. The peripheral nervous system (PNS) may also be involved in roughly 10-30% of all patients with primary SS. Involvement of the brain can be focal or diffuse, and may result in seizure disorders, stroke, aseptic meningoencephalitis, and symptoms mimicking multiple sclerosis. Polyneuropathy and entrapment neuropathy. Alexander, et al. investigated primary SS patients with magnetic resonance (MR) imaging. Abnormal MR findings were seen in 12/16 patients with active neuropsychiatric manifestations and in 2/22 patients with no clinical evidence of CNS disease. Of the patients with active nervous system disease, the majority had both psychiatric and cognitive dysfunctions. In our study, almost half the patients had psychiatric disturbances and 60-70% had impaired cognitive function based on the GQOL, i.e., reflected by impaired memory and concentration. This neuropsychological profile has been proposed by others to be an early possible sign of dementia. Indeed, rapidly progressive dementia has been reported in patients with primary SS. Dementia is frequently seen in the elderly population, and more often in females. Since primary SS is a common disease, affecting 2.7% of people 55-72 years old in Sweden, it is important that attention is paid to the possibility that impaired cognitive function may be linked to primary SS. The cause of the CNS disturbances in primary SS remains unclear, but reports have suggested the pathogenic possibility that anxiety and depression are mediated by immunopathological mechanisms. Cytokines or autoantibodies may play a role in mediating or potentiating vascular injury in the CNS of patients with primary SS. In this respect it is worthwhile to recall that patients with depression but without primary SS have increased circulating levels of interleukin 1β (IL-1β), IL-2, IL-6, IL-10, and interferon-γ.

Psychiatric symptoms in patients with primary SS are common. These patients have a chronic slowly progressing disease and worse well being, which can affect their quality of life. Importantly, their somatic symptoms may be connected to and secondary to their psychiatric disturbance. This insight may have an influence on their pharmacological treatment.

REFERENCES